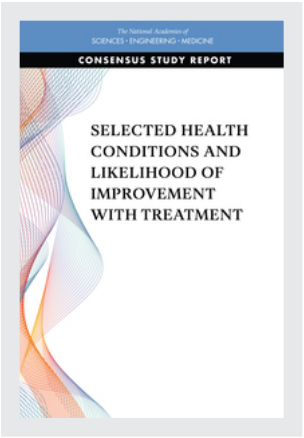

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Selected Health Conditions and Likelihood of Improvement with Treatment

Committee on Identifying Disabling Medical Conditions Likely to Improve with Treatment

Board on Health Care Services

Health and Medicine Division

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COMMITTEE ON IDENTIFYING DISABLING MEDICAL CONDITIONS LIKELY TO IMPROVE WITH TREATMENT

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **HAROLD C. SOX,** Dartmouth Geisel School of Medicine, and **BRADFORD H. GRAY,** The Urban Institute. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Contents

Acronyms and Abbreviations

ACR	American College of Rheumatology
ACS	American Cancer Society
ADA	Americans with Disabilities Act
ADHD/ADD	attention deficit hyperactivity disorder/attention deficit disorder
AHRQ	Agency for Healthcare Research and Quality
ALK	anaplastic lymphoma kinase
APA	American Psychiatric Association
ASCO	American Society of Clinical Oncology
BDI-II	Beck Depression Inventory II
BEP	brief eclectic psychotherapy
BPI	Brief Pain Inventory
BRCA1	breast cancer type 1 susceptibility gene
BRCA2	breast cancer type 2 susceptibility gene
CA-125	carbohydrate antigen 125
CAL	compassionate allowance
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	cognitive behavioral therapy
CD	cognitive dysfunction
CDC	Centers for Disease Control and Prevention
CDK	cyclin-dependent kinase
CDR	continuing disability review
CDT	complex decongestive therapy
CFR	Code of Federal Regulation
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CIPN	chemotherapy-induced peripheral neuropathy
CPT	cognitive processing therapy
CR	controlled release
CRF	cancer-related fatigue
CRP	c-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCIS	ductal carcinoma in situ
DMARD	disease-modifying antirheumatic drug
DoD	U.S. Department of Defense
DSM	*Diagnostic and Statistical Manual of Mental Disorder*
DSM-III	*Diagnostic and Statistical Manual of Mental Disorder, 3rd Edition*
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*

DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*
EBV	Epstein-Barr virus
ECT	electroconvulsive therapy
EGFR	epidermal growth factor receptor
EMDR	eye movement desensitization therapy
ER/PR/HER2	tumor markers
ERP	exposure and response prevention
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EX/RP	exposure and response prevention
FACT	Functional Assessment of Cancer Therapy (questionnaire)
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FNA	fine needle aspiration
GAD	generalized anxiety disorder
HAM-D	Hamilton Depression Rating Scale
HAQ	Health Assessment Questionnaire Disability Index
HDRS	Hamilton Depression Rating Scale
HER2	human epidermal growth factor receptor 2
HGSOC	high-grade serious ovarian cancer
HIV	human immunodeficiency virus
HNC	head and neck cancer
HPV	human papillomavirus
IASP	International Association for the Study of Pain
ICD	*International Classification of Disease*
ICF	*International Classification of Functioning, Disability and Health*
ICI	immune checkpoint inhibitor
IFNα	interferon alpha
IFNβ	interferon beta
IFNγ	interferon gamma
IGH	immunoglobulin heavy chain
IL-2	interleukin-2
IMPACT	Initiative for Molecular Profiling and Advanced Cancer Therapy
IOM	Institute of Medicine
IPT	interpersonal therapy
ISTSS	Society for Traumatic Stress Studies
KC	keratinocyte carcinoma
KPS	Karnofsky Performance Scale
Li/DVP	lithium/divalproex
LSAS	Liebowitz Social Anxiety Scale
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MIE	medical improvement expected

MINE	medical improvement not expected
MIP	medical improvement possible
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS-R	National Comorbidity Survey
NET	narrative exposure therapy
NHIS	National Health Interview Survey
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NMDA	N-methyl-D-aspartate receptor
NPRM	notice of proposed rule making
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
OA	osteoarthritis
OCD	obsessive compulsive disorder
ODT	orally dissolving tablet
OIG	Office of Inspector General
OMB	Office of Management and Budget
OR	odds ratio
PARP	poly (ADP-ribose) polymerase
PCT	present-centered therapy
PD	panic disorder
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PE	prolonged exposure
PET	positron emission tomography
PHQ	Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire-9
PIK3ca	a protein coding gene
PR	pulmonary rehabilitation
PsA	psoriatic arthritis
PT	physical therapy
PTSD	posttraumatic stress disorder
QDD	Quick Disability Determination
QoL	quality of life
RA	rheumatoid arthritis
RAI	radioactive iodine ablation
RCT	randomized controlled trial
RT	radiation therapy
SAD	social anxiety disorder
SCLC	small-cell lung cancer
SEER	Surveillance, Epidemiology and End Result
SGA	substantial gainful activity
SNRI	serotonin-norepinephrine reuptake inhibitor

SOT	Statement of Task
SRI	serotonin reuptake inhibitor
SSA	Social Security Administration
SSDI	Social Security Disability Insurance
SSI	Social Security Insurance
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression (study)
TG	thyroglobulin
TMS	transcranial magnetic stimulation
TNF	tumor necrosis factor
TNM	tumor, lymph nodes, metastasis
TSH	thyroid-stimulating hormone
UCSD	University of California, San Diego
VA	U.S. Department of Veterans Affairs
VA/DoD	U.S. Department of Veterans Affairs and U.S. Department of Defense
VO2peak	volume of oxygen uptake during peak exercise
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organization
XR	extended release
YBOCS	Yale–Brown Obsessive Compulsive Scale

Summary

In response to a request from the Social Security Administration (SSA), the National Academies of Sciences, Engineering, and Medicine (the National Academies) appointed a committee to conduct a study on identifying disabling medical conditions, in adults, that are likely to improve with treatment. Of particular interest to the SSA are those long-lasting conditions (12 months or more) in the categories of mental health disorders, cancers, and musculoskeletal disorders.

Specifically, the SSA tasked the National Academies committee with the following:

1. Identify and define the professionally accepted, standard measurements of outcomes improvement for medical conditions (for example, mortality and effectiveness of care);
2. Identify specific, long-lasting (12-month duration or longer) medical conditions for adults in the categories of mental health disorders (such as depressive disorders, anxiety disorders, attention-deficit/hyperactivity disorder), cancers (such as breast, skin, thyroid), and musculoskeletal disorders (such as disorders of the back, osteoarthritis, other arthropathies) that are disabling for a length of time, but typically (for most people with the condition) do not result in permanently disabling limitations, are responsive to treatment, and, after a specific length of time of treatment, improve to the point at which the conditions are no longer disabling; and
3. For the conditions identified in Objective 2 (above):
    a. Describe the professionally accepted diagnostic criteria, the average age of onset, and the gender distribution, for each condition;
    b. Identify the types of medical professionals involved in the care of a person with the condition;
    c. Describe the treatments used to improve a person's functioning, the settings in which the treatments are provided, and how people are identified for the treatments;
    d. Describe the length of time from start of treatment until the person's functioning improves to the point of which the condition is no longer disabling and specific ages where improvement is more probable;
    e. Identify the laboratory or other findings used to assess improvement, and, if patient self-report is used, identify alternative methods that can be used to achieve the same assessment; and
    f. Explain whether pain is associated with the condition, and, if so, describe the types of treatment prescribed to alleviate the pain (including alternatives to opioid pain management such as non-pharmacological and multi-modal therapies).

The findings of this National Academies study will assist SSA in the administration of its programs that provide disability benefits: the Social Security Disability Insurance (SSDI) program and the Supplemental Security Income (SSI) program. SSDI provides disability benefits to working-age Americans who are no longer able to work due to a disabling medical condition or terminal illness. SSI provides income assistance for disabled, blind, and aged people with limited income and resources regardless of their prior participation in the labor force. Both programs share a common disability determination process administered by SSA and a common definition of disability for adults, which is "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months." SSDI and SSI beneficiaries must undergo periodic review to determine their continued eligibility. The timeframe of review varies by medical condition and is set based on SSA's knowledge of the medical condition.

THE COMMITTEE'S APPROACH TO THE TASK

A 16-member committee was formed to address the task. Members with diverse backgrounds and expertise were appointed to focus on the different aspects of the task. Specifically, the members have expertise in various branches of clinical medicine (mental health, oncology, and musculoskeletal disorders) and in biostatistics and epidemiology, health care policy, and health-outcomes research.

The committee organized itself into three groups: cancer, mental health, and musculoskeletal. Each group had experts in the specific disease category that was being studied, in addition to a health outcomes researcher or a biostatistician and epidemiologist. Each group considered the specific disease categories listed in the statement of task and identified the diseases within those categories that they would study. Each disease outcome chapter provides criteria for the selection of the diseases chosen. The committee met five times in person.

In responding to the objectives in the Statement of Task, the committee examined systematic reviews, when available, for the medical conditions studied and also relied on published guidelines, particularly if they had been through an external review process. The committee instructed the National Academies staff to conduct targeted literature searches and to gather information from relevant texts, scientific journals and professional societies, and federal sources. The staff initially reviewed more than 1,157 titles and abstracts; those were narrowed to about 528 studies, which the committee members carefully reviewed for relevance to their task. Several disorders required additional searches to include randomized control trials, if there were a limited number of systematic reviews or meta-analyses.

COMMITTEE'S CONCEPTUALIZATION OF DISABILITY AND FUNCTION

The committee members considered the issue of general medical improvement versus functional improvement, as disability models have expanded beyond a one-dimensional conception of medical conditions as the sole determinants of disability. The models conceptualize disability as an entity that reflects an aggregate of individual, societal, and environmental factors. More specifically, an individual may be severely limited in one context, but able to maintain independence and gainful employment in another. The committee

considered the entire range of function even though higher levels may not directly pertain to SSA's definition of disability. That decision was driven by several factors. First, multiple impairments and medical morbidities typically combine to disable individuals with the target conditions. Second, these impairments and morbidities may affect different functional domains. Therefore, a measure of function that is specific to one domain may not capture deficits in other domains. Third, co-occurring impairments may interact synergistically rather than additively to disable patients. As a consequence, impairments with moderate impact on a discrete functional domain may exert profoundly disabling effects when combined with other impairments. Those effects may become particularly potent when patients are also afflicted by symptoms and co-morbidities.

DISABLING MEDICAL CONDITIONS AND LIKELIHOOD OF IMPROVEMENT WITH TREATMENT

The committee chose to examine disabling medical conditions within the categories of cancer, mental health, and musculoskeletal disorders to carry out the Statement of Task. The following sections summarize the committee's conclusions by disease category.

Cancer

Cancer is the second leading cause of death in the United States and a major cause of disability. In recent years, because of the development of new treatments such as immunotherapy and CAR T-cell therapy, there has been an increase in the overall survival of patients with cancers that would historically have had a poor prognosis. The committee notes the following cancers are likely to be disabling for a length of time (usually around the time of diagnosis) but might improve with treatment, particularly with recent developments in cancer therapy: breast cancer (excluding ductal carcinoma in situ), melanoma, renal cancer, head and neck cancers, advanced epithelial ovary cancer, non-small-cell lung cancer, and diffuse large B-cell lymphoma. The committee acknowledges that other cancers might also fit the criteria.

In addition to the effects of the medical condition itself, cancer treatments are well known to cause morbidity in cancer survivors. Though the treatments have generally improved to be both more effective and less debilitating, treatment-related impairments are still common and, in many instances, expected. Studies show that most types of cancers result in decreased work ability in patients, at least during active treatment or in the cancer's terminal phase, and that the decreased work ability is often associated not with the progression of the cancer itself, but rather with treatment, treatment-related side effects (also known as toxicities), and comorbidity with other health conditions. The adverse effects of some treatments can be profound, with serious implications for function and quality of life. At the core of cancer treatments are surgery, systemic therapy, and radiation therapy. Each of those modalities has evolved significantly in recent years. Systemic therapy, for instance, which historically centered on various combinations of cytotoxic chemotherapeutics, now includes hormonal and biologic (targeted, immune, and gene) therapies. The addition of these new agents has revolutionized the treatment of many types of cancer but also has introduced new types of morbidity. Treatment-related impairments include pain, fatigue, cardiotoxicity, peripheral neuropathy, lymphedema, pulmonary dysfunction, and cognitive dysfunction. The residual effects of cancer treatments can present decades after

treatment. Studies have shown that the majority of cancer patients will improve after treatment completion, although the time course is patient specific.

The most significant recent advance in our understanding of cancers that are likely to improve with treatment has been achieved through an influx of promising new pharmaceuticals. Improved prognoses for some cancers have been realized through the integration of novel, targeted immune checkpoint and PARP inhibitors (pharmacological inhibitors of the enzyme poly [ADP-ribose] polymerase), among others. The impact of those agents has, for some cancers, led to durable remissions in cancers previously considered to be imminently fatal. For example, their effects on metastatic melanoma have been particularly significant. The effective practice of precision medicine permitted by such agents will likely expand to include different types and stages of cancer as well as new agents. However, much uncertainty remains regarding their toxicities, and only patients whose tumors express targetable molecules are eligible for such therapies. Common, functionally morbid toxicities with the potential to affect all body systems have been attributed to those agents. Consequently, the body of evidence regarding their harms and benefits continues to evolve. Additional advances in cancer care that have improved treatment outcomes include enhanced imaging, earlier detection capabilities, and enhanced supportive care, among others.

Cancers are a heterogeneous class of medical conditions with impairments and recovery that are hard to generalize over the course of the disease. The committee developed three overall conclusions regarding their review of specific selected cancers. First, variation in the ability of a cancer to improve with treatment exists within cancers of a particular organ system—not only by stage, but also by cancer cell type and molecular and genomic characteristics. Prognosis and treatment decisions are likewise based on the cancer site, stage, cell type, and molecular and genomic characteristics. For example, triple-negative invasive breast cancer (breast cancer with tumors lacking estrogen, progesterone, and the HER-2 gene) is much more aggressive and has lower survival than many other invasive breast cancer cell types. Another example is that recent phase III trials show that targeted therapies demonstrate superior efficacy to chemotherapy in non-small-cell lung cancer patients with an activating EGFR (epidermal growth factor receptor) mutation and in patients with ALK (anaplastic lymphoma kinase) rearrangements. Patients' ultimate survival varies dramatically based on the treatments available for the specific cancer sites, the stage of the disease, cell types, molecular and genomic markers, and the individual patient characteristics, including the presence of comorbid disease and the patient's functional status and social determinants of health. Additionally, a few studies suggest that for certain combinations of cancer site and treatment, the response varies by age, although the direction of the relationship varies among the studies.

Second, success in cancer treatment does not predict improved functional outcomes. Long-term cancer survivors often experience multiple comorbidities and impairments related to the toxic effects of the cancer therapies they underwent, including surgery, radiation, and systemic therapy (chemotherapy, biologic therapy). These impairments are a major cause of morbidity and have their own trajectories, treatments, and treatment response considerations. There can various types of side effects: acute side effects that develop during treatment but are transient, long-term side effects that develop during treatment but are chronic, late effects that develop after completion of the treatment, and secondary effects that result from acute and long-term side effects. The committee suggests that the following common cancer-related impairments can be disabling for a period of time but managed, though not necessarily cured, with treatment: pain, cancer-related fatigue, cardiotoxicity, chemotherapy-induced peripheral

neuropathy, lymphedema, pulmonary dysfunction, and cognitive dysfunction. Additionally, the committee notes that improved functional outcomes do not predict return to work.

Finally, it is important to consider the recursive nature of cancer, cancer treatments, and impairments. Cancer is a dynamic process, and as cancer patients survive longer, they experience a higher probability of disease relapse that can reset an episode of treatment. Given that cancer treatments commonly result in functional impairment, and disease relapse is highly probable, the question of how long it takes from initiation of cancer treatment until functioning improves is a complex one. The committee suggests that the length of time from the start of cancer treatment until a person's functioning improves to the point at which the condition is no longer disabling involves two timeframes: (1) the time to remission of the cancer and (2) the time to recovery from toxicities, symptoms, and functional impairments. The committee notes that a cancer patient's disease status (i.e., whether the cancer is in complete, partial, or no remission), more so than the cancer site and stage, is an appropriate indicator of whether the patient's functional status should be assessed for improvement. If a patient's cancer achieves complete remission, functional status improvement is probable, and it is reasonable to evaluate the patient's functional status 12 months after achieving complete remission; if the cancer achieves stable partial remission, then functional status improvement is possible, and it is also reasonable to evaluate functional status 12 months after achieving stable partial remission; if the patient has no response to treatment or experiences progression of disease, then functional improvement is unlikely.

Mental Health Disorders

The committee selected eight mental health disorders for inclusion in the report: major depressive disorder, bipolar I disorder, bipolar II disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), panic disorder (PD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD). Those mental health disorders are highly prevalent, are associated with significant functional impairment, and may respond to treatment. Professionally accepted diagnostic criteria for these conditions are detailed in the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5).

People diagnosed with a mental health disorder are directed to a specific treatment depending on clinical practice treatment guideline recommendations, their treatment history, their treatment preference, and treatment availability, among other factors. The committee expects that most patients who are disabled by psychiatric disorders are receiving psychiatric services by combinations of mental health professionals, including a prescriber (e.g., psychiatrist, advanced practice nurse), psychologist, licensed clinician social workers, and individuals with counseling or rehabilitation degrees. The conclusions here, however, should be interpreted with the caveat that for some populations (e.g., those in rural areas or small towns) care from qualified mental health professionals (e.g., specialized in evidence psychotherapy) might not be available. Importantly, the committee cautions that even under ideal treatment, full remission of mental health disorders, particularly when already determined as disabling, is seldom achieved.

Disorder-specific clinical practice guidelines detail evidence-based treatments for the eight disorders that the committee reviewed. Generally, those mental health disorders can be treated effectively with psychotherapy, pharmacotherapy or other biologic treatments, or a combination of both. There is no indication that improvement varies with age. However, some individuals do not improve after receiving evidence-based treatments, and among those who do improve, some will relapse. Furthermore, it is uncertain whether the rates of remission and

response observed in the scientific literature can be generalized to those receiving SSDIs or SSIs on the basis of a mental health disorder.

For the most part, in the clinical trials of treatments for mental health disorders improvement is defined in terms of disorder-specific symptoms, not functioning. Work-related disability is rarely assessed as an outcome. Furthermore, because there are no evidence-based laboratory tests for mental health disorders, mental health outcomes are assessed using patient self-report measures or clinician assessments.

There is a dearth of data on the length of time from start of treatment until the person's functioning improves to the point where the mental health disorder is no longer disabling. Attempting to accurately describe time to functional improvement by drawing from the existing data has important limitations. First, as mentioned above, treatment efficacy in research trials is generally defined in terms of symptomatic improvement, not functional outcomes, and time to symptomatic improvement is restricted to the duration of the trials. Second, psychiatric disorders are often recurrent, so time until improvement cannot be adequately captured as a linear process. Thus, individuals may have periods of remission during which they no longer meet the criteria for disability and later have an exacerbation of illness and associated functional limitations during which they again meet the criteria for disability. Third, the relationship between changes in symptoms and functioning is complex, and symptomatic improvement may not correspond to contemporaneous improvements in functioning. Fourth, psychiatric disorders generally occur with other psychiatric disorders, chronic pain, and medical conditions, and time to improvement will depend on those and other factors. Any estimates of time to improvement needs to consider the fact that clinical trials generally exclude participants with comorbidities. Fifth, the mental health disorders discussed in the report are under-recognized and effective treatments, particularly evidence-based psychotherapies, are often unavailable. That is particularly true for OCD. However, based on the limited evidence, the committee made the following conclusions regarding time from the start of treatment to improvement in functioning:

With regard to major depression disorder, functional improvement may lag behind or not occur even when a person is in symptomatic remission and may require rehabilitation that targets a return to work. Even then, recovery of occupational functioning, if it occurs, may take 1–2 years and may be limited by environmental contingencies. Early response to treatment might predict likelihood of improvement.

For bipolar I disorder, the acute phase of treatment lasts 6–12 weeks, while the maintenance phase treatment, which focuses on functional recovery, lasts 6–24 months. Caveats include the fact that improvement in social and occupational functioning may be limited or delayed and require targeted rehabilitation efforts. High-quality research shows that even with the addition of vocational rehabilitation, the potential for return to gainful employment may be limited due in part to financial and other environmental impediments.

Time to improvement can range from 12 to 24 weeks in OCD. Individuals requiring higher doses of medication or more complex cases may take a year or more to receive the full treatment benefit. For PTSD, there is some evidence from clinical trials indicating that general functioning improves in response to psychotherapy modalities. The length of time to improvement in functioning varies across psychotherapy modalities and usually corresponds to clinical trial follow-up endpoints (e.g., 8 or 16 weeks). Evidence regarding improvement in functioning from pharmacotherapy studies is less convincing, and the literature on improvements in work functioning specifically following PTSD treatment is scant.

For PD, GAD, and SAD, the time to improvement in symptoms in clinical trials is generally about 3 months. A longer treatment period may be required for partial responders or after relapse. Time to improvement in routine practice is likely considerably longer than in randomized controlled trials because of patient clinical complexity, treatment history, psychosocial factors, and variability in treatment delivery. Notably, the relationship between symptoms and functioning in individuals with anxiety disorders is weak. Even after treatment response or remission from an anxiety disorder, individuals may continue to have significant functional impairments which in turn may predispose them to a relapse of the anxiety disorder.

The committee notes that all of those conditions may be associated with chronic pain, which may contribute to increased risk for mental health disorders, and mental health disorders may result in an increased risk of chronic pain. The types of chronic pain that commonly co-occur with mental health conditions include migraine headaches, neck and back pain, fibromyalgia, and abdominal pain.

Musculoskeletal Disorders

Musculoskeletal disorders are a diverse set of conditions affecting bones, joints, muscles, and connective tissues. Those disorders may result in pain and a loss of function and are among the most disabling and costly conditions in the United States. Chronic pain and a loss of function are the primary mechanisms through which musculoskeletal disorders lead to disability and work loss.

SSA noted three categories of musculoskeletal disorders in its Statement of Task to the National Academies: disorders of the back, osteoarthritis, and other arthropathies. Based on the committee's clinical expertise and knowledge of the medical and research literature on musculoskeletal disorders, the committee determined that those disorders encompass the most disabling musculoskeletal conditions and that although rheumatoid arthritis and psoriatic arthritis are classified by SSA as "immune disorders," their most common—and, in many cases, most disabling—manifestation is inflammation of the joints leading to joint destruction and deformity. The committee thus decided that those conditions merited consideration as leading causes of musculoskeletal impairment.

Chronic low back pain is a primary musculoskeletal pain condition defined by pain for more than 3 months. It is highly prevalent in all adult age groups and is the top cause of years lived with disability. Chronic low back pain is sometimes associated with pain that radiates to the lower extremity in a characteristic distribution (i.e., radicular pain, sometimes called "sciatica" or radiculopathy). The presence of radicular pain or radiculopathy is associated with worse chronic low back pain severity and functional outcomes. Other factors associated with worse functional outcomes are co-existing medical and psychiatric conditions and other chronic pain conditions. In addition, the overuse of biomedical approaches to treat chronic low back pain (e.g., opioids and spine surgery) has been identified as a potentially important contributor to disability. However, numerous treatments have been shown to be effective in improving function in chronic low back pain, including exercise therapies, behavioral/psychologic therapies, and manual therapies. Multidisciplinary approaches, including intensive chronic pain rehabilitation programs and less intensive primary-care-based collaborative care management interventions, also have demonstrated benefits for function. In general, medications are less beneficial for function than for pain in those with chronic low back pain, with most benefits demonstrated only in the short term. The committee did not identify evidence about the likelihood or duration of the treatment required to reach a point at which low back pain is no

longer disabling. There is no evidence that the efficacy of chronic back pain treatments differs by age.

Osteoarthritis is a disease that destroys synovial joints over time. There is no known cure or method of reversing the process. Chronic pain and joint stiffness are hallmarks of this condition. Osteoarthritis can become disabling if it is severe enough to make work and daily tasks difficult. It is most common in older people, and gender differences vary by age. Before age 45 more men than women have osteoarthritis, but after age 45 it is more common in women. The prevalence of symptomatic knee osteoarthritis increases with each decade of life, with the annual incidence being highest between 55 and 64 years old. Although there are numerous treatments available, progressive osteoarthritis may result in reduced mobility and the resulting systemic complications of immobility and deconditioning. There is moderate to strong evidence suggesting that exercise therapy and psychosocial interventions are effective for relieving pain and improving function for many patients with osteoarthritis pain. Complications can result from the use of anti-inflammatory medications. Although joint arthroplasties and fusions can relieve pain and improve function, they can also cause infection, deep vein thrombosis, and even intraoperative mortality. For those reasons, joint replacements and fusions should generally be considered only when non-surgical approaches have not been effective in controlling pain and providing acceptable function.

Inflammatory arthropathies are conditions characterized by inflammation of the joints and often other tissues. They include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and systemic lupus erythematosus, among others. Rheumatoid arthritis and psoriatic arthritis are among the most common inflammatory arthropathies and are important causes of disability in adults.

Rheumatoid arthritis and psoriatic arthritis are systemic inflammatory diseases whose most common and prominent clinical manifestations include inflammation and destruction of the joints. These conditions are an important cause of work-related functional impairment. Effective treatments exist for rheumatoid arthritis and psoriatic arthritis, and the number of treatment options has expanded significantly in recent years as newer biologic agents have been approved. Because physical functioning is commonly assessed as a secondary outcome in trials of rheumatoid arthritis and psoriatic arthritis therapies, there is more evidence available about the impacts of specific treatments on functional capacity than for many of the other disabling medical conditions considered here.

Many existing pharmacologic treatments for rheumatoid arthritis and psoriatic arthritis have been found to improve physical functioning as measured with the Health Assessment Questionnaire Disability Index (HAQ), including a number of biologic disease-modifying antirheumatic drugs (DMARDs), which are indicated for more severe disease. However, the extent to which those therapies can improve work-related functional capacity among individuals with such severe impairments as to qualify for SSDI remains uncertain, for several reasons. First, few clinical trials have tested therapies among individuals with such severe impairments, so the treatment outcomes in this population are not well understood. Second, because the likelihood of functional improvement declines as the duration of disease and the number of prior DMARDs trials increase, treatment response is likely to be more modest among those with refractory disease. Third, both rheumatoid arthritis and psoriatic arthritis can result in irreversible joint damage, which may limit how much functional improvement can be achieved through medical management alone in the absence of surgery. Early diagnosis and treatment to prevent joint destruction and deformity is therefore of critical importance for patients with rheumatoid arthritis

and psoriatic arthritis. It is unclear how much improvement might be expected among patients who do not receive early DMARD therapy. Finally, evidence linking specific rheumatoid arthritis and psoriatic arthritis therapies directly to work outcomes is extremely limited, although HAQ scores are highly correlated with work disability.

1

Introduction

The Social Security Administration (SSA) administers two programs that provide disability benefits: the Social Security Disability Insurance (SSDI) program and the Supplemental Security Income (SSI) program. SSDI provides disability benefits to people (under the full retirement age)[1] who are no longer able to work because of a disabling medical condition. SSI provides income assistance for disabled, blind, and aged people who have limited income and resources regardless of their prior participation in the labor force (SSA, 2019a). Both programs share a common disability determination process administered by SSA and state agencies as well as a common definition of disability for adults: "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months" (SSA, 2017a). Disabled workers might receive either SSDI benefits or SSI payments, or both, depending on their recent work history and current income and assets. Disabled workers might also receive benefits from other public programs such as workers' compensation, which insures against work-related illness or injuries occurring on the job, but those other programs have their own definitions and eligibility criteria.[2]

This chapter provides the committee's task and basic background information about SSA and its programs for adults as related to the committee's task. It begins with a presentation of general information on SSDI and SSI, which both employ the same disability determination process.[3] The chapter also presents information regarding the continuing disability reviews (CDRs), periodic reviews that determine if disability benefit recipients' conditions continue to be

[1] Full retirement age had been 65 for many years. However, beginning with people born in 1938 or later, that age gradually increases until it reaches 67 for people born after 1959. The 1983 Social Security Amendments included a provision for raising the full retirement age beginning with people born in 1938 or later. Congress cited improvements in the health of older people and increases in average life expectancy as primary reasons for increasing the normal retirement age (https://www.ssa.gov/planners/retire/ageincrease.html [accessed March 16, 2020]).

[2] There is no federal role in state workers' compensation. State compensation programs vary widely with regard to coverage, benefits, and administrative practices (*Social Security Bulletin*, Volume 65, No. 4, 2005).

[3] See 20 Code of Federal Regulations (CFR) Part 404, Subpart P.

disabling. SSA must conduct CDRs at least once every 3 years unless a beneficiary's condition is not expected to improve, in which case SSA will still perform a review once every 7 years. Thus the frequency of scheduled CDRs is determined by the likelihood of improvement and is closely related to the committee's task.

It should be noted that the focus of this report is on adults, and considerations of disabilities in children are not examined. Furthermore, the population of interest is those individuals whose condition significantly limits their ability to do basic work (such as lifting, standing, walking, sitting, and remembering) for at least 12 months. If the condition does not meet that requirement (i.e., 12 month minimum disability duration) SSA will find that the individual is not disabled.

The remainder of the chapter discusses the committee's approach to the task, the evolving concepts of disability, the committee's conceptualization of disability, and the organization of the entire report.

STATEMENT OF TASK

As SSA seeks to improve its criteria for determining the appropriate point at which it sets a "diary" for a CDR, it has requested that the National Academies of Sciences, Engineering, and Medicine (the National Academies) establish a consensus committee to study specific, long-lasting medical conditions for adults that are disabling for a length of time but that typically do not result in permanently disabling limitations, are responsive to treatment, and, after a specific length of time of treatment, improve to a point at which the conditions are no longer disabling.

In response to that request, the Health and Medicine Division (HMD) of the National Academies appointed a committee to conduct the study. Specifically, the National Academies convened a committee to:

1. Identify and define the professionally accepted, standard measurements of outcomes improvement for medical conditions (for example, mortality and effectiveness of care);
2. Identify specific, long-lasting (12-month duration or longer) medical conditions for adults in the categories of mental health disorders (such as depressive disorders, anxiety disorders, attention-deficit/hyperactivity disorder), cancers (such as breast, skin, thyroid), and musculoskeletal disorders (such as disorders of the back, osteoarthritis, other arthropathies) that are disabling for a length of time, but typically (for most people with the condition) do not result in permanently disabling limitations, are responsive to treatment, and, after a specific length of time of treatment, improve to the point at which the conditions are no longer disabling; and
3. For the conditions identified in Objective 2 (above):
    a. Describe the professionally accepted diagnostic criteria, the average age of onset, and the gender distribution, for each condition;
    b. Identify the types of medical professionals involved in the care of a person with the condition;
    c. Describe the treatments used to improve a person's functioning, the settings in which the treatments are provided, and how people are identified for the treatments;

d. Describe the length of time from start of treatment until the person's functioning improves to the point of which the condition is no longer disabling and specific ages where improvement is more probable;
e. Identify the laboratory or other findings used to assess improvement, and, if patient self-report is used, identify alternative methods that can be used to achieve the same assessment; and
f. Explain whether pain is associated with the condition, and, if so, describe the types of treatment prescribed to alleviate the pain (including alternatives to opioid pain management such as non-pharmacological and multi-modal therapies).

SSA specifically directed the committee not to discuss issues related to access to treatment. The following language is in the National Academies contract with the SSA:

> The committee shall not describe issues with respect to access to treatments. While SSA recognizes people may have difficulty accessing care or particular forms of treatment, some do successfully access those treatments, and the agency receives information about those treatments in the medical records SSA considers when making disability determinations and conducting continuing disability reviews (CDRs). SSA is interested in receiving information about the types of treatments available, the requirements for receiving the treatments, what receipt of the treatments indicates about the severity of the medical condition, the likelihood of improvement when receiving the treatments, and the period over which the improvement would be expected. SSA understands improvement is not certain in all cases. SSA is interested in learning about conditions that are more likely than not to improve. SSA makes individual decisions on each case based on all the evidence they receive.

THE SOCIAL SECURITY DISABILITY INSURANCE PROGRAM

The SSDI program was authorized by Title II of the Social Security Act and enacted in 1956 to provide benefits to disabled workers who have paid into the Social Security system and who are younger than the Social Security full retirement age. The goal of SSDI is to replace a portion of a worker's income in the event of illness or disability in amounts related to the worker's former earnings. The SSDI program also provides Medicare coverage after a 2-year waiting period. SSDI is financed by the Social Security payroll tax, so any person who qualifies as disabled, according to the SSA definition of *disability* (inability to engage in any substantial gainful activity) and has paid Social Security taxes long enough to achieve sufficient work credits can receive SSDI. In 2018 there were 2,073,293 applications filed at Social Security field offices, teleservice centers, and electronically on the internet, and 733,879 awards were granted (SSA, 2020).

About one-third of disabled-worker beneficiaries have musculoskeletal conditions (such as severe arthritis or back injuries) as a primary diagnosis (see Chapter 5). Another one-third has a diagnosis of a mental disorder (see Chapter 4). Others have life-threatening conditions, such as advanced stage cancer (see Chapter 3), end-stage renal disease, or amyotrophic lateral sclerosis (SSA, 2018a).

THE SOCIAL SECURITY SUPPLEMENTAL SECURITY INCOME PROGRAM

The SSI program, authorized by Title XVI of the Social Security Act and enacted in 1972, is a nationwide federal assistance program administered by SSA. It is funded through general revenues, and, in addition to establishing disability, the applicant must also meet the nonmedical income and resource eligibility requirements, which are based on need. The basic purpose of the SSI program is to ensure a minimal income to people who are blind or disabled and who have limited income and resources. In 2019 the SSI Federal Payment Standard was $771 per month for an individual and $1,157 per month for a couple. SSI recipients are also eligible to receive Medicaid coverage (without a waiting period as is required with SSDI and Medicare coverage).[4]

Disability Insurance Under the Social Security Administration

Social Security only pays benefits for total disability; it does not pay benefits for partial disability or for short-term disability. The SSA definition of disability is different from other disability program definitions. To be eligible for benefits, a person must be insured for benefits, be younger than full retirement age, have filed an application for benefits, and have a Social Security defined disability. An applicant must have worked long enough to meet the insured requirement. The number of work credits an applicant needs to qualify depends on the individual's age. The formal SSA definition of disability is described in Section 223(d)(1) of the Social Security Act. It is an "*inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, or in the case of an individual who has attained the age of 55 and is blind (within the meaning of blindness as defined in section 216(i)(1)), inability by reason of such blindness to engage in substantial gainful activity requiring skills or abilities comparable to those of any gainful activity in which the individual has previously engaged with some regularity and over a substantial period of time.*"

THE SOCIAL SECURITY ADMINISTRATION'S DISABILITY DETERMINATION PROCESS

SSA has a five-step sequential evaluation process (see Figure 1-1) to determine whether someone is medically eligible for SSDI or SSI benefits.[5] At the first step, SSA determines whether the applicant is currently engaging in substantial gainful activity (SGA), defined as earning more than the SGA threshold, which in 2019 was set at $1,220 per month for non-blind people and $2,040 per month if a person is blind (SSA, 2019c). If the applicant is currently engaging in SGA, SSA will find that the applicant is not disabled. At the second step, the disability examiner considers the medical severity and expected duration of the applicant's

[4] Some states have a separate process for determining Medicaid eligibility, but all states are required to offer Medicaid to disabled SSI beneficiaries. According to SSA, in "most states, if you are an SSI beneficiary, you might be automatically eligible for Medicaid; an SSI application is also an application for Medicaid. In other states, you must apply for and establish your eligibility for Medicaid with another agency. In these states, SSA will direct you to the office where you can apply for Medicaid" (SSA, 2019b).

[5] 20 CFR § 404.1520.

impairment. If the applicant's impairment or combination of impairments is not severe or has not lasted or is unlikely to last at least 12 months, SSA will find that the applicant is not disabled. At the third step, the disability examiner determines whether the impairment "meets" or "medically equals" one of the items on the listing of impairments (discussed in detail in the next section). If SSA finds that the applicant's impairment meets or medically equals a listing, then SSA will find that the applicant is disabled and allowed benefits.

Otherwise, the examiner moves on to the fourth step, at which point the disability examiner assesses the applicant's "residual functional capacity" (the maximum level of physical or mental performance that the applicant can achieve, given the functional limitations resulting from his or her medical impairment(s)) and determines whether the applicant is able to engage in any of his or her past relevant work; if so, the applicant will be found not to be disabled.[6]

At the fifth and last step, SSA will determine whether the applicant can perform any work in the national economy on the basis of the assessment of residual functional capacity and the applicant's age, education, and work experience. If the applicant can make an adjustment to other work that exists in significant numbers in the national economy, SSA will find that the person is not disabled; otherwise, SSA will find that he or she is disabled.[7] Figure 1-1 provides a visual model of the steps involved in the evaluation.[8]

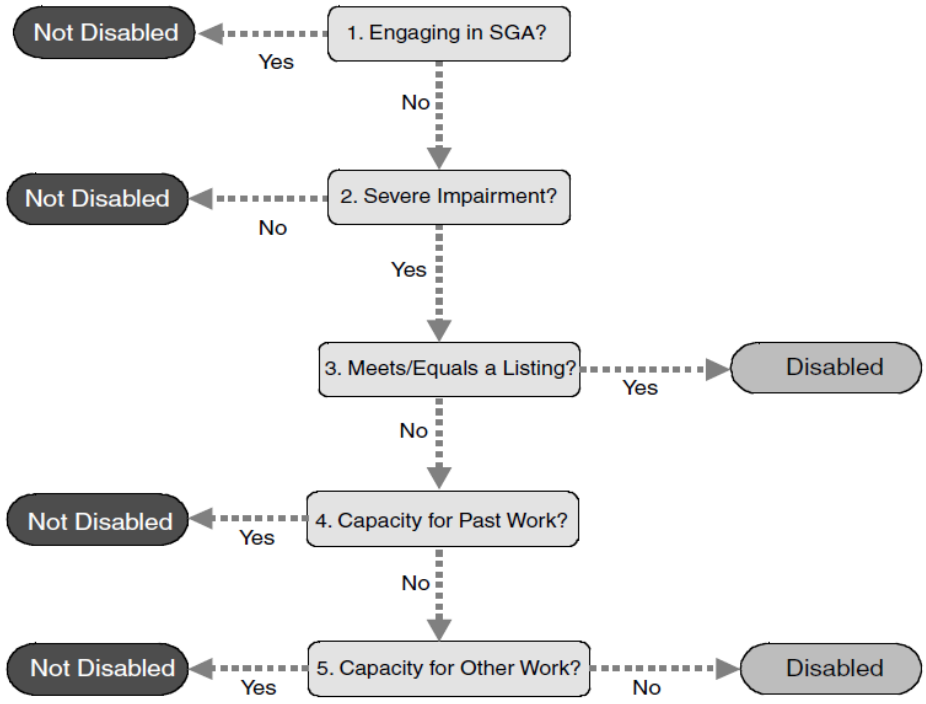

FIGURE 1-1 SSA's five-step sequential disability evaluation process.
NOTE: In 2019, substantial gainful activity (SGA) is defined as earning $1,220 or more per month from working, or $2,040 for blind people. If the Social Security Administration (SSA) determines that an individual is working at the SGA level, he or she is ineligible for benefits.
SOURCE: 20 CFR § 404.1520 and 416.920.

[6] CFR § 404.1560(b).
[7] CFR § 404.1560(c).
[8] For additional details on the types of medical evidence considered in the disability-determination process and on the training and credentials required of disability examiners and medical/psychologic consultants, refer to *The Promise of Assistive Technology to Enhance Activity and Work Participation* (NASEM, 2017).

Finally, SSA notes that it is committed to providing benefits quickly to applicants whose medical conditions are so serious that they obviously meet SSA's disability standards. Thus, SSA has two different fast-track processes—compassionate allowances (CALs) and Quick Disability Determination (QDD)—that enable SSA to expedite review and decisions for some applications. The CAL process incorporates technology to quickly identify diseases and other medical conditions that, by definition, meet SSA's standards for disability benefits. Those conditions include certain cancers, adult brain disorders, and a number of rare disorders that affect children (SSA, 2019d). The QDD process uses a computer-based predictive model to screen initial applications and identify cases in which a favorable disability determination is highly likely and medical evidence is readily available in an effort to fast-track a (positive) determination (SSA, 2019e). Those fast-track processes are only used to arrive at positive decisions; an applicant will be found not disabled only after SSA fully develops the evidence in the case and applies the full sequential evaluation process.

The Listing of Impairments

The third step of the sequential evaluation process relies on the Listing of Impairments[9] (hereafter Listings) to identify cases that can be allowed regardless of the applicant's age, education, or work experience. The Listings are organized by 14 body systems for adults (see Table 1-1) and, for each system, include impairments that SSA considers severe enough to prevent an adult from performing any gainful activity. According to the SSA Office of Inspector General (OIG) (2015), "the Listings help ensure that disability determinations are medically sound, claimants receive equal treatment based on the specific criteria, and disabled individuals can be readily identified and awarded benefits, if appropriate." Applicants whose impairments do not meet or medically equal a Listing can still be determined to be disabled at step 5 of the sequential evaluation process on the basis of the combination of their residual functional capacity, age, education, and work experience.

TABLE 1-1 Body Systems in SSA Listings for Adults

1. Musculoskeletal system
2. Special senses and speech
3. Respiratory disorders
4. Cardiovascular system
5. Digestive system
6. Genitourinary disorders
7. Hematological disorders
8. Skin disorders
9. Endocrine disorders
10. Congenital disorders that affect multiple body systems
11. Neurological disorders
12. Mental disorders
13. Cancer (malignant neoplastic diseases)
14. Immune system disorders

[9] Found at 20 CFR Part 404, Subpart P.

SOURCE: SSA, 2017a.

Although there has been an established "listing of medical impairments" since the disability program began in 1956, SSA did not publish the Listings in its disability regulations until 1968.[10] Since then it has revised the Listings periodically to reflect recent advances in medical knowledge. In 2003 SSA implemented a new process for revising the Listings, which was designed to ensure regular updates and monitoring of the Listings about every 3–4 years (OIG, 2009). Seven body systems, in the Listings, were last updated between 2009 and 2015. The SSA OIG recommended that by the end of fiscal year 2020, SSA should ensure that all Listings updates are less than 5 years old and that SSA continue to update them as needed to reflect current medical knowledge and advances in technology (OIG, 2015). Four more body systems (respiratory, neurologic, mental, and immune system disorders) were updated between 2016 and 2017.

After a body system is updated, SSA begins the process of identifying the necessary revisions again. The process begins with information gathering both within the agency (e.g., analyzing data, conducting a literature review, and obtaining feedback from adjudicators) and outside the agency (e.g., discussions with the public including medical experts and soliciting comments from the public via an advance notice of proposed rulemaking). SSA develops proposed changes to the body system(s) based on its information gathering and case reviews and drafts a notice of proposed rule making (NPRM). The Office of Management and Budget (OMB) as well as other federal agencies (e.g., the U.S. Department of Health and Human Services and the U.S. Department of Veterans Affairs) review and comment on the draft NPRM. SSA obtains OMB approval and publishes the NPRM in the *Federal Register* for public comment. SSA reviews and responds to public comments, revises the proposed rule as needed, and drafts a final rule. OMB reviews the final rule, and SSA obtains OMB approval and publishes the final rule in the *Federal Register*.

THE SOCIAL SECURITY ADMINISTRATION'S CONTINUING DISABILITY REVIEW

Individuals receiving SSDI benefits or SSI payments (based on disability or blindness) must continue to meet the disability requirements of the law. SSA periodically reviews the cases of SSDI beneficiaries and SSI recipients to determine if the individuals continue to be disabled. That review is called a continuing disability review (CDR). If SSA determines that an individual is no longer disabled (or blind), benefits will stop. The Social Security Act requires that SSA perform a CDR at least once every 3 years for beneficiaries with an impairment in which medical improvement is possible and more frequently if SSA determines that an individual has a medical condition that is expected to improve sooner. Even in the case of medical conditions that are not expected to improve, SSA will still review each claimant's case once every 7 years. Furthermore, income, resources, and living arrangements will also be reviewed during the CDR (SSA, 2019f).

If an individual is not engaging in SGA and does not meet or equal a listing in the current listing of impairments, SSA determines whether medical improvement has occurred in the individual's impairment(s). SSA defines "medical improvement" as any decrease in the medical

[10] See https://secure.ssa.gov/poms.nsf/lnx/0434101005 (accessed January 15, 2019) for an explanation of the Listing of Impairments before 1968 (SSA, 1990).

severity of a physical or mental condition that was present at the time of the person's most recent favorable medical decision when he or she was disabled or continued to be disabled. A determination that there has been a decrease in medical severity must be based on an improvement in the symptoms, signs, or laboratory findings associated with the person's medical condition.

SSA considers two categories of medical improvement to enable a careful consideration of all factors related to whether a person continues to receive SSDI or SSI:

- *Medical improvement not related to ability to do work:* Medical improvement is deemed to be not related to an individual's ability to work if there has been a decrease in the severity of the impairment(s) present at the time of the most recent favorable medical decision but the individual still meets or equals the listing, or any subsection of the listing, that that person met at his or her most recent favorable decision or there has been *no* increase in the individual's functional capacity to do basic work activities. If there has been any medical improvement in the individual's impairment(s), but it is not related to the person's ability to do work and none of the exceptions apply, that individual's benefits will be continued.
- *Medical improvement that is related to ability to do work:* Medical improvement is related to an individual's ability to work if there has been a decrease in the severity of the impairment(s) present at the time of the most recent favorable medical decision and that person no longer meets or equals the listing, or any subsection of the listing, that the individual met at his or her most recent favorable decision or, if that person did not meet a listing at his or her most recent favorable decision, there has been an increase in his or her functional capacity to do basic work activities. A determination that medical improvement is related to an individual's ability to do work has occurred does not necessarily mean that the person's disability will be found to have ended unless it is also shown that that person is currently able to engage in substantial gainful activity (see CFR § 404.159).

SSA Policy for the Frequency of Continuing Disability Reviews

As noted above, when SSA initially finds a person disabled, it sets a "diary" for an appropriate time at which to conduct a CDR. Under the law, SSA must review all disability beneficiaries at least once every 3 years (unless the beneficiary is permanently disabled). The frequency of the review is based on the likelihood of improvement. Thus, the diary is based on when, or if, SSA *expects* medical improvement. Categories of review schedules are briefly summarized below (see SSA [2018b] for a thorough description of this policy).

Medical Improvement Expected

SSA will schedule a review of an individual with an impairment expected to improve at intervals from 6 to 18 months following the most recent determination or decision that the individual is disabled or that disability is continuing. The review category, medical improvement expected (MIE), applies to individuals with impairments, which at the time of initial entitlement or after further review are expected to improve sufficiently to permit the individuals to engage in substantial gainful activity (SGA). An MIE schedule is set when individual will "probably" or "almost certainly" meet the medical improvement standard and be able to work or else "is in the process of a full recovery or is experiencing significant, sustained, and progressive

improvement" (SSA, 2015). This category is not used when an impairment is chronic or progressive.

Medical Improvement Not Expected

SSA schedules reviews of an individual with an impairment not expected to improve no less frequently than once every 7 years but no more frequently than once every 5 years. These medical improvement not expected (MINE) reviews apply to individuals with impairments at initial entitlement or after further review in which any improvement is not expected. These are extremely severe impairments shown, on the basis of administrative experience, to be at least static but more likely to be progressively disabling of themselves or by reason of impairment complications. The individual is unlikely to engage in SGA. SSA considers the interaction of the individual's age, impairment consequences, and the lack of recent attachment to the labor market in determining whether an impairment is expected to improve. A MINE schedule is generally set when an individual is 54.5 years or older, has certain case characteristics found to infrequently result in cessation, or "when the case facts clearly demonstrate that cessation under the MIRS is not medically possible" (SSA, 2009).

Medical Improvement Possible

SSA will schedule a review (at least once every 3 years) of an individual with an impairment in which any improvement is possible, but which cannot be accurately predicted within a given period of time, referred to as medical improvement possible (MIP). The review is applicable to individuals with impairments at the time of initial entitlement or after subsequent review in which SSA considers any improvement possible but not probable within 3 years. In such cases improvement may occur, so that an individual might return to SGA, but SSA cannot predict improvement with any accuracy based on current experience and the facts of the particular case. Generally this category is the catch-all for any individual who does not fit in the MIE or MINE categories.

APPROACH TO THE TASK

A 16-member committee was formed to address the task. Members with diverse backgrounds and expertise were appointed to focus on the different aspects of the task. Specifically, the members have expertise in various branches of clinical medicine (mental health, oncology, and musculoskeletal disorders) as well as in biostatistics and epidemiology, health care policy, and health outcomes research.

The committee organized itself into three groups: cancer, mental health, and musculoskeletal. Each group had experts in the specific disease category that was being studied in addition to a health outcomes researcher or a biostatistician and epidemiologist. Each group considered the specific disease categories listed in the Statement of Task (SOT) and identified the diseases within those categories that they would study. Each disease outcome chapter provides additional information about the diseases chosen, but in general the committee considered the burden of the disease or the possibility for improvement, or both.

The committee met five times. It sponsored two open meetings, which enabled SSA representatives and the committee members to interact directly and discuss the committee's charge. In support of the committee's discussions and deliberations, the committee instructed the

staff to conduct targeted literature searches and to gather information from relevant texts, scientific journals and professional societies, and federal sources.

Staff initially reviewed more than 1,157 titles and abstracts; those were narrowed to about 528 studies, which the committee members carefully reviewed for relevance to the committee's task. The review began with a search of online databases for U.S. and international English-language literature from 2008 through 2018. This search covered PubMed, Scopus, and Proquest as well as SSA and the National Academies Press websites. A second search of the same databases was conducted for the years 2008–2018 to capture systematic reviews and meta-analyses for key words not previously included in the first search. All of the searches performed were specifically related to the committee's chosen disorders and to those references that were most relevant to long-term disability with the potential to return-to-work. In the case of several disorders, for which there were a limited number of systematic reviews or meta-analyses, additional searches were carried out for reviews broadened to include randomized control trials. Committee members and project staff identified additional literature and information using traditional academic research methods and online searches throughout the course of the study.

The committee used a variety of resources to supplement its review of the literature. The committee examined systematic reviews, when available, for the medical conditions being studied, and also relied on published guidelines, particularly if they had been through an external review process. The committee notes, however, that a major limitation of the studies it reviewed is the lack of data on return-to-work. Additionally, it should be noted that the terms "disability," "function," and "impairment" are used differently by the various authors in the many studies and reports reviewed, and the committee did not attempt to harmonize or reinterpret the different uses of those terms.

EVOLVING CONCEPTS OF DISABILITY

The focus of this section is the evolution of the concept of disability, including its definitions and different disability frameworks. Disability has many different definitions depending on whether it is being discussed in a political/policy, societal, or medical setting. Disability is defined by the Merriam-Webster dictionary as "a physical, mental, cognitive, or developmental condition that impairs, interferes with, or limits a person's ability to engage in certain tasks or actions or participate in typical daily activities and interactions."[11]

In the context of the Americans with Disability Act (ADA), "disability" is a legal term rather than a medical one. The ADA's definition of disability is different from how it is defined in the dictionary and under various laws, such as those for Social Security Disability–related benefits. The ADA defines a person with a disability as a person who has a physical or mental impairment that substantially limits one or more major life activity. It includes people who have a record of such an impairment, even if they do not currently have a disability. In enacting the ADA, Congress recognized that physical and mental disabilities in no way diminish a person's right to fully participate in all aspects of society, yet many people with physical or mental disabilities have been precluded from doing so because of prejudice and the failure to remove societal and institutional barriers. While the ADA definition of disability focuses on a physical or mental impairment that substantially limits one or more major life activities, SSA's definition of disability (as noted above) is based on one's ability to work, specifically the "inability to engage

[11] See https://www.merriam-webster.com/dictionary/disability (accessed March 16, 2020).

in any substantial gainful activity (SGA) by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."[12]

Conceptual Frameworks of Disability

Conceptual frameworks and definitions of disability have evolved over the years from a "medical" model to a broader social model. For many years the prevailing model of disability was the medical model, in which disability was considered to be a result of impairment of body functions and structures, including the mind, and caused by disease, injury, or health conditions. As such, any disability was viewed primarily as an individual's medical problem in need of treatment (Goering, 2015; Haegel and Hodge, 2016). However, the medical model has limitations, including not accounting for comorbid conditions or symptoms; people with more comorbid conditions generally have more functional limitations (Hung et al., 2012). Furthermore, the medical model does not recognize that there is not a direct correspondence between disability (as measured by functional status) and the presence of disease. Most people with chronic disease have no reported disability, for instance (Reichard et al., 2015). Conversely, some people with a loss of function have no active disease as the cause of their loss of function, or their disease might be difficult to measure objectively in a medical setting (e.g., chronic pain). Impairment due to a specific loss of function caused by a specific disease does not capture a person's overall ability to function, which is likely affected by many other factors. Thus, disease and function might overlap, but not in a consistent way, and the overlap is likely to be different for each disease or existing comorbid conditions and diseases. The relationships between different diseases and disability have changed over time and likely parallel changes in treatment, life expectancy, comorbid conditions, and other factors (Hung et al., 2012).

According to the conceptual framework of disability developed by sociologist Saad Nagi (1965), disability is the expression of a physical or a mental limitation in a social context. Nagi specifically viewed the concept of disability as representing the gap between a person's capabilities and the demands created by the social and physical environments (Nagi, 1965, 1976, 1991).

Similarly, in *Disability in America* (IOM, 1991) it is noted that people with medically determinable functional limitations are not inherently disabled, that is, incapable of carrying out their personal, familial, and social roles, but rather it is the interaction of their physical or mental limitation with social and environmental factors that determine whether they have a disability. Thus it is important to have a conceptual framework for understanding disability not only as a series of consequences of disease or injury, but also as a consequence of people's relationship with their environments—environments that might be supportive of participation in society or that might present obstacles to such participation.

A later Institute of Medicine (IOM) report, *Enabling America* (IOM, 1997), relied on the conceptual framework found in *Disability in America* (IOM, 1991) but made some refinements to clarify the interaction between the person and the environment and the dynamics of the "enabling/disabling" process. The two IOM reports included quality of life as an important concept in understanding the impact of health conditions, impairments, functional limitations, and disabilities on people's sense of well-being in relation to their personal goals and expectations.

[12] 42 U.S. Code § 423.

The World Health Organization developed the *International Classification of Functioning, Disability and Health* (ICF),[13] a framework for describing and organizing information on functioning and disability. The ICF provides a standard language and a conceptual basis for the definition and measurement of health and disability, integrates the major models of disability, and recognizes the role of environmental factors in the creation of disability as well as the relevance of associated health conditions and their effects. Further, it provides a standardized, internationally accepted language and conceptual framework to facilitate communication across national and disciplinary boundaries. Similar to previous disability frameworks, the ICF attempted to provide a comprehensive view of health-related states from biologic, personal, and social perspectives (see *Towards a Common Language for Functioning, Disability and Health ICF*, WHO, 2002).

In contrast to the medical model, the social model of disability relies on a sharp distinction between impairment and disability (Goering, 2015). The social model takes into consideration the role of the environment and societal factors in the concept of disability. As noted in Patel and Brown (2017), disability is based on the fact that, by itself, any functional impairment at an individual level might not create disability, but sociocultural expectations combined with the built environment limit a person's ability to engage in a productive role. As researchers and practicing clinicians have recognized the important limitations of the medical model of disability, the conceptualization of disability has shifted towards a social model of disability, which does not consider the *cause* of the loss of a specific functional ability but rather the ability of the individual to function in a specific environment (Goering, 2015; Palmer and Harley, 2012). As noted by the United Nations Convention on the Rights of Persons with Disabilities (UN, 2019), disability is viewed as how people with disability interact with their environment: "Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others (Article 1)." Similarly, and as noted above, the ICF measures disability and includes multiple dimensions of human functioning, synthesizing biologic, psychologic, and social and environmental aspects (Kostanjsek, 2011; Palmer and Harley, 2012; Üstün et al., 2010).

Thus there are different models of disability, and different agencies and organizations have defined disability in different ways for various purposes. However, most definitions include the concept of a physical or mental impairment combined with the inability to fulfill social roles or expectations. The definition used by SSA incorporates a length of time and whether a person can perform work, i.e., "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."

The Committee's Conceptualization of Disability

The committee members considered the issue of general medical improvement versus functional improvement, as they are keenly aware that disability models have expanded beyond a linear conception of medical conditions as the sole determinants of disability. Contemporary models now include the potent social, economic, and environmental factors that determine the

[13] The ICF was endorsed in May 2001 by the World Health Assembly as a member of the family of International Classifications, the best known of which is the *International Classification of Diseases*.

extent to which an individual can meet his or her functional requirements. Those models conceptualize disability as a co-created entity that reflects an aggregate of individual, societal, and environmental factors. More specifically, an individual may be severely limited in one context but able to maintain independence and gainful employment in another. The committee strongly endorses the social model of disability and acknowledges that social and environmental factors greatly affect health outcomes. However, the committee focused on the medical model in this report, given the Statement of Task's focus on medical and functional improvement and its request that the committee "shall not describe issues with respect to access to treatments.

As has been amply and comprehensively highlighted in the National Academies' 2019 report *Functional Assessment for Adults with Disabilities*, correlations between medical and functional outcomes, even when driven by a common disease process, are moderate at best. As a consequence, inferences about an individual's work capability made solely on the basis of his or her medical outcomes are vulnerable to inaccuracies. Functional outcomes reflect the aggregate effects of physical and cognitive impairments as well as medical morbidities. As such they often align more closely than medical outcomes with the capabilities required for gainful employment. Additionally, when these outcomes accurately measure global functioning, they have the potential to reflect the net disabling effects of an individual's multiple impairments and comorbidities. That potential is notable since these latter processes are frequently dynamic, relapsing and remitting, and affected by treatments and toxicities in a manner that is imperfectly captured in health records.

ORGANIZATION OF THE REPORT

Chapter 2 briefly examines issues that overlap across the three disease categories, such as pain, comorbidities, and toxicities of therapies. Chapter 3 focuses on cancers and cancer-related impairments that might improve with treatment, Chapter 4 focuses on mental health disorders, and Chapter 5 concentrates on musculoskeletal conditions. Each of those chapters attempts to address all the questions in the SOT related to the specific medical condition being studied; however, the formats of the chapters are not identical. Chapters 3 to 5 each have their own internal organization that is specific to the condition discussed. There is an appendix to provide the reader with additional details relevant to the mental health disorders chapter.

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2

Cross-Cutting Issues

The focus of this chapter is on selected issues that affect people with disabilities across all types of medical conditions. These issues include the approach to pain and pain treatment, comorbidities and disability recovery, and variation in the availability and use of effective treatments.

APPROACH TO PAIN AND PAIN TREATMENT

Chronic pain has been linked to numerous physical and mental health conditions and contributes to high health care costs and lost productivity. It is one of the most common reasons that adults seek medical care and has been linked to restrictions in mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health. Updated population estimates from the National Health Interview Survey indicate that 50 million (20.4 percent) U.S. adults had chronic pain and 19.6 million (8.0 percent) had high-impact chronic pain in 2016. Both conditions were more prevalent among adults living in poverty, adults with less than a high school education, and adults with public health insurance (Dahlhamer et al., 2018).

Chronic pain is defined as pain that persists or recurs for 3 to 6 months or longer. It is frequently associated with disability, although many people with chronic pain live without disability. The National Pain Strategy, issued by the U.S. Department of Health and Human Services in 2016, emphasized the importance of differentiating between people with and without functionally limiting pain and defined "high-impact chronic pain" as pain associated with a restriction of participation in work, social, or self-care activities (IPRCC, 2016). Modern conceptualizations of chronic pain recognize that pain can be a symptom of an underlying health condition or a primary condition in itself and that interacting biologic, psychologic, and social factors contribute to the etiology, clinical course, and functional outcomes of all chronic pain conditions, regardless of their primary or secondary nature (IOM, 2011). That understanding is consistent with research findings that the experience of pain is highly variable among persons with similar anatomical findings or disease severity, even in well-described chronic pain conditions.

A systematic classification of chronic pain developed by the International Association for the Study of Pain and implemented by the World Health Organization in the *International Classification of Diseases, 11th Revision* (ICD-11) recognizes both primary and secondary chronic pain syndromes (Treede et al., 2019). According to that report, the new ICD category for chronic pain comprises the most common clinically relevant disorders, which were divided into seven groups: chronic primary pain, chronic cancer pain, chronic posttraumatic and postsurgical

pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain. Regardless of the etiology, chronic pain is a major source of emotional distress and functional disability (Nicholas et al., 2019). Chronic secondary pain syndromes are defined by an underlying disease or injury that is considered to be the cause of the pain (although the secondary pain syndrome may persist beyond the resolution of the inciting disease or injury).

Chronic primary and secondary pain conditions are relevant to all sections of this report. In common musculoskeletal conditions, including chronic primary back pain and chronic secondary musculoskeletal pain due to inflammatory disease or structural abnormalities, chronic pain is the major driver of functional impairment and disability. In cancer, chronic pain arising from the disease process or from the adverse effects of cancer treatment contributes substantially to the functional impairment and disability experienced by cancer survivors. Finally, common mental health conditions and pain conditions are frequently comorbid, with bidirectional associations and, potentially, shared central nervous system mechanisms. For example, chronic pain and depression appear to have mutual adverse influences on each other, so the presence of both conditions together is associated with greater disability than either condition alone.

The treatment of chronic pain includes therapies aimed at the underlying cause of pain (when applicable), therapies aimed at alleviating symptoms, and therapies that address factors involved in determining the course of pain and associated impairments. Biomedical approaches that focus on removing specific underlying causes of pain, such as surgery to correct anatomical abnormalities, often fail to resolve secondary pain syndromes and their associated impairments. Likewise, approaches that are narrowly focused on relieving symptoms, such as analgesic medications, often fail to restore functioning or provide long-term pain relief. Specifically, in chronic pain, opioid analgesics lack demonstrated advantages over other treatments and are associated with increased disability and reduced functional recovery; although they are commonly prescribed, opioids are not recommended by chronic pain guidelines. Current guidelines for common chronic pain conditions (e.g., low back pain) recommend active non-drug approaches such as exercise and behavioral therapies as core treatments. Unfortunately, individual therapies for chronic pain result in meaningful improvement for only a subset of patients, and active approaches require sustained patient effort over time to achieve optimal results. For many patients with high-impact chronic pain, the best treatment approach is multimodal integrated care that combines different types of therapeutic approaches to address medical, psychologic, and social factors in a coordinated and supportive fashion (IOM, 2011; IPRCC, 2016).

COMORBIDITIES AND RETURN TO WORK

Comorbidity, also known as multimorbidity, is defined as the coexistence of more than one distinct condition or disease in an individual (Valderas et al., 2009). Having multiple chronic medical conditions affects a range of medical outcomes, including mortality, health-related quality of life, and functioning (Fortin et al., 2007). Negative outcomes related to comorbidity occur beyond what would be expected from the summed effect of single conditions, as chronic diseases tend to interact with each other in such a way that leads to new clinical presentations (Vetrano et al., 2018). There is increasing evidence that the comorbidities prevalent with primary diagnoses have a significant impact on return-to-work after disability. The committee that produced a recent National Academies consensus study on functional assessments for adults with

disabilities acknowledged that the presence of multiple impairments and comorbidities can further impair functioning (NASEM, 2019). Therefore, it is necessary to consider that when assessing an individual's ability to sustain work on a regular and continuing basis, a person's capacity to work may be overestimated if, for example, a psychologic comorbidity is present.

Research suggests that the most important comorbidities affecting functionality and work-related disabilities involve mental health conditions co-occurring with other psychologic disorders or with physical conditions (Greenberg et al., 2015; Kessler, 2003). Symptoms associated with diagnoses such as depression and anxiety can affect a person's ability to manage one or more limitations in a work setting. For individuals with a wide range of physical and mental impairments, depression is the most common comorbidity limiting employment as well as rehabilitation from other events (NASEM, 2019). For many conditions that result in disability, co-occurring depression is frequent and is associated with poor outcomes. It is often unrecognized both as a primary diagnosis and as a powerful contributor to impairment from other diagnoses. The impact of treatment is clear when depression is the central diagnosis, but less is known about how to identify and address it as a complicating factor (Anderson et al., 2015; Scaratti et al., 2017; Sullivan et al., 1997).

The combined effects of mental health disorders, such as depression, and physical health disorders significantly affect work-related disability (Kessler and Frank, 1997; Rystälä et al., 2005). Data from a major mental health survey found that all physical disorders, except injury caused by accident, were significantly related to anxiety and mood disorders (Buist-Bouwman et al., 2005). Both physical and mental health disorders were significantly related to work loss, and the physical–mental health comorbidity was largely additive except for chronic back pain and hypertension, which interacted with mental health disorders synergistically. Thus, interactions between comorbidities complicate recovery. While mental health disorders exacerbate other conditions, physical comorbid conditions will increase both the likelihood of mental health-related disability and the extent of the work impairment. Without treating all of the conditions, the overall work-related disability is unlikely to be reduced.

Comorbidities, including clinical depression and anxiety (Bodurka-Bevers et al., 2000), are also common among individuals with cancer, and those with comorbidities experience poorer survival, poorer quality of life, and higher health care costs (Sarfati et al., 2016). While it has been well documented that comorbidities are common among adults over the age of 65 with cancer (Williams et al., 2016), a growing body of literature suggests that comorbid conditions such as depression, anxiety, asthma, high cholesterol, and hypertension result in a high burden in young adults with cancer, particularly those aged 15–39 (Smitherman et al., 2018). Young adults with cancer are more likely than their cancer-free peers to be frail and to experience a high level of comorbidities, a phenomenon known as accelerated aging (Smitherman et al., 2018). Cancers share many risk factors with comorbid conditions, such as older age, smoking, poor diet, obesity, and alcohol abuse (Sarfati et al., 2016; Sarna et al., 2016). Additionally, the biologic mechanisms associated with comorbid conditions may predispose an individual to cancer. Comorbidities can be caused by the toxicities of chemotherapy. A study by Chao et al. (2018) found that in a cohort of 6,778 cancer survivors of ages 15–39, chemotherapy exposure was associated with multiple comorbidities.

While most studies addressing factors related to return-to-work are disease specific, a single "review of reviews" across multiple studies of common mental health disorders, cardiovascular disease, and cancer identified six barriers related to a patient's ability to return to work. These were anxiety, depression, job strain, other comorbidities, older age, and low

education (Gragnano et al., 2018). The common factors identified here support the validity of a cross-disease approach when addressing recovery and return-to-work interventions. The identification and treatment of co- and multi-morbidities along with primary diagnoses may improve functional outcomes and the ability to return to work in patients receiving disability compensation.

VARIATION IN AVAILABILITY AND USE OF EFFECTIVE TREATMENT

While the committee understands that SSA did not intend for this report to discuss access to treatment, a brief discussion on variation in the availability and use of effective treatment helps illustrate the complexity of the relationship between available treatments and health outcomes. There can be enormous variations in many aspects of health care delivery that are not explained by medical need or patient preference. Furthermore, millions of Americans with long-lasting medical conditions do not receive effective care (IOM, 2001; Wennberg, 2011). Consistent with past Institute of Medicine reports (IOM, 2001, 2006), the committee defines effective care as care that is based on scientific knowledge and that includes providing services to those who might benefit while avoiding overuse and underuse. The factors that influence the availability and use of effective care are complex and include: the characteristics of the interventions (e.g., costs and complexity), the characteristics of the individuals (e.g., income, insurance, culture, and health literacy), health care providers (e.g., knowledge and beliefs), the health care system (e.g., staffing, wait times, incentives), and communities (e.g., rurality, transportation availability, social supports) as well as the information available through the media, policy, and regulations.

Noted disparities exist in cancer screening, treatment, and outcomes by sociodemographic characteristics (including race and ethnicity), income, employment status, geographic area (Du et al., 2011; Forrest et al., 2013; Singh and Jamal, 2017; Wheeler et al., 2013). One major barrier to care is a lack of insurance or underinsurance. Cancer treatment is very expensive, and its cost may be a barrier to the most effective treatment (Banegas et al., 2016, 2018; Yabroff et al., 2016). Geographic barriers to cancer treatment also exist, including the lack in some areas of a geographically accessible supply of providers (Ambroggi et al., 2015; Dragun et al., 2011; Jacobsen, 2017; Lin et al., 2015). Oncology centers, particularly the most advanced, are geographically skewed and not often located in rural areas (Dragun et al., 2011). People who live farther from effective care are less likely to receive it (Jacobsen et al. 2017; Lin et al., 2015). Previously disabled persons also have lower treatment rates (Iezzoni et al., 2008). The availability of nonmedical treatments that affect recovery from cancer, such as social supports, job retention programs, and employment accommodations, also vary by income level, geographic area, education, culture, race and ethnicity, gender, and other factors (Mustian et al., 2017). Among the population of individuals who would qualify for SSDI on the basis of a cancer diagnosis, there is known variation in the availability of evidence-based and effective cancer treatments (Jacobsen et al., 2017; Mougalian et al., 2015; Murphy et al., 2016; Shalowitz et al., 2015; Shugarman et al., 2009). Some disparities in treatment in this population stem from differences in the stage at diagnosis and in comorbidities at diagnosis (Iezzoni et al., 2008; Yang et al., 2010). Others, however, stem from nonmedical factors, including income, geography, and insurance (or uninsured status).

For many cancers, an effective treatment, while causing remission in the diagnosed cancer, is the cause of subsequent disability due to the side effects of treatment, which can

include fatigue, depression, pain, and the loss of physical and cognitive function (Jones et al., 2016; Mustian et al., 2017). People with better access to such cancer screening services as mammography, colorectal screening, and Pap smear tests—or who simply have more frequent contacts with the medical care system—might be diagnosed at an earlier stage and thus avoid both subsequent cancer-related disability and death (Hall et al., 2018; Joseph et al., 2012; White et al., 2017). However, an interesting dynamic appears when patients with better access to screening, early cancer interventions, or effective treatments for later-stage disease may end up with longer periods of disability due to the disabling side effects of effective treatment.

Mental health disorders affect about one in five Americans (IOM, 2015; Kessler et al., 2005). Fortunately, there are effective psychosocial and pharmacologic treatments, and evidence continues to accumulate for new interventions. However, not all individuals with mental health disorders receive high-quality mental health care and have the opportunity to benefit from treatment. Two problems impede clinically meaningful improvement among individuals with mental health disorders: no care (Kessler et al., 2005; Mojtabai et al., 2011) and, among those who do receive health services, poor care (e.g., IOM, 2006, 2015). The structural barriers to receiving needed care are further complicated by poor insurance coverage for mental health disorders, the separation of mental health from other medical care (IOM, 2006), and significant limitations in the availability of skilled specialty mental health providers in remote geographic areas (President's New Freedom Commission on Mental Health, 2003). Shame, stigma and discrimination further impede individuals from recognizing they have a problem and seeking treatment for mental health disorders (IOM, 2006).

Even if individuals overcome the barriers and seek mental health treatment, they may not receive evidence-based care and therefore may experience minimal benefit, no benefit, or even harm from the health services they received. The lack of availability of evidence-based mental health services is a known problem (Bauer, 2002; IOM, 2006 2015; Simon et al., 2001; Stein et al., 2004), and consumers often do not have a way of judging the quality of the mental health care they do receive. An additional concern is that some treatments are not only ineffective but may be unsafe and have risks that outweigh any potential short-term benefit (see, e.g., Guina et al., 2015). Gaps in provider training (Weissman et al., 2006), a broad array of mental health provider specialty types, the fragmentation in care, the lack of high-quality monitoring systems and decision support tools, and other individual, organizational, and system level factors all contribute to the problem of ineffective care for mental health disorders (Aarons et al., 2012; IOM, 2006, 2015).

Musculoskeletal disorders are among the most prevalent and disabling conditions in adults (USBJI, 2014). The problem of unwanted variation in and ineffective treatment of musculoskeletal conditions is well known (e.g., Brand et al., 2013; Foster, 2018; Skinner et al., 2003). People often have multiple musculoskeletal disorders simultaneously and are likely to experience pain as part of the condition. Low back pain is the most frequently reported musculoskeletal disorder (IOM, 2011; USBJI, 2014; Woolf and Pfleger, 2003). Individuals with musculoskeletal disorders often experience barriers to adequate pain treatment (Becker et al., 2017; IOM, 2011). Additionally, policies on coverage and reimbursement often encourage the choice of pharmacologic treatment over evidence-based psychosocial or comprehensive approaches that integrate pharmacologic and non-pharmacologic approaches (Heyward et al., 2018; Lin et al., 2018). Chronic musculoskeletal pain is the most common target of opioid therapy despite its unfavorable risk–benefit profile (although that situation is likely changing), and it has contributed to prescription opioid-use disorder and overdose deaths (CDC, 2018).

The considerable variability in the availability and use of effective health care for cancers, mental health disorders, and musculoskeletal disorders has implications for this report. In particular, because nonmedical factors contribute to the types and quantity of treatments that patients receive, information about treatments cannot be used to reliably evaluate the severity of a medical condition. SSA previously asked the National Academies to examine the association between health care utilization and impairment severity. Cancers, mental health disorders, and musculoskeletal disorders as well as other conditions were included in that analysis. The resulting report, *Health-Care Utilization as a Proxy in Disability Determination*, concluded that there was "no evidence that health-care utilizations alone can predict disability, impairment severity, or disease severity" (NASEM, 2018). However, experts on this committee believe that there may be instances when the use of certain treatments for select cancers, musculoskeletal disorders, or mental health disorders might serve as an indicator of severity. Such instances are explicitly discussed in the relevant chapters.

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3

Cancer

Cancer is the term used to refer to a group of diseases in which some of the body's cells divide without stopping and spread into surrounding tissue, forming growths called tumors (NCI, 2015a). Cancerous tumors are malignant, meaning that they can both invade nearby tissues and form new tumors far from the original tumor (NCI, 2015a). Cancer can start almost anywhere in the body, and it is broadly classified by the type of tissue that the growths originate from (e.g., carcinoma begins in the epithelial tissue, and leukemia is from the white blood cells in bone marrow) and the location in the body where the cancer first develops (e.g., breast cancer or colon cancer) (NIH, 2019a). In this way, a patient with breast cancer can be more specifically said to have a breast carcinoma.

Cancer-related functional impairment can be caused by the cancer itself (e.g., a direct invasion of the lungs causing compromised breathing, or of the bone marrow causing anemia) or caused by cancer treatments such as surgery, radiation therapy, and systemic therapy (e.g., fatigue or lymphedema). Cancer treatment–related functional impairments can be those that develop during treatment but are transient (e.g., post-surgical pain), long-term side effects that develop during treatment but are chronic (e.g., neuropathic pain from chemotherapy), late effects that develop after the completion of treatment (e.g., radiation fibrosis syndrome), or secondary effects that result from acute and long-term side effects. Comorbidities frequently occur with cancer (as noted in Chapter 2). Impairments related to cancer have their own trajectories, diagnostic methodologies, treatments, and outcomes. Given the importance of cancer-related impairments to disability, the committee will address the items in the Statement of Task for common cancer-related impairments in addition to the cancers themselves.

This chapter responds to the items in the Statement of Task related to cancers and disabling conditions related to cancers. The Statement of Task asks the committee to identify specific, long-lasting (12-month duration or longer) medical conditions in adults that are temporarily disabling and that improve with treatment after a period of time to a point that the condition is no long disabling. Based on those criteria, the committee chose cancers with the potential to cause cancer- or treatment-related morbidity but that have also seen promising advances in their treatment and in the management of the impairments they cause. The committee selected the following cancers, acknowledging that others might also fit the criteria: breast cancer (excluding ductal carcinoma in situ), melanoma, renal cancer, head and neck cancers, advanced epithelial ovary cancer, non-small-cell lung cancer (NSCLC), and diffuse large B-cell lymphoma. The committee excluded cancers less likely to be disabling, including two of the examples given in the Statement of Task—non-melanoma skin cancer and thyroid cancer. The committee also excluded cancers less likely to improve with treatment, such as most advanced stage cancers. In addition, they have selected the following disabling cancer-related

impairments as those that might improve or be managed with treatment: pain, cancer-related fatigue, cardiotoxicity, chemotherapy induced peripheral neuropathy, lymphedema, pulmonary dysfunction, and cognitive dysfunction.

The chapter first presents general U.S. cancer statistics and discusses diagnostic criteria, treatments, treatment settings, and other items delineated in the committee's Statement of Task that are common among all of the selected cancers, including a framework for considering the length of time from treatment to functional improvement that accounts for the fact that cancer does not fit neatly into the concept of a disease whose symptoms typically improve with safe treatment. Then, for each cancer and cancer-related impairment chosen the committee reviews the specific professionally accepted diagnostic criteria, treatments, the length of time of treatment, and standard measures of outcomes for those conditions. Each cancer-specific discussion includes a table of diagnostic criteria, treatments, outcomes, and monitoring by cancer stage. Information on advanced stage cancers are included in the tables for reference and comparison, though it should be noted that advanced stage cancers are unlikely to improve with treatment. Finally, the chapter discusses new and developing cancer treatments that might improve survivorship or functional status, discusses variation in treatment response, and reviews papers related to cancer and return to work. The committee acknowledges the importance of access to treatment in the improvement of cancer status, functional improvement, and return to work. However, as noted in Chapter 1, information on issues related to access to treatment are not addressed in this report at the request of the study sponsor.

EPIDEMIOLOGY OF CANCER IN THE UNITED STATES

Mortality and survival are the most commonly reported cancer outcomes. They are tracked by federal and state statistical agencies to assess whether preventive efforts and treatments are improving for specific cancers (NCI, 2019a). Data are collected from medical records and death certificates. This section reviews statistics for cancers in the U.S. population, which will help the reader understand the comparative burden and epidemiologic trends of the various cancers in the United States.

Incidence

In 2019, 1,762,450 new cancer cases are projected to occur in the United States (Siegel et al., 2019). Overall, cancer incidence is higher among men than women, except in the 30–55 age range (see Figure 3-1). Between 2010 and 2020 the number of new cancer cases in the United States is expected to increase by about 24 percent in men and 21 percent in women to more than 1 million cases per year in men, and 900,000 cases per year in women (CDC, 2018).

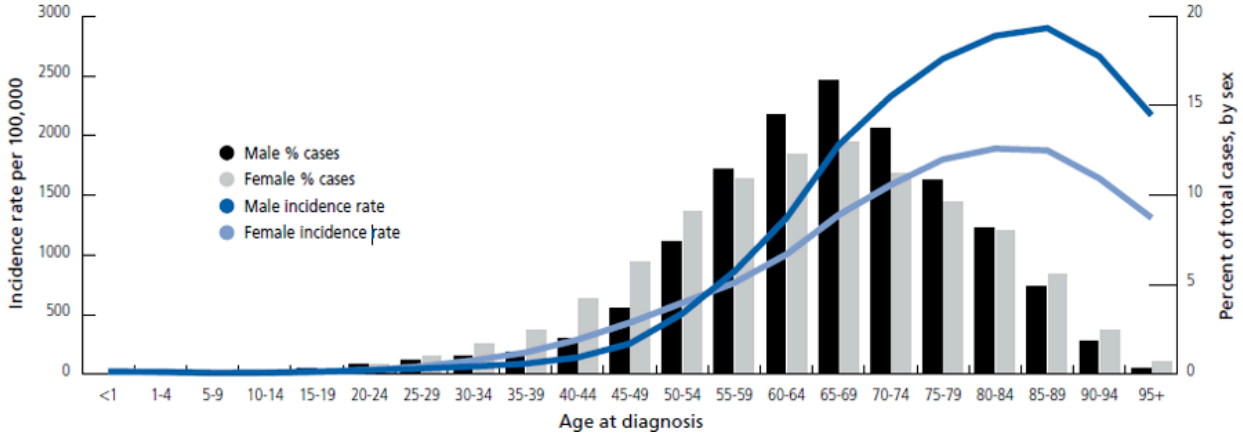

FIGURE 3-1 Average annual cancer incidence rates and case distribution by age, United States, 2011–2015.
SOURCE: ACS (2019) analysis of 18 SEER registries (2000–2015). Reproduced with permission.

Figure 3-2 depicts the most common sites of new cancer estimated for 2019 by sex according to the American Cancer Society (ACS). In 2019 an estimated 268,600 women were diagnosed with breast cancer, making it the most common cancer diagnosis. Lung and bronchus cancers were the second most common cancer diagnoses, with an estimated 116,440 new cases among men and 111,710 new cases among women. Prostate cancer was the leading cancer diagnosis among men and the third most common diagnosis overall, with 174,650 expected cases (see Figure 3-2). The 12 most common cancer sites estimated for 2019 account for more than three-quarters of all new cancer cases (ACS, 2019).

	Males			Females	
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	8%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%		Pancreas	26,830	3%
Pancreas	29,940	3%		Leukemia	25,860	3%
All Sites	**870,970**	**100%**		**All Sites**	**891,480**	**100%**

FIGURE 3-2 Ten leading sites of new cancer cases—2019 estimates.
SOURCE: Siegel et al., 2019. Reproduced with permission.

The incidence rates of lung cancer have seen a steady decline among both men and women across all age groups since 1985, in part reflecting the effectiveness of public health and regulatory tobacco control programs and policies (Farrelly, 2008; Siegel et al., 2019). Meanwhile, the rates of new liver cancers are rising faster than for any other cancer. People infected with hepatitis C virus are at greater risk for liver cancer. From 2013 through 2016 nearly

2.4 million Americans, or 1 percent of adults, were living with hepatitis C, and the incidence of hepatitis C infection has been increasing since 2010 (Hofmeister et al., 2019). Other risk factors for liver cancer include obesity, alcohol consumption, and smoking (ACS, 2019a; Calle and Kaaks, 2004; Calle et al., 2003). Data published by Sung and colleagues (2019) also suggest that the risk of obesity-related cancers seems to be increasing in a stepwise manner in successively younger birth cohorts in the United States. The rates of new cases rose for melanoma skin cancer, thyroid cancer, endometrial cancer, and pancreatic cancer (ACS, 2019a).

While incidence rates remain markedly higher among older adults, several troubling trends in increasing incidence are occurring among younger, working-age adults. Increasing colorectal cancer incidence is of particular concern among young adults. Siegel and colleagues (2017) examined Surveillance, Epidemiology and End Result (SEER) data and found that among adults ages 20–39, colon cancer incidence rates have increased by 1.0–2.4 percent annually since the mid-1980s, and rectal cancer incidence rates have increased even more drastically, by 3.2 percent annually from 1974 to 2013 in adults ages 20–29. In contrast, for adults age 55 years and older, incidence rates have generally declined since the mid-1980s for colon cancer and since 1974 for rectal cancer. Although the incidence rates have declined, the risks of colon and rectal cancers remain greater than previous decades. Compared with adults born in 1950, those born in 1990 have double the risk of colon cancer and quadruple the risk of rectal cancer (Siegel et al., 2017).

Survivorship

During the 1970s about one in every two people diagnosed with cancer survived at least 5 years. Now, more than two out of every three survive that long (ACS, 2014). As a result, the number of cancer survivors is steadily increasing—from 14 million in 2014 to almost 18 million expected by 2022 (Fuentes et al., 2017). Much of the increase can be traced to earlier detection and improvements in cancer therapies for many cancers (ACS, 2014; Fuentes et al., 2017).

The Social Security Administration (SSA) asked the committee to examine cancers that are "long-lasting," meaning 12 months in duration or longer. One might assume that the "duration" could be measured using survival statistics. However, survival statistics are usually expressed as 5-year survival rates (Mayo Clinic, 2018a) and are often not indicative of survival for patients diagnosed in more recent time periods. This is because computations are often based on patients who were diagnosed many years ago, as they require many years of data that are not typically available of recent patients.

Additionally, survival statistics are usually presented without consideration of the stage or treatment of the cancer. Survival rates can be expressed in terms of overall survival or relative survival. Overall survival rates include all people who have been diagnosed with the cancer and do not distinguish those diagnosed with early-stage, localized tumors from those diagnosed with late-stage, metastatic cancer. In many cases they aggregate different cell types diagnosed in the same organ system, which may have different prognoses. Overall survival rates do not specify whether cancer survivors are still undergoing treatment at 5 years or if they have achieved remission, meaning they have become cancer-free. The following cancers have overall 5-year survival rates of 80 percent or higher: uterine, Hodgkin lymphoma, breast, melanoma, testis, thyroid, and prostate (NCI, 2019a). Survival depends on many factors, including the aggressiveness of the disease, the stage at diagnosis, available treatments, and the age and health of the patient. Additionally, black patients have lower survival rates than white patients for every cancer type except for kidney and pancreatic cancers. Disparities are greatest for melanoma

(absolute difference of 26 percent) and uterine cancer (absolute difference of 21 percent), in part due to later stage diagnoses in black patients (Siegel et al., 2019).

Relative survival refers to the proportion of people who are alive for a designated time (usually 5 years) after a cancer diagnosis divided by the proportion of people of similar age, race, and other recorded characteristics that are expected to be alive in the absence of cancer, based on normal life expectancy. As with overall survival rates, relative survival rates do not distinguish among patients who no longer have evidence of cancer and those who have relapsed or are still in treatment; nor does it represent the proportion of people who are cured, because cancer death can occur beyond 5 years after diagnosis (ACS, 2019b). Although relative survival rates provide some indication about the average experience of cancer patients, they should be interpreted with caution for several reasons. First, 5-year survival rates do not reflect the most recent advances in detection and treatment because they are based on patients who were diagnosed at least 5 years in the past. Second, they do not account for many factors that influence individual survival, such as access to treatment, comorbid conditions, and biologic or behavioral differences among patients. Third, improvements in survival rates over time do not always indicate progress against cancer. For example, increases in average survival rates may occur when screening results in the detection of cancers that may never have caused harm if left undetected (ACS, 2019b).

Table 3-1 shows 5-year relative survival rates by stage at diagnosis, illustrating that while survival is high for most cancers that are confined to the organ of origin, it is low for malignant cancers with distant metastases. For example, breast cancer, melanoma, and prostate cancer all have 5-year relative survival rates of nearly 100 percent for local tumors, but the survival rates for distant metastases are between 20 percent and 30 percent (see Table 3-1). Many cancers are often not diagnosed until they have spread to other organs, and some cancers spread more quickly than others, so survival is affected both by the stage at diagnosis and also by the natural progression of the cell type. For example, only one-third of people diagnosed with local pancreatic cancer survive for 5 years, compared with 90 percent of people diagnosed with local colon cancer.

TABLE 3-1 Five-Year Relative Survival Rates (%) by Stage at Diagnosis, United States, 2008–2014

	All Stages	Local	Regional	Distant
Breast (female)	90	99	85	27
Colon	64	90	71	14
Colon and rectum	65	90	71	14
Esophagus	19	45	24	5
Kidney	75	93	69	12
Larynx	61	78	46	34
Liver	18	31	11	2
Lung and bronchus	19	56	30	5
Melanoma of the skin	92	98	64	23
Oral cavity and pharynx	65	84	65	39
Ovary	47	92	75	29
Pancreas	9	34	12	3
Prostate	98	>99	>99	30
Rectum	67	89	70	15
Stomach	31	68	31	5
Testis	95	99	96	74
Thyroid	98	>99	98	56
Urinary bladder	77	69	35	5
Uterine cervix	66	92	56	17
Uterine corpus	81	95	69	16

SOURCE: NCI, 2019a.

Table 3-2 presents trends in 5-year survival by cancer site and year of diagnosis from 1981 through 2015. The table shows small increases in survival rates for selected cancers.

TABLE 3-2 Trends in Cancer 5-Year Survival Rates (Percent by Year of Diagnosis)

	All Cancers	Breast	Thyroid	Melanoma	Non-Small-Cell Lung and Bronchus (Invasive)	Ovarian (Invasive)	Leukemia	Hodgkin Lymphoma	Myeloma	Oral Cavity and Pharynx	Renal
1981–1983	50.2	76.1	93.6	82.8	17.1	38.9	37.3	74.3	27.5	51.7	5(
1984–1986	52.4	79	93.2	86.6	16.6	38.4	40.5	78.4	27.3	54.1	54.5
1987–1989	55.3	84	94.4	88.1	16.9	38.2	42.9	79.2	27.2	53.6	56.7
1990–1992	59.9	85.2	94.3	89.3	17.7	40.6	45.2	81.8	29.3	55.4	60.2
1993–1995	61.3	86.4	95.4	89.7	18.7	41.6	47.6	81.7	31.7	57.7	61.5
1996–1998	63.3	88.2	95.6	91	19.4	43.9	48.4	85.1	32.5	57.8	62.5
1999–2001	66	89.7	96.5	92.2	20	43.9	51	85.1	34.6	60.3	64.9
2002–2004	67.1	90	97.3	93.2	19.6	43.8	58.3	86.2	42.6	63.9	69.2
2005–2008	68.7	90.8	98	93.3	21.8	45.3	62.3	89	47.5	65.5	74.5
2009–2015	69.3	91.3	98.5	94.2	25.1	48.4	65.8	88.5	53.7	68.4	75.5

SOURCE: NCI, 2019a.

Mortality

Cancer is the second leading cause of death in the United States (Siegel et al., 2019). Cancer death rates (mortality rates) are a good measure of progress against the disease because they represent a final outcome, whereas survival rates are only finite time periods and do not signify if the patient will survive for any period beyond what is measured (e.g., 5 years). The overall age-adjusted cancer death rate rose during most of the 20th century, peaking in 1991 at 215 cancer deaths per 100,000 people, mainly because of the tobacco epidemic. Data from U.S. death certificates show that from 1999 to 2017 cancer death rates for adults ages 45–64 declined by 19 percent (Curtin, 2019). Additionally, from 2007 to 2016, the cancer death rate declined annually by 1.4 percent in women and 1.8 percent in men (Siegel et al., 2019). Declines in cancer mortality over the past two decades are primarily the result of steady reductions in smoking and advances in early detection and treatment, which are reflected in the rapid declines for the four major cancers—lung, breast, prostate, and colorectal (ACS, 2018). Specifically, the death rate for lung cancer dropped by 45 percent from 1990 to 2015 among males and by 19 percent from 2002 to 2015 among females; the death rate for breast cancer dropped by 39 percent from 1989 to 2015; for prostate cancer, the death rate dropped by 52 percent from 1993 to 2015; and for colorectal cancer the death rate dropped by 52 percent from 1970 to 2015 (ACS, 2018). Death rates rose from 2012 through 2016 for cancers of the liver, pancreas, and uterine corpus as well as for cancers of the brain and nervous system, soft tissue, and sites within the oral cavity and pharynx associated with the human papillomavirus (Siegel et al., 2019).

The Charlson Comorbidity Index, NCI Comorbidity Index, and Elixhauser scores use physician-reported data on comorbid conditions to predict mortality risk in cancer patients based on a combined comorbidity score (NCI, 2019b; Austin et al., 2016). These summary comorbidity measures are considered to be valid prognostic tools in cancer research (Austin et al., 2016; Frankel et al., 2014; Elixhauser et al., 2018).

Median Age of Onset for Selected Cancers

Table 3-3 presents the median age at diagnosis by gender for the selected cancers from 2011 to 2015. The age of onset for most of the cancers that the committee chose to discuss is 62 years or older.

TABLE 3-3 Median Age of Cancer Patients at Diagnosis, 2011–2015

Site	Total	Males	Females
Breast	62	68	62
Thyroid	51	55	50
Melanoma of the skin	64	66	60
Other non-epithelial skin	71	72	70
Lung and bronchus	70	70	71
Ovary	63	–	63
Non-Hodgkin lymphoma	67	66	68
Oral cavity and pharynx	63	62	65

Kidney and renal pelvis	64	64	65

SOURCE: NCI, 2019a.

Gender Distribution for Selected Cancers

Figure 3-3 shows gender distribution for the selected cancers based on U.S. prevalence on January 1, 2016. Renal cancer, cancers of the oral cavity and pharynx, myeloma, Hodgkin lymphoma, leukemia, and melanoma are more common among men, while non-small-cell lung and bronchus cancers and thyroid cancer are more common among women. Women make up nearly all of the population living with breast cancer, although about 0.5 percent of those living with breast cancer were men.

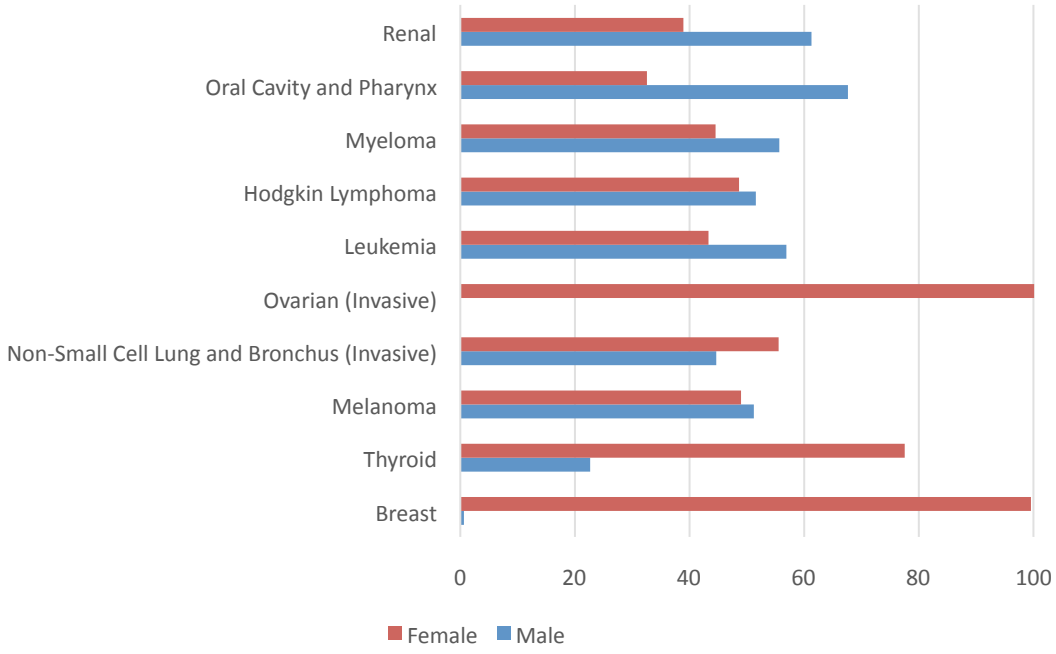

FIGURE 3-3 Gender distribution (%) of selected cancers, based on U.S. prevalence on January 1, 2016.
SOURCE: NCI, 2019a.

Cancer Statistics as Measures of Outcomes Improvement

The committee was asked to identify standard measures of outcomes improvement for medical conditions, with mortality given as an example. The committee notes that although the population statistics reviewed in this section, including mortality, are the most commonly reported cancer outcomes, they do not reflect individual cancer patients' functional impairments such as pain or cognitive dysfunction. To address those important outcome measures, patients are assessed primarily through the use of patient-rated scales (e.g., the Patient-Reported Outcomes Measurement Information System [PROMIS] scale), with results recorded on medical records and used to assess changes in patient function. Various stages of remission for cancer,

and symptoms and impairments associated with cancer treatments such as lymphedema, discussed later in the chapter, are also recorded on medical records and are considered professionally accepted standard measures of outcomes improvement for cancer.

CROSS-CUTTING ISSUES FOR SELECTED CANCERS

Many of the selected cancers share the same diagnostic criteria, treatments, treatment settings, and other items delineated in the committee's Statement of Task. In an effort to avoid redundancy, those items that are common to the selected cancers are described in this section. This section covers the following topics broadly as they relate across all of the selected cancers: diagnostic criteria, medical professionals involved in cancer care, cancer treatments, treatment settings, a framework for understanding length of time from treatment to functional improvement, standard measures of outcomes for the selected cancers, and pain. Whether and how these characteristics differ for each of the selected cancers and any additional specifics relevant to the Statement of Task are described in the sections that follow devoted to each of the selected cancers.

Professionally Accepted Diagnostic Criteria for Selected Cancers

Tissue biopsy with an accurate pathology review is the standard for diagnosing cancer. A complete evaluation also requires other elements, including a thorough history and physical examination, laboratory tests (including tests for tumor markers), and imaging, to determine the stage and characteristics of the cancer and to guide treatment (NCI, 2019b). Testing is also used to monitor progression and to gauge the effectiveness of the treatment. In some cases, it is necessary to repeat testing when a person's condition has changed. Following initial cancer diagnosis, it is important to monitor for improvement, treatment response, and recurrence (Graham et al., 2014).

Diagnostic criteria specific to each of the selected cancers are discussed in the cancer-specific sections and summarized in Tables 3-5 through 3-13. The tables, summarized from the National Comprehensive Cancer Network (NCCN)[1] guidelines, are meant to guide readers in identifying diagnostic tests that are particular to each cancer and are not meant to serve as clinical guidance. Tissue biopsy is common to all cancers as the standard diagnostic criteria, and it is not repeated in the tables.

Biopsy

During a biopsy, a sample of cells is collected for testing. In most cases, a biopsy is the only way to definitively diagnose cancer (Mayo Clinic, 2019a). Methods by which a sample may be collected include:

1. Needle biopsy of tissue or cytologic exam of body fluid. This method is used for bone marrow aspirations, lumbar puncture (spinal tap), and organ biopsies (breast, lung, liver, prostate),

[1] The National Comprehensive Cancer Network is the organization that develops the NCCN Clinical Practice Guidelines in Oncology to help health care professionals diagnose, treat, and manage cancer patient care.

2. Endoscopy, in which an endoscope is inserted into natural body openings, such as the mouth or anus, to visualize internal areas of the body. If abnormal tissue is observed, it will be removed along with some of the surrounding normal tissue through the endoscope. Examples include colonoscopy (for colon and rectum), bronchoscopy (for trachea, bronchii and lungs), and upper endoscopy (esophagus and stomach). And
3. Surgery during which an area of abnormal cells is removed during an operation either as excisional (removing the entire area of abnormal cells) or incisional (just part of the abnormal area is removed). Tissue samples are subsequently analyzed in the pathology laboratory for analysis (NCI, 2015b).

If the biopsy and other tests indicate the presence of cancer, additional tests may be ordered to help in making decisions about the treatment plan. The tumor may also be tested further for other tumor or genetic markers. Staging studies are then required once a tissue diagnosis of cancer has been confirmed (Mayo Clinic, 2019a).

History and Physical Examination

During the physical examination, the physician may palpate areas of the body for lumps that may indicate a tumor. In addition, he or she may look for abnormalities, such as changes in skin color or an enlargement of an organ, which may indicate the presence of cancer (NCI, 2019b).

Laboratory Tests

High or low levels of specific substances in the body may be a sign of cancer. Laboratory assays of blood, urine, other body fluids, or tissues that are used to evaluate these substances can help diagnose cancer. However, abnormal lab results are not a sure sign of cancer. Blood chemistry tests may examine metabolites, electrolytes, fats, proteins, and enzymes and usually include tests for blood urea nitrogen and creatinine (NCI, 2013). Most laboratory tests used in cancer diagnosis and assessment include a complete blood count, which measures the amount of various types of blood cells in the body and indicates whether abnormal cells are found (Mayo Clinic, 2019a).

Testing for cancer gene mutations (in somatic cells) may also be used to detect the presence or absence of specific inherited mutations in genes known to play a role in cancer development. Examples include the epidermal growth factor receptor (EGFR) receptor mutation or the anaplastic lymphoma kinase (ALK) mutation, which may be a target for treatment. Genetic testing (in germline) is often used to assess cancer risk, such as testing for the breast cancer type 1 (BRCA1) and breast cancer type 2 (BRCA2) gene mutations which play a role in breast, ovary, and other cancers (NCI, 2013). Cytogenetic analysis measures changes in the number or structure of chromosomes in a patient's white blood cells or bone marrow cells and may be used for diagnosis and help in treatment decisions. Immunophenotyping, used to identify cells based on the types of antigens present on the cell surface, is also used for the diagnosis, staging, and monitoring of cancers of the blood system and other hematologic disorders, such as leukemias and lymphomas. It is most often done on blood or bone marrow samples, but it may also be done on other bodily fluids or biopsy tissue samples. Sputum cytology is used to look for the presence of lung cancer. Tumor marker tests are used to identify a broad range of specific proteins or genes in tissue, blood, or other bodily fluids that may be signs of cancer or certain

benign conditions. In addition to aiding diagnosis, the results of these tests may be used to guide treatment (NCI, 2013).

Imaging

Imaging tests allow the examination of bones and internal organs in a noninvasive way. Imaging tests used in diagnosing cancer may include a computerized tomography (CT) scan with or without contrasting material, a bone scan, magnetic resonance imaging (MRI) with or without a contrasting agent, a positron emission tosmography (PET) scan, ultrasound, and X-rays, among others (Bashir et al., 2015). Bone scans, which are a type of nuclear scan that check for abnormal areas or damage in the bones, may be used to diagnose bone cancer or cancer that has spread to the bones (also called metastatic bone tumors). There are several types of PET scans. An FDG-PET (glucose) scan, also a type of nuclear scan, is able to produce detailed three-dimensional images of areas where glucose is taken up, which can be valuable because cancer cells often take up more glucose than healthy cells. An ultrasound exam, or sonogram, uses high-energy sound waves, while X-ray scans use low doses of radiation to create images of structures within the body (Bashir et al., 2015).

Medical Professionals Involved in the Care of Selected Cancers

A cancer diagnosis is usually traumatic and introduces the patient to a confusing system of physician generalists and specialists, diagnostic tests, and treatments, which are not always seamlessly coordinated. Cancer patients may see, over the course of their treatment, surgeons, medical oncologists, radiation oncologists, interventional radiologists, internal medical subspecialties such as endocrinology and dermatology, advanced practice providers such as nurse practitioners and physician assistants, nurses, social workers, clinical trials coordinators, patient navigators, and genetics counselors. During and after treatment the patients may see registered dietitians; physical, speech, and occupational therapists; and rehabilitation physicians (Fennell et al., 2010; IOM, 2013; Ko and Chaudhry, 2002; Litton et al., 2010). Their primary care doctors may treat non-cancer-related conditions that may affect their treatment or health. High-quality cancer care depends on the effective management of a great number of factors. Optimum outcomes require careful coordination between multiple treatments and treatment providers, the exchange of technical information, and regular communication between all the providers and physician disciplines involved in the treatment (NASEM, 2013).

The composition of cancer care teams varies with the type and stage of cancer (Taplin et al., 2015), and members of the cancer care teams involved with specific cancer tumor sites are listed in the below sections devoted to the particular cancers. Multimodal care is the current standard and requires the collaboration of multiple disciplines (Bayat Mokhtari et al., 2017). Care can be classified as being directed toward the cancer, toward the medical complications, or toward symptoms and impairments. Cancer-directed care is delivered to patients with disease deemed appropriate for cancer therapy. The goal of treatment is cure, temporization (i.e., delaying the progression of the disease), or palliation (i.e., easing the symptoms without curing the disease). A majority of patients with curable disease receive care delivered by surgical, radiation, and medical oncology teams. Other team members include interventional radiologists and various surgical subspecialties, depending on the tumor location. A similar array of clinicians may deliver temporizing and palliative treatments (NASEM, 2013). However, because cancer is often metastatic at the point when temporizing and palliative treatments are used,

systemic treatments administered by medical oncologists are the mainstay. Radiation and surgical oncologists may palliate late-stage disease, but this is highly variable, depending on the location of metastatic spread and the severity of the symptoms and impairments caused by metastatic foci (Ko, 2018).

Medical complication–directed care is frequently delivered by oncologic specialists when complications are temporally associated with treatment. However, as this linkage becomes less obvious, the care teams that manage complications become more disparate. Depending on the nature of the complications, various medical specialties, including cardiology, endocrinology, pulmonology, and gastroenterology, may assume primary management responsibilities (NASEM, 2013).

Symptom/impairment–directed care is principally delivered by supportive care disciplines (Stark and Lewis, 2013). The participation of oncologic specialties in managing symptoms and impairments has been robustly shown to be sporadic, with under-treatment being common. Supportive care disciplines include palliative care, physical medicine and rehabilitation, psychiatry/psychology, and pain medicine (Kumar et al., 2012). Depending on the phase of the disease and the goals of care, supportive care teams may also include physical, occupational, or speech therapists; social workers; and vocational counselors (Kumar et al., 2012).

Cancer Treatments for Selected Cancers

There are many types of treatments used in cancer therapy. Systemic therapies involve the use of drugs that spread throughout the body and include chemotherapy, hormonal therapy, targeted drug therapy, and immunotherapy. Other treatments such as radiation and surgical treatments target a particular site. The type of treatment an individual undergoes depends on the results of diagnostic testing and the site and stage of the cancer as well as individual factors and, to some degree, patient preference. Although some people with cancer undergo only one treatment, most cancers are treated with a combination (Bayat Mokhtari et al., 2017; NCI, 2019b).

Table 3-4 shows the cancers that the committee chose and their common curative treatments. Treatments that are specific to each cancer site are discussed in the cancer-specific sections and summarized in Tables 3-5 through 3-11. It should be noted that the NCCN encourages patients to choose to undergo clinical trial therapy rather than the standard of care outlined in their guidelines when the clinical trial therapy is available and appropriate for the patient (NCCN, 2019a,b,c,d,e,f,g). Additionally, Tables 3-5 through 3-11 summarize the NCCN guidelines current as of this publication; readers should understand that, given the rapidly developing field of cancer treatments, the guidelines change frequently. Toxic effects of cancer therapy cause much of the disability that occurs in patients with cancer. Those effects will be discussed in the section on common cancer impairments.

TABLE 3-4 Selected Cancers and Commonly Used Treatments

	Cancers						
Therapy	Invasive Breast	Cutaneous Melanoma	Renal	Head and Neck	Advanced Epithelial Ovary	Non-Small Cell Lung	Diffuse Large B-Cell Lymphoma
Chemotherapy	✓	✓		✓	✓	✓	✓
Hormone therapy	✓				✓		
Immune modulators	✓	✓	✓	✓	✓	✓	✓
Targeted therapy	✓	✓	✓	✓	✓	✓	✓
Radiation therapy	✓	✓	✓	✓	✓	✓	✓
Surgery	✓	✓	✓	✓	✓	✓	

SOURCES: NCCN, 2019a,b,c,d,e,f,g.

Chemotherapy

Chemotherapy is a drug treatment that uses chemicals to kill fast-growing cells. Many different chemotherapy drugs are available, and they are used alone or in combination to treat a wide variety of cancers. One example of how chemotherapy is used in combination with other treatments is a process called neoadjuvant chemotherapy, or chemotherapy that is used prior to surgery or radiation therapy to reduce tumor size (NCI, 2015c). In a variation called adjuvant therapy, chemotherapy is used to destroy cancer cells that might remain after treatment with surgery or radiation therapy (NCI, 2015c). Although chemotherapy can effectively eliminate cancer cells, it also harms normal tissues, resulting in treatment toxicities. While some chemotherapy toxicities are mild and treatable, others cause serious disablement (Mayo Clinic, 2017). Chemotherapy is used in the treatment of all of the selected cancers with the exception of renal cancers.

Hormone Therapy

Hormone therapy, also called endocrine therapy, is a cancer treatment that slows or stops the growth of cancers that use hormones to grow, such as breast, thyroid, and ovarian cancers. Hormone therapy is most often used in combination with other cancer treatments. As with chemotherapy, hormone therapy can be used as a neoadjuvant or adjuvant therapy (NCI, 2015d). Hormone therapy falls into two broad groups: those that block the ability to produce hormones

and those that interfere with how hormones behave. Because of these mechanisms of action, toxicities from hormone therapy include those related to the inability to produce the hormones that are being treated (NCI, 2015d).

Immune Modulators

Immune modulators treat advanced cancer by enhancing the body's immune response against cancer. Immune-modulating agents include cytokines and immunomodulatory drugs. Cytokines are proteins made by white blood cells, and they include interferons and interleukins, which activate natural killer cells and killer T cells. Other cytokines are erythropoietin, IL-11, GM-CSF, and G-CSF, which promote the growth of red and white blood cells damaged by chemotherapy. Immunomodulatory drugs stimulate the immune system by causing cells to release cytokines (NIH, 2019). A review of the immune modulator drugs concludes that based on preliminary studies of CTLA-4, PD-1, and PD-L1-blocking antibodies, immune modulation is a viable treatment across malignancy types (Naidoo et al., 2014). A relatively new type of therapy, immune modulator drugs have now become a standard of care and are used in the treatment of a subset of all of the selected cancers (NCCN, 2020).

Targeted Therapy

Much of the current cancer drug development focuses on targeted agent therapies (NCI, 2018). Unlike chemotherapies, which act on all rapidly dividing normal and cancerous cells, targeted agent therapies block the growth of cancer by interfering with specific molecules that are involved in the growth, progression, and spread of cancer. Targeted therapies generally act by blocking tumor cell proliferation, rather than killing tumor cells, which is the case with standard chemotherapies (NCI, 2018). Targeted therapies have become standard practice for treating patients with NSCLC (Sgambato et al., 2018; Shea et al., 2016; Stinchcomb, 2016). Phase III trials showed that targeted therapies have greater efficacy than chemotherapy in treating non-small-cell lung cancer patients with an activating epidermal growth factor receptor (EGFR) mutation and in patients with anaplastic lymphoma kinase (ALK) rearrangements (Stinchcomb, 2016). Targeted therapies are now used in the treatment of all of the selected cancers (NCCN, 2019a,b,c,d,e,f,g).

Radiation Therapy

Radiation therapy is a type of cancer therapy that uses X-rays and other types of high-energy particles or waves to destroy or damage cancer cells. Radiation works by damaging the DNA in cancer cells, keeping them from growing and dividing. Unlike chemotherapy, radiation therapy is a local treatment, carried out with the goal of destroying as few normal cells as possible. Nearby normal cells that are affected generally recover (ACS, 2018). Radiation therapy can be used alone or in combination with other therapies. It can be used as neoadjuvant therapy or adjuvant therapy in early stage cancers, and it can be used to treat symptoms in advanced cancers. It can be administered externally using a machine that directs high-energy rays from outside the body into the tumor, internally by inserting a radioactive source into the body in a process called brachytherapy, and systemically using oral or intravenous drugs (ACS, 2018). More than half of people with cancer undergo radiation therapy (ACS, 2018). Radiation therapy is used in the treatment of all of the selected cancers (NCCN, 2019a,b,c,d,e,f,g).

Surgery

Surgery is often used to treat solid tumors that are locally contained. The surgical treatment of cancer involves the removal of cancer from a patient's body through an open or minimally invasive procedure; the specific details of the procedure depend upon the purpose of the surgery, the site and amount of tissue that needs removal, and, in some cases, the patient's preference (NCI, 2015b). Surgery is used in the treatment of all of the selected cancers except for diffuse large B-cell lymphoma, a liquid cancer (NCCN, 2019a,b,c,d,e,f,g).

Cancer Treatment Settings

Cancer care is most often provided in outpatient settings (NASEM, 2019). The initial patient encounter with a cancer care system often occurs in an office or clinic, where cancer-related procedures such as history and physical examinations, blood samples, and endoscopies, take place. Cancer therapies are typically delivered in specialized facilities in hospital outpatient units and community-based medical offices or clinics (Gospodarowicz et al., 2015). Cancer patients in the last phases of an incurable disease might live out the remainder of their lives in hospice care. Cancer treatment settings specific to each cancer site are noted in the sections devoted to the selected cancers.

Length of Time from Treatment to Functional Improvement

The length of time from start of cancer treatment until a person's functioning improves to the point that the condition is no longer disabling involves two timeframes: (1) the time to remission of the cancer, and (2) the time to recovery from toxicities, symptoms, and functional impairments.

In each of the sections devoted to the selected cancers, the committee provides suggested timeframes for reviewing whether the cancer has achieved remission. These timeframes indicate the average time it takes to complete therapy for the selected cancers and are not an estimate of the time to remission of cancer, which the committee was not able to determine. The committee calculated the timeframes based on the 2019 NCCN guideline indications of time to recovery from surgery (typically 6 weeks), radiation (typically 7 weeks), chemotherapy cycles, and other therapies that are generally prescribed in the treatment of the selected cancers.

Cancer treatments will cause functional decline, which is expected and anticipated. If the cancer is cured, then the functional status can be treated for and might improve. The committee notes that it is the cancer patient's disease status (i.e., whether the cancer is in complete, partial, or no remission) more than the cancer site and stage that is an appropriate indicator of whether the patient's functional status might improve. It is clearly the case that fewer functional impairments exist for early-stage malignancies, but disease status is a global indicator of functional status improvement across all stages. If a patient's cancer achieves complete remission, functional status improvement is probable, and it is reasonable to evaluate the patient's functional status 12 months after complete remission; if the cancer achieves stable partial remission, then functional status improvement is possible, and it is also reasonable to evaluate the patient's functional status 12 months after achieving stable partial remission; if the patient has no response to treatment or experiences progression of disease, then functional improvement is unlikely.

The data on the time interval to review impairments for progression and relapse depend on the average survival time and on the treatments available for each impairment. The committee

reviewed the literature on the time from treatment to functional improvement for each of the selected cancer-related impairments. The data that the committee found, if any, are noted in each of the sections devoted to the selected impairments. The times given assume that the cancer is in complete remission, with the expectation that functional declines will improve over time. As will be described in subsequent sections, there are many instances where treatment-related functional declines are permanent or progressive.

Standard Measures of Outcomes for the Selected Cancers

Outcomes to monitor for patients with cancer include the various lengths of remission and progression, depending on the cancer site and stage. The ideal outcome of cancer treatment is *complete remission*, meaning that the treatment has resulted in the disappearance of all measurable signs of cancer. *Partial remission* means the cancerous tumors are reduced by at least 50 percent. When cancers grow, spread, and worsen, it is called *cancer progression*. If the cancer has not changed, it is called a *stable disease* (ACS, 2019c). It is important to understand that these outcomes are episodic, meaning a person can be in remission for a month or more, and then the cancer recurs. There is no way to predict how long a remission will last, and remission does not equate to cure. Some cancers, such as ovarian cancer, follow a natural cycle of recurrence and remission and can be managed as chronic diseases (ACS, 2019c). Even while a patient's cancer is in complete remission, he or she might experience a number of functional impairments, which are discussed in the next section.

Pain

Disabling pain is common across all types and stages of cancer. Pain prevalence rates reported in a recent review and meta-analysis were 39.3 percent after curative treatment; 55.0 percent during anticancer treatment; and 66.4 percent in metastatic disease (Van den Beuken-van Everdingen et al., 2016) Across all stages, 38.0 percent of patients in this study reported experiencing moderate to severe pain (operationalized as a numerical rating scale score ≥5 out of 10). The diversity of cancer types, treatments, and potential pain generators renders a comprehensive characterization of cancer pain unfeasible. This section, therefore, focuses on common pain syndromes, principally among disease-free cancer survivors, as these individuals are most likely to improve with treatment.

A majority of the large-scale epidemiologic efforts that have used patient-reported outcomes to characterize pain among survivors have not distinguished the locations or sources of the pain; furthermore, few of the reports have compared cancer survivors to the general population. As a consequence, the literature is limited in ascribing pain to cancer alone. While pain is clearly common among cancer survivors, with nearly 50 percent of patients in some cohorts reporting pain (Gartner et al., 2009; Green et al., 2011; Jiang et al., 2019), it is difficult to demonstrate whether the pain is a direct result of cancer since co-existent pain generators are common and tend to reinforce each other. The aggregate effects of these various sources of pain ultimately determine whether a cancer survivor becomes disabled. Few high-quality data from long-term follow-up are available to inform expectations of the persistence and treatment responsiveness of specific cancer pain syndromes. Additionally, limited research has been devoted to accurately distinguishing the etiologic contributors to different pain syndromes that might inform their treatment.

All cancer treatments, including surgery, radiation, and systemic therapies, have the potential to produce chronic pain among disease-free survivors. Because multimodal cancer treatment is the current standard, it is not uncommon for survivors to have multiple different treatment-associated pain generators. Combined nociceptive and neuropathic pain is common (Leysen et al., 2019), and recently a group of clinicians proposed a set of guidelines for classifying the pain experienced by cancer survivors as predominant neuropathic, nociceptive, or central sensitization pain (Nijs et al., 2016). Awareness of a survivor's prior treatment exposures as well as the time course, distribution, and quality of the pain can help to clarify the probable duration, likelihood of spontaneous resolution, and treatment responsiveness.

Treatment-related pain tends to conform to specific patterns. Post-surgical pain, for example, is generally localized and restricted to the treated area. However, nerves are often sacrificed or injured during surgical procedures for cancer, which leads to pain that may be referred far from the operative site. Common syndromes include post-thoracotomy and post-mastectomy pain (Hetmann et al., 2017; Tait et al., 2018; Wang et al., 2018) The latter is a misnomer, since any surgical manipulation used to treat breast cancer—biopsy, lumpectomy, or axillary dissection—has the potential to cause lasting pain, although the more extensive and aggressive surgeries have a higher likelihood. Post-mastectomy pain is also representative in that other components of multimodal treatment plans, e.g., radiation and chemotherapy, have the potential to exacerbate the localized pain that is initially triggered by surgery. Psycho-emotional distress is associated with pain severity and persistence (Katz et al., 2005; Schreiber et al., 2014). This "multi-hit" phenomenon may contribute to pain after amputation or limb salvage surgeries as well as to chronic abdominal pain, particularly in the presence of recurrent cancer (Mercadante et al., 2014).

Pain syndromes engendered by systemic therapies are fewer and less diverse, although they are no less harmful. Multiple chemotherapy subtypes cause persistent neuropathy, which may produce burning pain or dysesthesias. Taxane chemotherapy may be complicated by arthralgias or myalgias that persist after acute treatment in as many as 50 percent of survivors (Chiu et al., 2018). Aromatase inhibitors may also produce severe, multifocal arthralgias (Beckwee et al., 2017). This syndrome may improve modestly with pharmacologic treatment (Henry et al., 2018). The functional impact of both taxane and aromatase inhibitor-induced arthralgias can be devastating since movement and activity may aggravate the pain. However, the long-term functional impacts of both syndromes have been only poorly characterized (Chiu et al., 2017). The potential for targeted biological treatments, such as the immune checkpoint inhibitors (ICIs), to produce persistent pain is a topic of active scrutiny and discovery. Reports indicate that the ICIs have the potential to cause arthralgias (Cappelli et al., 2017) and to engender new rheumatoid arthritis and polymyalgia rheumatic (Belkhir et al., 2017). The ICIs may also cause neuropathies, though these have yet to be robustly characterized with respect to incidence, associated pain, and chronicity (Hottinger, 2016).

The long-term severity and persistence of cancer-related pain among disease-free survivors remains under-researched. A landmark population-based study on Danish women reported a 47 percent prevalence of pain among disease-free breast cancer survivors 2–3 years following the completion of therapy (Gartner et al., 2009). A higher prevalence—60 percent—was found in a 3-year study of a more limited cohort of breast cancer survivors (Rietman et al., 2004). Additionally, some evidence suggests that the proportion of breast cancer survivors who report severe pain may increase over time. For example, in the long-term follow-up of 1,183 survivors, 27.8 percent reported severe pain at 40 months, which increased to 32.3 percent at 10

years (Forsythe et al., 2013). Similar estimates from non-breast-cancer cohorts are generally lacking, but the few reports that have been published suggest that pain remains similarly an issue. For example, among a cohort of 175 head and neck cancer survivors at a median of 6.6 years after diagnosis, 45.1 percent reported pain, and 11.5 percent reported severe pain (Cramer et al., 2018)

Cancer pain is most prevalent among patients with metastatic disease. Bone metastases are the most common pain generator (Falk et al., 2014; Milgrom et al., 2017) Among patients with advanced cancer, it is estimated that 60 percent to 84 percent experience bone pain (Mercadante, 1997). Patients with metastatic disease are subject to the aforementioned treatment-related pain syndromes which are frequently more cumulative and severe in later stages. Additional pain syndromes common to this population include liver capsule distension, brain-tumor-related headache, neural compression, and extrinsic visceral compression which may affect the gastrointestinal tract or ureter (Cherny et al., 2015). While most pain syndromes in late-stage disease can be ameliorated, many patients experience residual pain and remain prone to the development of new pain generators. Therefore, although the pain is inadequately characterized, it is reasonable to assume that few patients with advanced-stage cancer and disabling pain will improve sufficiently to resume gainful employment.

BREAST CANCER

It is estimated that in 2019 there will be 268,600 new cases of invasive breast cancer diagnosed in women and 2,670 new cases diagnosed in men (ACS, 2019a). The female breast cancer death rate peaked at 33 per 100,000 in 1989, then declined by 40 percent—to 20 per 100,000—in 2016. This progress reflects improvements in both early detection (through screening as well as increased awareness of symptoms) and treatment and translates to an estimated 348,800 fewer breast cancer deaths than would have been expected if the death rate had remained at its peak. From 2007 to 2016 the breast cancer death rate declined by 1.8 percent per year (ACS, 2019a). The 5- and 10-year relative survival rates for women with invasive breast cancer are 90 percent and 83 percent, respectively. Sixty-two percent of cases are diagnosed at a localized stage (no spread to lymph nodes, nearby structures, or other locations outside the breast), for which the 5-year survival is 99 percent.

Most breast cancers (80 percent) are invasive, meaning that the cancer has spread beyond the tissue of origin and into surrounding healthy tissue (ACS, 2017). Ductal carcinoma in situ (DCIS), a non-invasive presence of abnormal cells inside a milk duct in the breast, is considered a precursor to invasive cancer and is also associated with an increased risk for developing a new invasive breast cancer (Mayo Clinic, 2018a). This section focuses on invasive breast cancer. Table 3-5 describes the diagnostics, therapy, outcome, and monitoring for invasive breast cancer, excluding DCIS.

TABLE 3-5 Diagnostics, Treatments, Outcomes, and Monitoring for Breast Cancer (Excludes DCIS)

	Early stage	Locally advanced	Advanced stage
Diagnostics*	• Diagnostic bilateral mammogram/ultrasound, breast MRI • Tumor biopsy with ER/PR/HER-2 tissue testing • Axillary ultrasound/imaging plus percutaneous biopsy if suspicious node • Genetic counseling and testing as indicated, tumor multigene assay (if ER/PR positive and HER-2 negative) • CT, FDG PET/CT, MRI, bone scan as clinically indicated	Same as early stage	• Chest CT, abdominal/pelvic CT or MRI, bone scan, FDG PE • Biopsy with ER/PR/HER-2 tissue testing, tumor PIK3CA mutation testing if ER/PR positive and HER-2 negative; germ BRCA 1/2 testing if HER-2 negative; PDL-1 biomarker testin for triple negative (HR and HER-2 negative), genetic counsel • Brain/spine MRI, symptomatic and long and weight bearing b x-rays if clinically indicated
Treatment	• Lumpectomy/surgical axillary staging/RT • Total mastectomy/surgical axillary staging/reconstruction ± RT • Adjuvant endocrine therapy (premenopausal ovarian suppression/ablation), chemotherapy, HER-2 targeted agents • Option of neoadjuvant chemotherapy (pre surgery)	• Neoadjuvant chemotherapy, HER-2 targeted therapy • Total mastectomy/surgical axillary staging/reconstruction + RT • Lumpectomy/surgical axillary staging/RT • Adjuvant hormonal therapy, HER-2 directed therapy, occasional oral chemotherapy (capecitabine)	• Hormonal therapy (plus premenopausal ovarian suppression/ablation), targeted agents (HER-2, CDK, PICK3A m-TOR, PARP), chemotherapy, immunotherapy, palliative R • Orthopedic bone stabilization, skeletal directed agents if bone metastases

Disease outcomes of treatment	Complete remission Recurrence	Same as early stage	• Complete remission (rare) • Partial remission • Stable disease • Progressive disease
Post-treatment monitoring	• History and physical, 1-4 times annually through 5 years and then annually • Annual mammogram • Monitor for lymphedema • Monitor for family history change for new genetic counseling • Other imaging and labs as clinically indicated	Same as early stage	

	Chemotherapy	Hormonal Therapy
History & physical	Every cycle	Every 1–3 months
Labs	Every cycle	Every 1–3 months
CT CAP	Every 2-4 cycles	Every 2–6 months
Bone scan	Every 4 cycles	Every 4–6 months
PET/CT	Optional	Optional

NOTES: *In addition to history and physical examination, and laboratory exams. CAP = chest abdomen pelvis; CDK = cyclin-dependent kinase; CT = computed tomography; ER/PR/HER-2 = tumor markers; FDG = fluorodeoxyglucose (a positron-emitting substance injected for diagnostic purposes in conjunction with PET); MRI = magnetic resonance imaging; PET = positron emission tomography; PIK3CA = a protein coding gene; RT = radiation therapy. Routine lab studies/ all CT and MRI imaging is with contrast unless otherwise designated. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019a.

Professionally Accepted Diagnostic Criteria for Breast Cancer

Breast cancer is typically detected during either a screening mammographic or an MRI examination, either before symptoms have developed or after a woman has noticed a lump. When cancer is suspected, a microscopic analysis of breast tissue is necessary for a diagnosis and to determine the stage and characterize the type of the disease. The tissue for microscopic analysis can be obtained from a needle biopsy (fine-needle or wider-core needle) or surgical excision. The diagnostic procedure for breast cancer differs according to multiple factors, including cancer stage, the size and location of the mass, and patient factors, preferences, and resources (ACS, 2017).

Hormone receptor tests should be ordered to provide insight into which treatment options would be most effective for the patient. Hormone receptor testing typically uses a specialized staining process on the breast tissue sample to see if hormone receptors are present (National Breast Cancer Foundation, 2016). Although breast cancer generally has been referred to as a single disease, there are at least four different molecular subtypes which differ from one another in terms of risk factors, presentation, response to treatment, and outcomes (ACS, 2017). Gene expression profiling techniques have allowed a better understanding of the molecular subtypes of breast cancers. Approximations of molecular subtypes have been identified using routinely evaluated biological markers, including the presence or absence of hormone (estrogen or progesterone) receptors (HR+/HR−) and excess levels of human epidermal growth factor receptor 2 (HER2, a growth-promoting protein) or extra copies of the HER2 gene (HER2+/HER2−) (ACS, 2017). Treatment is determined by testing of these biological markers.

Breast ultrasound is often used to evaluate abnormal findings from a mammogram or physical exam. For inflammatory and advanced breast cancers where the tumors might have metastasized to other parts of the body, other diagnostic tests should be performed, such as whole-body CT, PET, MRI, and bone scans. Another type of test called FDG (fluorodeoxyglucose) PET/CT may be used, where FDG, composed of fluoride and glucose, acts as a radiotracer to find cancer in lymph nodes, organs, and bones. This can be done simultaneously with the diagnostic CT (NCCN, 2019a). Genetic testing gives people the chance to learn if their breast cancer or family history of breast cancer is due to an inherited gene mutation. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced (cancer that has spread from its origin to nearby tissue) or metastatic cancer. FDG PET/CT may also help identify unsuspected regional nodal disease or distant metastases in locally advanced breast cancer when used in addition to standard staging studies (NCCN, 2019a).

Treatments for Breast Cancer

The medical professionals involved in the care of individuals with breast cancer include surgeons, radiation oncologists, medical oncologists, genetic counselors, rehabilitation physicians, physical therapists, occupational therapists, speech language pathologists, and exercise physiologists, in addition to the specialists noted in the “Medical Professionals Involved in the Care of Selected Cancers” section (NCCN, 2019a). The treatment settings include radiology facilities, surgery suites, radiation facilities, and outpatient infusion centers (NCCN, 2019a).

As with diagnosis, treatment for breast cancer differs according to the stage of the cancer and other factors such as the biological markers noted in the diagnostic criteria section. In general, the treatment involves either breast-conserving surgery (i.e., surgical removal of the tumor and surrounding tissue) or a mastectomy (i.e., surgical removal of the breast), depending on tumor characteristics (e.g., size and extent of spread) and patient preference (ACS, 2019b). Radiation to the breast is recommended for most patients having breast-conserving surgery. For women with early-stage breast cancer (without spread to the skin, chest wall, or distant organs), studies indicate that breast-conserving surgery plus radiation therapy results in long-term outcomes that are equivalent to a mastectomy. Although many patients undergoing total mastectomy do not need radiation, it is sometimes recommended when the tumor is large or the lymph nodes are involved. One or more underarm lymph nodes are usually evaluated during surgery to determine whether the tumor has spread beyond the breast. Women undergoing mastectomy who elect breast reconstruction typically have several options, including the type of tissue or implant used to restore breast shape. The reconstruction may be performed at the time of mastectomy (also called immediate reconstruction) or as a second procedure (delayed reconstruction), but it often requires more than one surgery (ACS, 2019b).

The treatment may also involve chemotherapy before (neoadjuvant therapy) or after (adjuvant) the surgery, hormone (anti-estrogen) therapy, or targeted therapy, or some combination of those, depending on the cancer stage, subtype, and anticipated benefits of each treatment component. Women with early-stage breast cancer that tests positive for hormone receptors benefit from treatment with hormone therapy for 5 or more years (ACS, 2019b). Tumor genomic analysis may predict the benefits of hormonal therapy alone or of adding chemotherapy or early-stage adjuvant therapy (Vieira and Schmitt, 2018).

Chemotherapy and other treatments that target cancer treat the invasive disease and improve survival, but they do not necessarily improve functioning. In fact, the treatment itself could reduce functioning.

Length of Treatment Time for Breast Cancer

A treatment using non-hormonal therapy for early or locally advanced disease that achieves complete remission is generally complete in 12 to 18 months, although hormonal therapy may be carried out for an additional period of time, which can be as much as 10 years (NCCN, 2019a).

Standard Measures of Outcomes for Breast Cancer

For early-stage as well as locally advanced breast cancers, the ideal outcome of cancer therapy is complete remission. For advanced-stage diseases, complete remission is rare; other possible outcomes of therapy include partial remission, stable disease, or progressive disease (NCCN, 2019a). Metastatic diseases are typically incurable.

Breast cancer patients with early-stage and locally advanced disease achieving complete remission should receive frequent (one to four times a year) physical examinations for the first 5 years post-treatment, then yearly physical examinations after the first 5 years to assess for possible metastatic recurrence and tolerance to ongoing therapies, and to monitor or treat any treatment effects. Patients should be monitored for lymphedema. Other imaging and laboratory tests should be conducted as determined by the patient's treating physician. Those with advanced-stage cancer are likely undergoing chemotherapy or hormonal therapy, or both. The

monitoring of those undergoing chemotherapy includes carrying out a history and physical and laboratory tests at every cycle of chemotherapy, performing a CT chest abdomen pelvis (CT CAP) scan every two to four cycles, and carrying out a bone scan every four cycles. Those undergoing hormonal therapy should receive a history and physical and laboratory tests every 1–3 months, a CT CAP every 2–6 months, and a bone scan every 4–6 months or as clinically indicated (NCCN, 2019a).

CUTANEOUS MELANOMA

Over the past several decades there has been a significant rise in cutaneous melanoma incidences in white populations, and it has grown from a very rare malignancy into a disease of considerable clinical importance (Canavan and Cantrell, 2016). Between 2007 and 2009, the overall melanoma incidence in the United States was 21.87 cases per 100,000 person-years, which was up significantly from the 13.94 cases per 100,000 person-years in 1989 to 1991. Men in the United States have a 1 in 33 lifetime risk for developing melanoma, compared with 1 in 52 for U.S. women. In contrast to non-melanoma skin cancers, malignant melanoma affects a younger population with the median age at diagnosis of 55 years. Melanoma is associated with significant morbidity and mortality; however, mortality has leveled over since 1990, though it remains high in those with metastatic disease (Canavan and Cantrell, 2016). Table 3-6 describes the diagnostics, therapy, outcome, and monitoring for cutaneous melanoma.

TABLE 3-6 Diagnostics, Treatment, Outcomes, and Monitoring for Cutaneous Melanoma

	Early Stage	Locally Advanced	Advanced Stage
Diagnostics*	Sentinel lymph node biopsy	Tumor molecular testing	Same as locally advanced stage
Treatment	Primary tumor wide excision	• Primary tumor wide excision • Regional lymph node dissection • Regional lymph node RT • Adjuvant immunotherapy or kinase inhibitor	• Resection of limited metastases • Immunotherapy • Kinase inhibitor • Chemotherapy • Palliative RT
Disease outcomes of treatment	Complete remission Recurrence	Same as early stage	• Complete remission • Partial remission • Progressive disease
Post-treatment monitoring	History and physical every 6–12 months for 5 years and annually thereafter	• History and physical every 3–6 months for 2 years, every 3–12 months for 3 years then as clinically indicated • Imaging every 3–12 months for 3 years	• History and physical • Imaging (same length of follow-up as locally advanced if no evidence of disease after therapy)

NOTES: * In addition to history and physical examination, imaging, routine laboratory studies. RT = radiation therapy. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019b.

Professionally Accepted Diagnostic Criteria for Cutaneous Melanoma

A clinical suspicion of a melanoma is based on the visual appearance of a skin lesion. Skin lesion abnormalities raising suspicion include asymmetry, irregular borders, multiple colors, diameter, and change. An early melanoma diagnosis is essential for improving patient prognosis and survival. More superficial, thinner lesions are associated with improved clinical outcomes; therefore, early diagnosis with excisional biopsy is imperative. A full-thickness excisional biopsy is required at the time of initial biopsy in order to determine a potential melanoma's Breslow thickness. Punch and shave biopsies provide insufficient histologic information and are not recommended (Canavan and Cantrell, 2016).

Treatments for Cutaneous Melanoma

Medical professionals involved in the care of individuals with melanoma include dermatologists, radiation oncologists, medical oncologists, plastic surgeons, and providers that help manage side effects of immunotherapy (e.g., endocrinologists, pulmonologists, gastroenterologists, and neurologists) (NCCN, 2019b). Treatment settings include surgery suites, radiation facilities, and outpatient infusion centers (NCCN, 2019b).

Treatment modalities are based upon the stage at diagnosis. Early-stage disease is treated by primary tumor complete excision with a clear margin. Locally advanced disease may be identified by sentinel node biopsy and might also include dissection and radiation therapy of regional lymph nodes, adjuvant immunotherapy, or kinase inhibitors. Advanced-stage treatment can involve resection of limited metastases, immunotherapy, kinase inhibitors, chemotherapy, and radiation therapy of the brain (NCCN, 2019b).

Surgical excision with adequately conservative margins is the cornerstone of treatment for localized disease without lymph node involvement. Lymph node involvement that is identified clinically or through imaging is treated with lymph node dissection. Adjuvant therapy is an option for high-risk patients, the goal of which is to eliminate subclinical micrometastases. As the understanding of the molecular genetics of melanoma has expanded, there has been great interest in developing targeted treatments, and there are now numerous adjuvant treatment options. Some of the recently approved treatments have targeted BRAF V600E mutations (cobimetinib, trametinib, dabrafenib, and vemurafenib), some target the programmed cell death receptor (pembrolizumab and nivolumab), and others act through immunomodulation (ipilimumab) (Canavan and Cantrell, 2016).

Length of Treatment Time for Cutaneous Melanoma

Therapy for early-stage or locally advanced disease that achieves complete remission is generally complete in 12 to 18 months (NCCN, 2019b). Metastatic disease is typically incurable.

Standard Measures of Outcomes for Cutaneous Melanoma

For early-stage and locally advanced melanoma, the ideal outcome of cancer therapy is complete remission. For advanced-stage diseases, complete remission is rare; other possible outcomes of therapy include partial remission or progressive disease (NCCN, 2019b).

Patients with early stage melanoma achieving complete remission should receive a history and physical examination every 6–12 months for the first 5 years and then annually

thereafter. Those with locally advanced and advanced-stage disease should receive a history and physical every 3–6 months for 2 years, then every 3–12 months for the next 3 years, and then as clinically indicated, as well as having imaging every 3–12 months for 3 years (NCCN, 2019b).

RENAL CANCER

Kidney cancer among adults consists of malignant tumors arising from the renal parenchyma and renal pelvis. Despite an overall increase in the incidence of renal cancers from 1992 to 2015, there has been a recent plateau in renal cancer incidence rates with a significant decrease in mortality (Saad et al., 2018).

Evidence suggests an etiologic role for physical activity, alcohol consumption, occupational exposure to trichloroethylene, and high parity among women. Genetic susceptibility and environmental exposures are believed to influence renal cell cancer risk, but limited studies based on gene approaches have not produced conclusive results. Large-consortium efforts employing genome-wide scanning technology are under way, and they hold promise for novel discoveries in renal carcinogenesis (Capitanio and Montorsi, 2016; Chow et al., 2010).

Table 3-7 describes the diagnostics, therapy, outcome, and monitoring for renal cancer.

TABLE 3-7 Diagnostics, Treatment, Outcomes, and Monitoring for Renal Cancer

	Early Stage	Locally Advanced	Advanced Stage
Diagnostics*	• Abdominal/pelvic CT or MRI • Chest X-ray • If clinically indicated: bone scan, chest CT, brain MRI • Consider needle biopsy if small lesion	Same as early stage	Same as early stage
Treatment	• Partial or radical nephrectomy • Ablative therapy (cryotherapy, radiofrequency ablation) for small lesions	• Partial or radical nephrectomy • Adjuvant kinase inhibitor therapy for clear cell variety	• Cytoreductive nephrectomy • Metastasectomy or stereotactic body RT for oligometastatic disease • Kinase inhibitor • Immunotherapy • Antiangiogenics • High-dose interleukin-2
Disease outcomes of treatment	• Complete remission • Recurrence	Same as early stage	• Partial remission • Complete remission (rare) • Stable disease • Disease progression

Post-treatment monitoring	• Postoperative abdominal CT, MRI, or ultrasound and then annually for 3 years • Chest X-ray or CT annually for 5 years	Same as early stage	• Chest, abdominal, pelvic CT or MRI imaging every 6–16 weeks • Head CT/MRI baseline and then as clinically indicated • Bone scan, spine MRI as clinically indicated

NOTES: * In addition to history and physical examination, routine and systemic therapy directed labs. CT = computed tomography; MRI = magnetic resonance imaging; RT = radiation therapy. Routine lab studies/all CT and MRI imaging is with contrast unless otherwise designated. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019c.

Professionally Accepted Diagnostic Criteria for Renal Cancer

With the expansion of routine imaging for many disorders, patients with renal cell carcinoma are increasingly being identified incidentally. Only 30 percent of patients are diagnosed on the basis of symptoms (Capitanio and Montorsi, 2016). Although renal cell carcinoma is frequently detected by abdominal ultrasound scanning, limitations in its specificity and accuracy make it necessary to use CT or MRI to confirm suspicious findings. The main goals of imaging are to characterize the mass and possible abdominal metastases, tumor extension, and venous involvement for the purpose of staging. If malignant renal cell carcinoma is suspected, additional imaging (e.g., thoracic and brain CT scan, total body bone scan) can be considered in symptomatic patients or in cases of bulky abdominal disease. New technologies for cancer detection and characterization are being investigated for renal cell carcinoma; for example, advanced MRI techniques, such as diffusion-weighted and perfusion-weighted imaging, are being explored for the assessment of renal masses (Capitanio and Montorsi, 2016).

Treatments for Renal Cancer

Individuals with renal cancer are identified for treatment via imaging, including CT and MRI (NCCN, 2019c). The medical professionals involved in the care of individuals with renal cancer include surgeons, medical oncologists, and invasive radiology specialists (NCCN, 2019c). Treatment settings include invasive radiology facilities, surgery suites, and medical oncology clinics (NCCN, 2019c). Notwithstanding advances in the understanding of renal cell carcinoma biology, surgery remains the mainstay of curative treatment. Although radical nephrectomy was historically the standard of care for management of renal tumors, the detection of small renal lesions and accumulating evidence that surgically induced chronic kidney disease can increase patients' morbidity have led to more conservative approaches. Specifically, nephron-sparing surgery, active surveillance, and minimally invasive techniques have been introduced into daily clinical practice. These approaches limit invasiveness, iatrogenic renal function impairment, and overtreatment (Capitanio and Montorsi, 2016).

Length of Treatment Time for Renal Cancer

Disease therapy for early disease is generally complete in 12 weeks, therapy for locally advanced disease that achieves complete remission with surgery is complete in 12 weeks, and clear-cell variety receiving adjuvant therapy is usually complete in 60 weeks (NCCN, 2019c).

Standard Measures of Outcomes for Renal Cancer

For early-stage and locally advanced renal cancer, the ideal outcome of cancer therapy is complete remission. For advanced-stage diseases, complete remission is possible but rare; partial remission is more probable (NCCN, 2019c). Eventual progression and death are likely for advanced disease.

Post-treatment monitoring for patients with early-stage and locally advanced renal cancers who achieve complete remission includes CT, MRI, or ultrasound immediately after operation, then annually for 3 years; a chest X-ray or CT should also be performed every 5 years. For those with advanced stage disease, chest, abdominal, pelvic CT, or MRI imaging should be performed every 6–16 weeks. Head CT/MRI should be taken at baseline postoperatively and then as clinically indicated. A bone scan and a spine MRI should be performed as clinically indicated.

HEAD AND NECK SQUAMOUS CELL CANCERS

Head and neck squamous cell cancers develop in the mucous membranes of the mouth, nose, and throat (NLM, 2019) and are classified by location: the mouth (oral cavity), the middle part of the throat near the mouth (oropharynx), the space behind the nose (nasal cavity and paranasal sinuses), the upper part of the throat near the nasal cavity (nasopharynx), the voicebox (larynx), or the lower part of the throat near the larynx (hypopharynx). Depending on the location, the cancer can cause abnormal patches or open sores (ulcers) in the mouth and throat, unusual bleeding or pain in the mouth, sinus congestion that does not clear, sore throat, earache, pain when swallowing or difficulty swallowing, a hoarse voice, difficulty breathing, or enlarged lymph nodes (NLM, 2019). Cancers of the brain, thyroid, and esophagus are separately categorized because these cancers are very different in their symptoms and treatment from the previously listed cancers of the head and neck (Cohen et al., 2016a). Head and neck cancers accounted for an estimated 61,760 new cancer cases in the United States in 2016. Currently, there are approximately 436,060 head and neck cancer survivors living in the United States, accounting for 3 percent of all cancer survivors, and long-term survival is becoming more common in this population. Tobacco use and alcohol consumption combine to account for an estimated 75 percent of head and neck cancer cases. In addition, the human papillomavirus (HPV) accounts for as many as 70 percent of oropharyngeal cancers. HPV-related head and neck cancer is a biologically and clinically distinct disease from tobacco-related head and neck cancer, with now well described differences in molecular alterations, clinical presentation, and prognosis. Approximately 20 percent of the population is positive for exposure to high-risk HPV (Cohen et al., 2016a). An estimated 53,000 new cases of cancer of the oral cavity and pharynx (throat) are expected to be diagnosed in the United States in 2019. Incidence rates are more than twice as high in men as in women. Unlike most other cancer sites, stage IV head and neck

cancers are still potentially curable (Cohen et al., 2016b). Table 3-8 describes the diagnostics, therapy, outcome, and monitoring for head and neck squamous cell cancers.

TABLE 3-8 Diagnostics, Treatment, Outcomes, and Monitoring for Head and Neck Squamous Cell Cancer

	Early Stage	Locally Advanced	Advanced Stage
Diagnostics*	• Biopsy (or FNA of neck) • HPV tissue testing (oropharynx) • EBV/DNA testing (nasopharynx) • Mirror and fiberoptic exam • Examination under anesthesia with endoscopy • CT/MRI of primary and neck • Dental evaluation • As clinically indicated: chest CT; PET/CT; nutritional, speech, swallowing evaluation/therapy	Same as early stage	Same as early stage
Treatment	• Primary resection • RT	• Primary resection • Neck sentinel node biopsy • Neck node dissection • RT • Chemotherapy • Targeted agent therapy	• Chemotherapy • Targeted agent therapy • Immunotherapy
Disease outcomes of treatment	• Complete remission • Recurrence	• Complete remission • Partial remission	• Complete remission • Partial remission • Progressive Disease
Post-treatment monitoring	• History and physical (including mirror and fiberoptic exam) o Year 1: every 1–3 months o Year 2: every 2–6 months o Year 3-5: every 4–8 months o Years 5+: every 12 months • Neck RT: TSH every 6–12 months • Intraoral RT: dental monitoring • Nasopharyngeal: EBV DNA monitoring • Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated • Repeat primary and neck baseline	Same as early stage	Same as early stage and routine CT or CT/PET imaging to monitor therapy response for metastatic disease

	imaging within 6 months of therapy completion • Annual routine imaging if poor visualization of primary site

NOTES: * In addition to history and physical examination and laboratory tests. CT = computed tomography; EBV = Epstein-Barr virus; FNA = fine needle aspiration; HPV = human papillomavirus; MRI = magnetic resonance imaging; PET = positron emission tomography; RT = radiation therapy; TSH = thyroid-stimulating hormone. Routine lab studies/ all CT and MRI imaging is with contrast unless otherwise designated. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019d.

Professionally Accepted Diagnostic Criteria for Head and Neck Squamous Cell Cancer

The diagnostic criteria are the same for all stages of head and neck cancer and may include biopsy (such as fine-needle aspiration of the neck), HPV tissue testing for oropharynx cancer, Epstein-Barr virus (EBV) DNA testing for nasopharynx cancers, mirror and fiberoptic exams, CT/MRI or the primary site and neck, and dental evaluation. As clinically indicated, diagnosis may also include chest CT, PET/CT, nutrition consultation, speech consultation, and swallowing evaluation and therapy.

Fine-needle aspiration is a common type of biopsy used in diagnosing head and neck cancer. This involves inserting a thin needle directly into the tumor or lymph node and then examining the cells under a microscope for cancer cells, in a process called a cytologic examination. The biopsy might include testing to see whether the person has HPV, which has been linked to a higher risk of head and neck cancers. In some cases, whether a person has HPV can help determine which treatments would be most effective (NLM, 2019). Molecular testing of the tumor may be done to identify specific genes, proteins, and other factors unique to the tumor and also to help determine treatment options. A CT scan or MRI can be used to determine the tumor's size. In addition, if swallowing is impaired, physicians may consult a nutritionist and speech language pathologist. A barium swallow study can help identify abnormalities in the swallowing passage (NLM, 2019).

Treatments for Head and Neck Squamous Cell Cancer

Medical professionals involved in the care of individuals with head and neck squamous cell cancer include surgeons, radiation oncologists, medical oncologists, and dentists (NCCN, 2019b). Therapy takes place is the surgery suite, radiation facilities, and outpatient infusion centers (NCCN, 2019d). Radiation therapy or surgery or a combination of the two are standard treatments; chemotherapy is often added for high-risk or advanced disease. Chemotherapy or targeted therapy may be combined with radiation as an initial treatment in some cases. Immunotherapy is a newer option for advanced or recurrent cancer (ACS, 2019b)

Standard management of head and neck cancers is based largely on anatomic considerations and TNM (tumor, lymph nodes, metastasis) stage. Early-stage disease (stage I and II) is treated with a single modality—surgery or radiation therapy (RT)—depending primarily on the tumor's location but also on the tumor's extent, the anticipated cure rate, and functional and esthetic outcome. About 80 to 90 percent of early-stage patients will go into complete remission. Advanced-stage patients (stages III, IVa, and IVb) are treated with multimodal therapy,

including surgery, RT, chemotherapy, and targeted agent therapy. The sequencing and combination of therapies are based on the stage, tumor location, expertise of treating physicians, and patient preference. Despite the use of more aggressive treatment for advanced stage disease, cure rates remain low primarily because of locoregional recurrence. However, HPV-related head and neck cancer is associated with a significantly better prognosis even with stage IV disease, especially in never smokers. Cure rates, often based on 5-year survival rates, for HPV-related head and neck cancer in some large studies has approached 90 percent (Cohen et al., 2016a).

Much of the current research in head and neck cancers is focused on personalizing therapy based on molecular phenotypes, improving treatment efficacy, and reducing long-term morbidity. The latter is predominantly being studied in HPV-related head and neck cancer, where reductions in radiation dose or volume are being studied with the goal of reducing acute and chronic toxicities (Cohen et al., 2016a).

Length of Treatment Time for Head and Neck Squamous Cell Cancer

Disease therapy for early disease is complete in 12 weeks, and therapy for locally advanced disease that achieves complete remission with combination therapy is complete in 6 to 12 months (NCCN, 2019d).

Standard Measures of Outcomes for Head and Neck Squamous Cell Cancer

For all stages of head and neck cancer, the ideal outcome of cancer therapy is complete remission. For advanced-stage disease, partial remission is more probable, and progressive disease is also a possible result of cancer therapy (NCCN, 2019d).

Post-treatment monitoring for all stages of head and neck cancer in which complete remission has been achieved should include a history and physical examination that includes mirror and fiberoptic exam and which is performed every 1–3 months in the first year following treatment, every 2–6 months in the second year, every 4–8 months at 3–5 years post-treatment, and once a year after 5 years post-treatment (NCCN, 2019d).

Other factors to monitor depend on the site of the head and neck cancer. If radiation therapy is performed on the neck, TSH should be monitored every 6 to 12 months to look for radiation-induced hypothyroid, a toxicity of the radiation. Dental monitoring should be performed for those undergoing intraoral radiation therapy. EBV DNA monitoring should be performed for those treated for nasopharyngeal cancer. If the cancer resulted in impaired speech, hearing, or swallowing, those functions should be rehabilitated and monitored closely. Primary and neck baseline imaging should be performed within 6 months of therapy completion. Annual routine imaging should also be performed if there is poor visualization of the primary site of cancer. For those with advanced-stage head and neck cancer, routine CT or CT/PET imaging should also be performed to monitor therapy response for metastatic disease (NCCN, 2019d).

ADVANCED EPITHELIAL OVARY CANCER

Ovarian cancer is the most lethal gynecologic malignancy among women in the United States (Thrall et al., 2011). In 2019 an estimated 22,530 American women will be newly diagnosed with ovarian cancer and 13,980 women will die of the disease (ACS, 2020). Survival in epithelial ovarian cancer is strongly related to the stage of the disease, and the majority of

patients present with advanced-stage (III/IV) disease at the time of diagnosis (Thrall et al., 2011). Although survival remains low for advanced epithelial ovary cancer (see Table 3-1), for a subset of patients with certain biological characteristics, the disease is curable and long-term survival (of 10 or more years) is possible (Cress et al., 2015; Hilal et al., 2016). Researchers have theorized that individuals with advanced stage ovary cancer who carry mutations in the tumor suppressor genes BRCA1 and BRCA2 respond better to chemotherapy than those who do not (Cress et al., 2015). Additionally, data show that younger women generally have better prognoses, partially due to a better ability to tolerate aggressive therapy (Cress et al., 2015).

Table 3-9 describes the diagnostics, therapy, outcome, and monitoring for advanced epithelial ovary cancer.

TABLE 3-9 Diagnostics, Treatment, Outcomes, and Monitoring for Advanced Epithelial Ovary Cancer

	Advanced Stage
Diagnostics*	• Chest, abdomen, pelvis CT • CA-125 marker • Genetic counseling and testing
Treatment	• Total abdominal hysterectomy with bilateral salpingo-oophorectomy, surgical staging and debulking, followed by (adjuvant) chemotherapy (intravenous or intraperitoneal and intravenous) with or without antiangiogenics agent, maintenance antiangiogenics agent or targeted agent (PARP inhibitor) • Preoperative chemotherapy (neoadjuvant) followed by same surgery and same adjuvant therapy • Chemotherapy with or without antiangiogenics agent for nonsurgical candidate. Chemotherapy, targeted agent, hormonal therapy, immunotherapy, palliative RT for persistent/progressive disease
Disease outcomes of treatment	• Complete or partial remission • Persistent and progressive disease.
Post-treatment monitoring	• Complete remission: o History and physical examination (including pelvic exam) every 2–4 months for 2 years, 3–6 months for 3 years, and then annually o CA-125 monitoring o Imaging and labs as clinically indicated o Genetic counseling if not done initially • Relapsed, progressive disease o Chest/abdomen/pelvic CT, MRI, PET/CT, or PET o CA-125 monitoring, labs as therapy and clinically indicated o Tumor molecular testing

NOTES: * In addition to history and physical examination (including pelvic exam). CA-125 = carbohydrate antigen 125 (a protein detected through blood test); CT = computed tomography; MRI = magnetic resonance imaging; PARP = poly (ADP-ribose) polymerase (a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death); PET = positron emission tomography; RT = radiation therapy. Routine lab studies/all CT and MRI imaging is with contrast unless otherwise designated. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019e.

Professionally Accepted Diagnostic Criteria for Advanced Epithelial Ovary Cancer

Diagnostics for advanced epithelial ovarian cancer include CT of the chest, abdomen, and pelvis using the CA-125 (carbohydrate antigen 125) marker and genetic counseling and testing (NCCN, 2019e; Pepin et al., 2014). CT of the abdomen and pelvis is the first-line imaging modality for staging, selecting treatment options, and assessing disease response in ovarian cancer (Sahdev, 2016). Genetic counseling and testing can play a role in screening for ovarian cancer (Neff et al., 2017). Recent advances in the hereditary understanding of this disease have shown a significant role for inherited BRCA1 and BRCA2 gene mutations. A positive test result for the BRCA gene mutations indicates a higher susceptibility to breast and ovarian cancers (Neff et al., 2017). A positive deleterious BRCA germline mutation also directs utilization of PARP inhibitor therapy (NCCN 2019e).

Treatments for Advanced Epithelial Ovary Cancer

The medical professionals involved in the care of individuals with advanced epithelial ovary cancer include gynecologic oncologists, surgeons, medical oncologists, and genetic counselors (NCCN, 2019e). Treatment settings include surgery suites and outpatient infusion centers (NCCN, 2019e). Optimal care for most patients with advanced ovarian cancer generally includes both surgery and chemotherapy (NCCN, 2019e; Thrall et al., 2011). People with advanced epithelial ovary cancer are identified for treatments via examination, imaging (ultrasound, CT, and MRI), and laparascopic examination (NCCN, 2019e). The treatment of newly diagnosed advanced epithelial ovarian cancer is rapidly evolving. Targeted therapies are now available based on positive phase III clinical trials (Monk et al., 2019). Current NCCN guidelines (2019e) recommend the following treatments:

1. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, surgical staging, and debulking, followed by (adjuvant) chemotherapy (intravenous or intraperitoneal and intravenous) with or without antiangiogenics agent, maintenance antiangiogenics agent, or targeted agent (PARP inhibitor)
2. Preoperative chemotherapy (neoadjuvant) followed by same surgery and same adjuvant therapy
3. Chemotherapy with or without antiangiogenics agent for nonsurgical candidate. Chemotherapy, targeted agent, hormonal therapy, immunotherapy, palliative RT for persistent/progressive disease

The timing and extent of surgery has direct implications for the selection of subsequent treatment as well as for the patient's prognosis. The newest class of agents approved by the U.S. Food and Drug Administration (FDA) to treat newly diagnosed advanced ovarian cancer are inhibitors of the enzyme poly (ADP ribose) polymerase, or PARP. PARP inhibitors are recommended for maintenance therapy after completion of chemotherapy for women identified with a BRCA 1/2 mutation (Jiang et al., 2019). The early initiation of chemotherapy following surgery has been found to improve survival. One study of 1,718 patients with stage III and IV advanced ovarian cancer found that survival was adversely affected when chemotherapy was initiated more than 25 days following surgery (Tewari et al., 2016).

Length of Treatment Time for Advanced Epithelial Ovary Cancer

Early-stage or locally advanced disease therapy that achieves complete remission is usually complete in 12 to 18 months, with a possible extension with PARP-inhibitor therapy (NCCN, 2019e).

Standard Measures of Outcomes for Advanced Epithelial Ovary Cancer

For those with advanced epithelial ovary cancer, the ideal outcome of cancer therapy is complete remission, although partial remission and persistent and progressive disease are also possible (NCCN, 2019e).

For those in complete remission, a history and physical examination including a pelvic examination are recommended every 2–4 months for the first 2 years after treatment, then every 3–6 months for 3 years, then annually. CA-125 monitoring, imagining, laboratory tests, and genetic counseling should also be conducted as clinically indicated. For those with relapsed, progressive disease, CT, MRI, PET/CT, or PET should be performed in the chest, abdomen, and pelvis. Other post-treatment monitoring for those with relapsed, progressive disease includes tumor molecular testing and laboratory tests (generally, a comprehensive metabolic panel and a complete blood count) as clinically indicated and depending on the type of therapy (NCCN, 2019e).

NON-SMALL-CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths in the United States, with five-year survival improving incrementally (see Table 3-2) given recent advances in therapy. Although survival for lung cancer remains low, for a subset of patients, long-term survival is possible (Davis et al., 2019). Lung cancer comprises small-cell lung cancer (SCLC; approximately 15 percent of all lung cancers) and non-small-cell lung cancer (NSCLC; approximately 85 percent) (Reck and Rabe, 2017). In the past decade, advances have been made in the science of non-small cell lung cancer (Duma et al., 2019). Lung cancer screening has demonstrated early-stage detection resulting in reduced mortality. The National Lung Screening Trial found a lung cancer mortality benefit of 20 percent and a 6.7 percent decrease in all-cause mortality with the use of low-dose chest CT in high-risk individuals. The treatment of lung cancer has also evolved, with the introduction of several lines of tyrosine kinase inhibitors in patients with EGFR, ALK, ROS1, NTRK mutations and BRAF V600 mutations and NTRK gene fusion. Similarly, immune checkpoint inhibitors (ICIs) have changed the landscape of NSCLC treatment. ICI therapy is recommended first-line therapy as either monotherapy or combined with chemotherapy for advanced disease that demonstrates overexpression of the programmed death-ligand 1 (PD-L1). ICI therapy is also recommended for stage III disease following the completion of combined chemotherapy and radiation (Duma et al., 2019).

Table 3-10 describes the diagnostics, therapy, outcome, and monitoring for NSCLC.

TABLE 3-10 Diagnostics, Treatment, Outcomes, and Monitoring for Non-Small-Cell Lung Cancer

	Early Stage	Locally Advanced	Advanced Stage
Diagnostics*	• CT chest and upper abdomen, FDG PET/CT • Brain MRI • Bronchoscopy • EBUS/EUS (endobronchial ultrasound/endoscopic ultrasound) • Mediastinoscopy • Biopsy • Pulmonary function tests	• Same as early stage, and • MRI spine and thoracic outlet (for primary abutting spine or subclavian vessels) • Thoracentesis/pericardiocentesis	• CT chest and upper abdomen • Brain MRI, FDG PET/CT • Biopsy, tissue molecular testing (broad molecular profiling) and PDL-1 testing
Treatment	• Surgical resection • RT • Chemotherapy/RT • Adjuvant chemotherapy, radiation	• Chemotherapy/RT • Post chemotherapy/RT immunotherapy • Pleural local therapy (thoracentesis, small catheter drainage, pericardial window)	• Targeted agents, immunotherapy, chemotherapy, RT • Endobronchial stent/laser • Orthopedic bone stabilization, skeletal directed agents for bone metastases
Disease outcomes of treatment	• Complete remission • Recurrence	• Complete remission • Persistent disease	• Complete remission • Partial remission, stable disease • Progressive disease
Post-treatment monitoring	• History and physical and low-dose non-contrast chest CT annually • Chest CT every 6 mo. for 2–3 years	For complete remission: History and physical and chest CT every 3–6 mo. for 3 years, then every 6 mo. for 2 years, then history and physical and low-dose non-contrast chest CT annually	• History and physical and labs every cycle • Imaging every 3 cycles

NOTES: * In addition to history and physical examination and laboratory tests. CT = computed tomography; MRI = magnetic resonance imaging; RT = radiation therapy. Routine lab studies/all CT and MRI imaging is with contrast unless otherwise designated. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019f.

Professionally Accepted Diagnostic Criteria for Non-Small-Cell Lung Cancer

Often, NSCLC is not diagnosed until advanced-stage disease is present. Cough, seen in 50 percent to 75 percent of patients, is the most common symptom, followed by hemoptysis, chest pain, and dyspnea. Other less common symptoms include laboratory abnormalities or paraneoplastic syndromes. Diagnosis requires a biopsy for histologic confirmation (Duma et al., 2019). Diagnosis also requires a determination of the extent of the tumor to define the TNM stage, which will ultimately guide cancer treatment options. Chest and upper abdomen CT, PET, and MRI can determine the stage, with CT scans being the most commonly used imaging modality for staging (Purandare and Rangarajan, 2015). On its own, the FDG/PET component does not have the optimal spatial resolution to provide information about infiltration of adjacent structures and, thus, has limitations for staging. However, if FDG/PET is performed along with contrast-enhanced CT, then the integrated image has a similar accuracy to a CT scan (Purandare and Rangarajan, 2015). Any positive node on PET-CT must be sampled, as confirmed by the analysis of a secondary objective from another randomized study (Duma et al., 2019). Additionally, NCCN (2019f) recommends bronchoscopy for early and locally advanced stages. Broncoscopes, which can be rigid or flexible, aid clinicians in providing an accurate diagnosis and lymph node staging. Technologies such as endobronchial ultrasound, navigational bronchoscopy, and autofluorescence have improved the efficacy of endobronchial diagnosis and sample collection (Bauer and Berkheim, 2016). CT or MRI of the head is recommended for patients to be treated with curative intent or for those with signs or symptoms suggestive of brain metastasis (Duma et al., 2019).

Treatments for Non-Small-Cell Lung Cancer

The medical professionals involved in the care of individuals with non-small-cell lung cancer include surgeons, radiation oncologists, medical oncologists, pulmonologists, and radiologists (NCCN, 2019f). The treatment settings include radiology facilities, surgery suites, radiation facilities, and outpatient infusion centers (NCCN, 2019f). People with non-small-cell lung cancer are identified for treatment via imaging, broncoscopy, and mediastinoscopy (NCCN, 2019f). The treatment of NSCLC is stage specific. Patients with early-stage or locally advanced cancers should be treated with complete surgical resection when not contraindicated. Nonsurgical patients should be considered for conventional or stereotactic radiation therapy (Duma et al., 2019). Chemotherapy and immunotherapy are also options if the surgical resection does not succeed (NCCN, 2019f). Lobectomy, the surgical resection of a single lobe, is generally accepted as the optimal procedure for early-stage NSCLC (Duma et al., 2019). Data regarding lobectomy versus sublobar resection are mixed but generally favor lobectomy. The rationale for adjuvant chemotherapy for patients with early-stage lung cancer is based on the observations that distant metastases are the most common site of failure after potentially curative surgery. Adjuvant therapy consists of cisplatin-based combination regimens and is indicated in patients with stage II and IIIA disease after surgical resection (Duma et al., 2019).

Immunotherapy has dramatically changed the landscape of NSCLC treatment (Duma et al., 2019). An essential role of the immune system is to recognize and destroy neoplastic cells before they become clinically meaningful. To limit damage to healthy cells, this process is highly regulated by a network of activating and inhibitory pathways in equilibrium. By altering this equilibrium, malignancies can escape immune surveillance and thrive. This strategy has been proved to be an effective therapy option for many cancers, including NSCLC. One of the most

attractive features of this type of treatment is that a subset of patients seems to have long-lasting benefits, with a subgroup of patients being alive 5 years after diagnosis, something that was unthinkable a decade ago (Duma et al., 2019).

A small subset of individuals with NSCLC have the potential to be cured, and survivorship depends largely on the type of treatment used. Davis and colleagues (2019) studied a cohort of patients with stage IV NSCLC in the SEER database who were diagnosed from 1991 to 2007 and followed through 2012. They found that the 10 percent of patients were long-term survivors (defined as living 21 months or longer) had a median survival time of 10 times that of the remaining 90 percent and were more likely to be younger, female, and treated with surgery. Uhlig and colleagues (2019) studied patients in the National Cancer Database who were diagnosed with stage IV NSCLC from 2010 through 2015 and found those treated with surgery in addition to systemic therapy survived longer than those treated with systemic therapy alone. Xia and colleagues (2017) likewise found remarkable improvements in patients in the SEER database diagnosed with NSCLC from 1988 to 2008 who underwent curative surgical resection. Another study of patients in the SEER database diagnosed with NSCLC from 1999 to 2008 concluded that radiation therapy was correlated with greater survival, especially coupled with surgery (Cheng et al., 2019). Otaibi and colleauges (2019) studied patients in the National Cancer Database with stage IV NSCLC and found improved survival in patients who received immunotherapy. They also found that the use of immunotherapy rose from 1 percent of patients to 12 percent from 2004 to 2015.

Length of Treatment Time for Non-Small-Cell Lung Cancer

Disease therapy for early-stage disease requiring surgery is usually complete in 12 weeks, therapy for early-stage disease requiring adjuvant therapy is complete in 6 months, and therapy for locally advanced disease that achieves complete remission with combination therapy is complete in up to 15 months (NCCN, 2019f).

Standard Measures of Outcomes for Non-Small-Cell Lung Cancer

The ideal outcome of NSCLC therapy is complete remission. For locally advanced stage cancers, persistent disease is a possible result of treatment. For advanced stage diseases, complete remission is rare; other possible outcomes of therapy include partial remission, stable disease, or progressive disease (NCCN, 2019f).

NSCLC patients with early-stage disease who achieve complete remission should receive a history and physical and chest CT every 6 months for 2–3 years post-treatment, then an annual history and physical with low-dose non-contrast chest CT. For those with locally advanced disease in complete remission, a history and physical and chest CT should be performed every 3–6 months for the first 3 years after treatment, then every 6 months for 2 years. After 2 years, a history and physical with low-dose non-contrast chest CT should be performed annually. For those with advanced stage disease, a history and physical and laboratory tests including a comprehensive metabolic panel and a complete blood count should be performed at every cycle of chemotherapy. Imaging should be performed at every three cycles of chemotherapy (NCCN, 2019f).

DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma in the United States, representing approximately 24 percent of new cases of non-Hodgkin lymphoma each year. The disease is aggressive, and patients typically present with rapidly enlarging lymphadenopathy and constitutional symptoms, necessitating immediate treatment (Liu and Barta, 2019). The disease is characterized by age, stage, the number of extranodal sites, performance status, and levels of serum lactate dehydrogenase. Recently, next-generation sequencing and comprehensive genomic analysis has allowed further subclassification of the disease by recurrent, high-frequency mutations, which provides a solid foundation for the development of novel targeted approaches (Liu and Barta, 2019). Table 3-11 describes the diagnostics, therapy, outcome, and monitoring for diffuse large B-cell lymphoma (excluding high-grade).

TABLE 3-11 Diagnostics, Treatment, Outcomes, and Monitoring for Diffuse Large B-Cell Lymphoma (Excluding High-Grade)

	Early Stage	Advanced Stage	Relapsed/Refractory
Diagnostics*	• General blood laboratory studies, incisional or excisional biopsy • Tissue for immunohistochemistry, flow cytometry, PCR for IGH and TCR gene rearrangements, karyotype, FISH for major translocations, next-generation sequencing (NGS) • Whole body PET/CT with or without C/A/P CT, bone marrow biopsy, International Prognostic Score calculation • Hep B testing, echocardiogram or MUGA scan, International Prognostic Index (IPI) calculation • As clinically indicated: head CT/MRI, neck CT/MRI, HIV and hep C testing, beta-2 microglobulin level, lumbar puncture, pregnancy testing (as indicated)	Same as early stage	Same as early stage

Treatment	• Targeted monoclonal antibody • Chemotherapy • RT	• Targeted monoclonal therapy, chemotherapy, RT • Intrathecal chemotherapy for leptomeningeal disease • High dose methotrexate for parenchymal CNS disease	• Targeted monoclonal therapy, chemotherapy, RT • Kinase inhibitor, immunomodulator, immunotherapy • High-dose chemotherapy with autologous stem cell rescue • Allogeneic hematopoietic cell transplant • Chimeric antigen receptor (CAR) T-cell therapy
Disease outcomes of treatment	• Complete remission • Recurrence	Complete remission	Complete remission
Post-treatment monitoring	• History and physical and labs every 3–6 mo. for 5 years, then annually or as clinically indicated • C/A/P CT with contrast only as clinically indicated	• History and physical and labs every 3–6 mo. for 5 years, then annually or as clinically indicated. • C/A/P CT with contrast every 6 months for 2 years, then as clinically indicated	• History and physical and labs every 3–6 mo. for 5 years, then annually or as clinically indicated. • C/A/P CT with contrast every 6 mo. for 2 years, then as clinically indicated

NOTES: * In addition to history and physical examination (including pelvic exam). C/A/P = chest/abdomen/pelvis; CNS = central nervous system; CT = computed tomography; FISH = fluorescence in situ hybridization; IGH = immunoglobulin heavy chain; PCR = polymerase chain reaction; PET = positron emission tomography; RT = radiation therapy; TCR = T-cell receptor. Clinical trial therapy is also an option for treatment.
SOURCE: NCCN, 2019g.

Professionally Accepted Diagnostic Criteria for Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma is best diagnosed from an excisional biopsy of a suspicious lymph node, which shows sheets of large cells that disrupt the underlying structural integrity of the follicle center and stain positive for pan-B-cell antigens, such as CD20 and CD79a. The cell of origin is determined by immunohistochemical stains, while molecular features such as double-hit or triple-hit disease are determined by fluorescent in situ hybridization (FISH) analysis. Commercial tests for frequently recurring mutations are currently not routinely used to inform treatment (Liu and Barta, 2019). In parallel to cell-of-origin studies, the subtypes of diffuse large B-cell lymphoma based on molecular features such as genetic rearrangements have also been found to have prognostic implications. These genetic rearrangements are identified by FISH. FISH studies should be done at the time of diagnosis and, ideally, again at the time of recurrence for prognostic and treatment implications (Liu and Barta, 2019). Whole-exome sequencing and the associated next-generation sequencing modalities have not yet been adopted into clinical practice, and tailored therapeutic approaches to these different subtypes have yet to be defined (Liu and Barta, 2019).

Treatments for Diffuse Large B-Cell Lymphoma

The medical professionals involved in the care of individuals with diffuse large B-cell lymphoma include radiation oncologists and medical oncologists (NCCN, 2019g). The treatment settings include radiation facilities and outpatient infusion centers (NCCN, 2019g). Patients with large B-cell lymphoma are identified for treatments via examination and imaging (CT, MRI, PET/CT) (NCCN, 2019g). NCCN (2019g) recommends targeted monoclonal antibody therapy, chemotherapy, and radiation therapy for all stages of diffuse large B-cell lymphoma. More advanced stages may require additional treatments, such as kinase inhibitors and immunotherapy.

The improved knowledge of the pathogenetic mechanisms underlying lymphomagenesis and the discovery of the critical role of tumor microenvironments have enabled the design of new drugs against cell targets and pathways. FDA has approved several monoclonal antibodies for targeted therapy in hematology (Crisci et al., 2019). Therapeutic monoclonal antibodies target specific antigen molecules, such as extracellular growth factors and transmembrane receptors. In some cases, monoclonal antibodies are conjugated with radioisotopes or toxins to allow the specific delivery of these cytotoxic agents to the tumor cell target (Crisci et al., 2019).

Length of Treatment Time for Diffuse Large B-Cell Lymphoma

Disease therapy that achieves complete remission is usually complete in 6 months (NCCN, 2019g). Therapy for disease that does not achieve complete remission will take a longer course.

Standard Measures of Outcomes for Diffuse Large B-Cell Lymphoma

The ideal outcome of diffuse large B-cell lymphoma therapy is complete remission. (NCCN, 2019g). Monitoring for all stages of disease with complete remission includes a history and physical and laboratory tests (including a comprehensive metabolic panel and a complete blood count) every 3–6 months for the first 5 years post-treatment, then annually or as clinically indicated. Chest/abdomen/pelvis CT is also recommended as clinically indicated for those with early stage lymphoma and every 6 months for the first 2 years post-treatment or as clinically indicated for those with advanced stage or relapsed/refractory disease.

DISABLING IMPAIRMENTS RELATED TO THE SELECTED CANCERS AND CANCER TREATMENTS

Cancer treatments are well known to cause morbidity in cancer survivors. Although the treatments have generally improved to the point that they are both more effective and less debilitating than previously, treatment-related impairments are still common and, in many instances, expected. Studies show that most types of cancers result in decreased work ability in patients, at least during active treatment or in its terminal phase, and that the decreased work ability is often associated not with the progression of the cancer itself, but rather with treatment, treatment-related side effects (also known as toxicities), and comorbidity with other health conditions (Munir et al., 2009). The adverse effects of some treatments can be profound, with serious implications for function and quality of life. At the core of cancer treatments are surgery, systemic therapy, and radiation therapy (RT). Each of these modalities has evolved significantly

in recent years. Systemic therapy, for instance, which historically centered on various combinations of cytotoxic chemotherapeutics, now includes hormonal and biologic (targeted, immune, and gene) therapies. The addition of these new agents has revolutionized the treatment of many types of cancer but has also introduced new types of functional morbidity.

For instance, fatigue and exhaustion are the most frequent problems reported by breast cancer survivors. Fatigue is one of the most important factors that prevent cancer survivors from rejoining the workforce or reduce their capability to work (Islam et al., 2014). Clinically relevant levels of cancer-related fatigue have been seen in approximately one-third of cancer survivors, lasting up to 6 years post-treatment, and this is associated with high levels of disability (Jones et al., 2015). A study by Cheville and colleagues (2008) of 163 patients with metastatic breast cancer found that 92 percent of the patients in the study had at least one physical impairment. Among the identified impairments, 92 percent required a physical rehabilitation intervention, and 88 percent required physical therapy or occupational therapy, or both.

The residual effects of cancer treatments can appear decades after treatment. Certain types of radiation and chemotherapy for breast cancer are associated with an increased risk of developing cardiovascular complications, which may not present until up to 20 years after the cancer treatments (Okwuosa et al., 2017). Use of cisplatin has been shown to increase the risk of cardiovascular events even decades after treatment (Feldman et al., 2018; Herradó et al., 2017). About 58 percent of breast cancer survivors experience chemotherapy-induced peripheral neuropathy (CIPN), which can persist up to 1–3 years after treatment completion, with significant impairment of quality of life (Bao et al., 2016). In some breast cancer survivors CIPN can result in permanent impairment. Likewise, cognitive impairment is common among colorectal cancer survivors who receive adjuvant chemotherapy. Associated impairments include processing speed, verbal memory, and attention or working memory. Studies have shown that the majority will improve after treatment completion (Vardy et al., 2014).

As described in Chapter 1, the definition of "impairment" and its relationship to disability and functioning varies across disciplines. In this section, the committee defines cancer-related impairments as sequelae of cancer that interfere with a person's ability to function.

Time Course and Trajectory of Treatment Effects

The effects of cancer treatment vary profoundly. They may be local or systemic, transient or chronic, functionally irrelevant or profoundly disabling. Many are morbid, and some are mortal. Their natural histories range widely. Some resolve spontaneously over time, such as mucositis, anemia, and alopecia. Those that do not resolve can cause variable degrees of permanent tissue changes that differ in functional impact. The majority of durable treatment effects can be clinically mitigated but not eliminated. Lacking an accepted taxonomy, these treatments effects on healthy tissue are variably referred to as treatment toxicities, side effects, long-term effects, and late effects. Unfortunately, these terms have not been formally defined, a situation that has resulted in inconsistent usage. The situation is made more complex by the fact that some treatment effects engender secondary effects. For example, a hip joint contracture due to radiation-induced scarring may stress the contralateral hip, accelerating the development and progression of osteoarthritis. For clarity and consistency in the chapter, the committee defines *acute side effects* as those that develop during treatment but are transient, *long-term side effects* as those that develop during treatment but are chronic, *late effects* as those that develop after completion of treatment, and *secondary effects* as those that are engendered as a result of acute and long-term side effects.

The need for precise categorical definitions is particularly critical in identifying disabling conditions that may improve with treatment. Most cancer survivors develop multiple effects in all of the aforementioned categories, with their net impact changing progressively over time. Figure 3-4 presents theoretical trajectories for each effect category. By examining various time points on the x-axis, it becomes apparent that multiple evolving processes may co-occur and contribute to an individual's residual treatment burden. Acute side effects may lessen, long-term side effects stabilize, late effects emerge, and secondary effects develop. Determining the relative contributions of each on an individual's ability to engage in gainful employment may be challenging for even seasoned clinicians, particularly as some effects are symptoms that fluctuate over time, such as pain, fatigue, and insomnia.

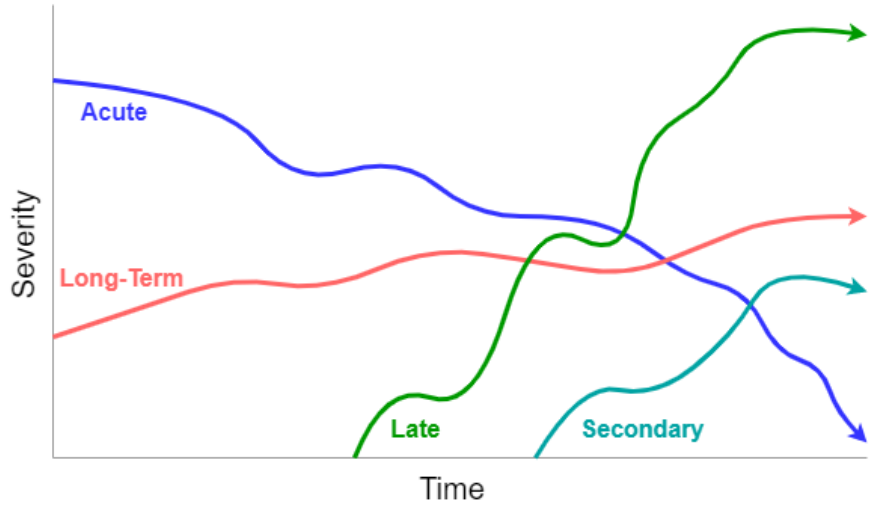

FIGURE 3-4 Theoretical trajectories for acute, long-term, late, and secondary effects of cancer.

The impact of any single effect can be dramatically altered by the nature and number of co-occurring effects. Cross-sectional reports demonstrate that the number of physical impairments and the presence of symptoms potently mediate disability to a greater degree than the presence of any specific impairment (Cheville et al., 2011). Among disease-free cancer survivors, disablement is less often due to a single symptom or impairment than to the toxic interplay and reinforcing effects of multiple mild to moderate issues (Sarfarti et al., 2016). Each effect tends to further erode a survivor's functional reserve, making it difficult for the survivor to engage in or benefit from treatment. For example, fatigue and pain often amplify the impact of weakness and limit patients' participation in rehabilitation treatments (Alfano et al., 2016). More recent models of function and disability, such as the World Health Organization's *International Classification of Functioning, Disability and Health* (WHO, 2002), acknowledge the web of dynamic, interacting factors that drive disability and highlight the difficulty in attributing functional loss to a single toxicity or impairment.

A full accounting of adverse cancer treatment effects is beyond the scope of this report; however, a limited group of impairments and symptoms are common disabling factors across diverse cancer types and stages. The presence and severity of these treatment effects—pain, cancer-related fatigue, cardiotoxicity, CIPN, lymphedema, pulmonary dysfunction, and cognitive dysfunction—are key determinants of whether a survivor is likely to functionally improve with treatment. Anticipating whether a survivor is likely to resume gainful employment and

estimating the interval before he or she can do so requires a comprehensive inventory of residual treatment effects with consideration given to the natural history and treatment responsiveness of each. Table 3-12 presents a matrix of cancers with their associated impairments.

TABLE 3-12 Selected Cancers and Associated Impairments Caused by Cancer or Cancer Treatment

	Impairments						
Cancers	Pain	Lymphedema	Fatigue	Cardiotoxicity	Cognitive Dysfunction	Pulmonary Dysfuction	Nerve Dysfunction
Invasive breast	✓	✓	✓	✓	✓	✓	✓
Cutaneous melanoma	✓	✓	✓	✓	✓	✓	✓
Renal	✓		✓		✓		
sHead and neck	✓	✓	✓		✓	✓	✓
Advanced epithelial ovary	✓	✓	✓	✓	✓	✓	✓
Non-small cell lung	✓		✓	✓	✓	✓	✓
Diffuse large b-cell lymphoma	✓	✓	✓	✓	✓	✓	✓

NOTE: Many impairments are mediated by cancer treatments and are not caused by the cancers themselves (see Table 3-13).
SOURCES: Gamper et al., 2015; Kim et al., 2010; Pachman et al., 2012; Runowicz et al., 2016; Silver et al., 2013.

Table 3-13 shows a matrix of impairments related to particular cancer therapies.

TABLE 3-13 Selected Cancer Therapies and Associated Impairments

	Impairments						
Therapy	Pain	Lymphedema	Fatigue	Cardiotoxicity	Cognitive Dysfunction	Pulmonary Dysfuction	Nerve Dysfunction
Chemotherapy	✓	✓	✓	✓	✓	✓	✓
Hormone therapy	✓		✓	✓	✓		
Immune modulators	✓	•		✓	•	✓	✓
Targeted therapy	✓		✓	✓		✓	
Radiation therapy	✓	✓	✓	✓	✓	✓	✓
Surgery	✓	✓	✓		✓	✓	✓

NOTE: • indicate that the literature does not show a clear linkage at the time of this report.
SOURCES: Amir et al., 2011; Chamberlain, 2010; Giglio and Gilbert, 2013; Glare et al., 2014; Kim et al., 2010; Livshits et al., 2014; Piperis et al., 2012; Stone et al., 2000; Vasiliadis et al., 2014; Wang et al., 2017; Warren et al., 2014; Wilkes, 2018; Wu and Amidi, 2018.

The follow sections describe key symptoms and impairments that have been empirically implicated in cancer-related disablement.

PAIN

Pain is unfortunately prevalent and potentially damaging at all stages of cancer. The most common causes of cancer-related pain are local and remote tumor effects and the cancer treatment itself, although many other causes exist. Chronic musculoskeletal and other types of "benign," non-cancer pain are frequently exacerbated among survivors due to stress, altered kinetics, and deconditioning, among the many other unwelcome changes that characterize the cancer experience. Pain has well-documented erosive effects on all quality-of-life (QOL) domains. Physical and cognitive functions are particularly susceptible to the damaging effects of pain, which affects survivors' ability to work.

Professionally Accepted Diagnostic Criteria for Pain

The diagnosis of cancer-related pain is most commonly made through patient report. Pain assessments are administered to patients via diverse modes including verbal, print, and telephonic questioning as well as via tablets at point-of-care and through web-based platforms and portals. The data collected through these assessments are frequently recorded in patients' medical records, increasingly as structured elements. However, some pain assessments may be solely accessible as unstructured data in providers' notes. Common pain assessment tools include 11-point numerical rating scales, the Brief Pain Inventory (BPI) and the three-item PEG questionnaire that was derived from it, the Patient-Reported Outcome Measurement Information System (PROMIS) pain short forms, and computer adaptive tests (Kean et al., 2016). In addition, many multi-domain QOL assessment tools such as the Functional Assessment of Cancer Therapy (FACT) and the European Organisation for Research and Treatment of Cancer QOL Core Questionnaire 30 include pain-related items that may allow the calculation of pain subdomain scores (Kean et al., 2017; Iravani et al., 2018).

Thresholds at which pain is considered moderate or severe vary across assessment tools. The BPI has been most studied with respect to score strata that indicate pain significant enough to cause problems. For this tool ratings of 1–3 are considered mild, 4–7 moderate, and 8–10 severe (Cleeland et al., 2009). One report noted that pain greater than 5/10 was sufficiently severe to negatively affect patients' function (Zalon, 2015).

Concern that pain may reflect cancer spread or recurrence frequently leads providers to evaluate pain loci with imaging and other tests. Imaging may include plain films, MRI, bone scans, PET, CT, or some combination of these, depending on the pain distribution and quality. Focal neuropathic pain, particularly with co-occurring sensory and motor deficits, may indicate the need for nerve conduction studies and electromyography. More diffuse neuropathic pain may additionally require laboratory tests to assess for a paraneoplastic syndrome. In some cases invasive testing, including biopsy and lumbar puncture, may be needed to determine whether cancer recurrence or progression contributes to a patient's pain. All evaluations strive to identify treatable sources of pain, rather than to inform estimates of pain intensity or its functional interference.

The post-mastectomy pain syndrome occurs more frequently in younger survivors (Tait et al., 2018). Other instances of cancer-related pain that are more common in age- or gender-defined subgroups have not been widely reported.

Cancer pain is treated by medical, radiation, and surgical oncologists. Supportive and palliative care practitioners including nurses, hospice and palliative medicine physicians, rehabilitation service providers (physical medicine and rehabilitation, physical therapists, and occupational therapists), and pain management specialists frequently contribute to pain care among cancer populations. Psychologists and social workers may be available at some centers to provide cognitive behavioral therapy, mindfulness training, and other behavioral pain management strategies. Primary care providers may coordinate pain management, with the assistance of the aforementioned professionals, among disease-free cancer survivors who are no longer in regular contact with their cancer care teams (Nersesyan and Slavin, 2007).

Treatments for Pain

The treatment patterns, clinical responsibility, and team constituencies for the management of persistent pain among cancer survivors are not well defined. The shortage of

oncologists (Yang et al., 2014) and a burgeoning population of cancer survivors makes it clear that there is a need to shift survivorship care from oncology to primary care clinicians. However, this shift has been operationalized with varying degrees of success, making it difficult to determine which discipline is most likely to coordinate pain care. Depending on availability, the clinical disciplines involved in the management of cancer pain may include, in addition to oncology specialties and primary care, physical and occupational therapists, physiatrists, pain management specialists, and orthopedists (Ashburn and Staats, 1999).

Medications are the most commonly used way to treat pain (Paice et al., 2016). As concern has grown about the harms associated with-long term opioid exposure, analgesic use among disease-free survivors has shifted to non-opioid analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs, and topical formulations and to co-analgesics such as anticonvulsants and antidepressants with pain-relieving properties (Swarm and Dans, 2018). Rehabilitative approaches have the potential to concurrently address pain and enhance function among survivors, but reports suggest persistent under-use (Cheville et al., 2018). Interventional analgesic procedures, including local nerve blocks, neuro-axial drug delivery, and spinal cord stimulation, are therapeutic options; however, their use and effectiveness among disease-free cancer survivors is not well characterized. Reports are largely restricted to pilot studies (Karmakar et al., 2014; Wijayasinghe et al., 2016). Multimodal chronic pain management programs have been proven effective in reducing pain and opioid use among diverse clinical populations, including cancer survivors (Pollak et al., 2018). Behavioral pain management approaches including cognitive behavioral therapy and mindfulness-based stress reduction achieve pain relief for some patients. A growing body of evidence suggests that exercise can be effective in relieving pain. For example, three randomized controlled trials show that exercise improved outcomes for women with breast cancer who used exercise to treat their aromatase inhibitor-induced arthralgias (Arem et al., 2016; Baglia et al., 2019; Nyrop et al., 2017;).

Length of Time to Improvement for Pain

The effectiveness of pain treatments may become rapidly apparent. Blocks take effect immediately, or in days to weeks if steroids or botulinum toxin are instilled, respectively. Rehabilitative therapies achieve more gradual effects, but they are generally not continued if the benefit is not apparent within a month or two. Medications are more variable. Opioids and non-opioid analgesics, if appropriately titrated, offer rapid benefit. Co-analgesics may require more protracted titration, but the treatment response should be evident within 2–3 months. Often analgesics are combined to capitalize on their complementary mechanisms of action. Optimizing the doses of a combined analgesic regimen may require a longer interval, though seldom more than 6 months. Opioid use in pain treatment is also discussed in Chapter 2. Patients' responses to behavioral therapies are typically more gradual, and improvement may take one or more months. Multi-modal pain management programs take a similar amount of time for improvement.

Data are not currently available regarding differences in responsiveness to pain management approaches across age groups. Younger women are more likely to develop post-mastectomy pain, but it remains unclear whether they are a more or less likely to respond to treatment (Tait et al., 2018).

Standard Measures of Outcomes for Pain

Cancer pain among survivors is similar to other pain in that it is ultimately a subjective experience that requires reporting by the patient to assess the pain's severity and the response to treatment. The persistence and durability of cancer pain cannot be directly associated with imaging finding or tumor markers. Although imaging is frequently used to identify cancer sites that cause pain, imaging findings may not correlate with pain intensity. Despite clear evidence that patient-reported outcomes accurately and precisely measure pain, they are not routinely captured during the care of cancer survivors, making it difficult to define an individual's trajectory over time and thus challenging to define a length of time from start of treatment until functioning improves. Pain's adverse effects on other quality-of-life domains make assessment of these domains a reasonable surrogate for gauging treatment response when pain ratings are not available. Specifically, mood, sleep quality, function, and social role participation generally improve or deteriorate in parallel with pain intensity (Tavoli et al., 2008; Whibley et al., 2019). Other indicators of treatment response are the types and dosages of pain medicine that an individual consumes during a defined time interval (e.g., 1 day or 1 week).

CANCER-RELATED FATIGUE

Cancer-related fatigue is very common among those treated for cancer, especially patients undergoing treatment with radiation therapy and chemotherapy, with an estimated prevalence of 28 percent to 91 percent (Runowicz et al., 2016). The NCCN guidelines define cancer-related fatigue (CRF) as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (NCCN, 2019h). Compared with the fatigue experienced by healthy individuals, CRF is more severe, more distressing, and less likely to be relieved by rest. An often profound but subjective sense of tiredness is a key feature of CRF, as is its interference with the usual activities of daily living (NCCN, 2019h). CRF is more common with certain malignancies such as pancreatic and breast cancer and lymphoma and is also more common during treatment (Ebede et al., 2017). While gender differences in the incidence of CRF have not been well studied, it is known that older adults report more CRF than younger adults (Butt et al., 2010; Miaskowski, 2004).

CRF is by far the most common symptom affecting people with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or a treatment with biological response modifiers. It is notoriously under-reported, under-diagnosed, and under-treated. In a survey of 1,569 patients with cancer, CRF was found in 80 percent of individuals undergoing chemotherapy or radiation therapy or both (Henry et al., 2008). In patients with metastatic disease undergoing any type of therapy the prevalence of CRF exceeded 75 percent (Curtis et al., 1991; Portenoy et al., 1994; Ventafridda et al., 1990). Moderate or severe fatigue was found in 45 percent of patients undergoing active outpatient treatment and in 29 percent of patients with complete remission from breast, prostate, colorectal, or lung cancer (Wang et al., 2014). A meta-analysis that examined 27 studies of 12,237 breast cancer survivors found that both a more advanced disease stage (II or III versus 0 or I) and chemotherapy treatment were predictors of severe fatigue (Abrahams et al., 2016).

Cancer survivors report that fatigue persists months or even years after the treatment ends (NCCN, 2019h). Persistent CRF affects the qualify of life, as patients become too tired to

participate in daily activities that make life meaningful (Behringer et al., 2016; Crom et al., 2005; Janda et al., 2000). CRF may influence the time it takes to return to work following treatment (Islam et al., 2014). Because of the successes in cancer treatment, health care professionals are now more likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are especially relevant and challenging for patients with cancer who are cured of their malignancy and have continued fatigue (Morrow et al., 2002).

Professionally Accepted Diagnostic Criteria for Cancer-Related Fatigue

Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other data sources. Because it is a symptom perceived by the patient, it can be described most accurately by self-report. Patients should be screened for the presence and severity of fatigue at their initial clinical visit, at regular intervals during and following cancer treatment, and as clinically indicated (Berger et al., 2015). There are multiple instruments available to assess fatigue in the clinical setting (NCCN, 2019h). The Visual Analogue Fatigue Scale is one such instrument that can be quick and easy to administer even in a busy clinical setting (Glaus, 1993). Patients with fatigue should be evaluated for treatable contributing conditions such as pain, depression, anxiety, anemia, sleep disturbance, nutritional deficits, cardiac dysfunction, pulmonary dysfunction, infection, etc. (NCCN, 2019h).

All members of the oncology and rehabilitation teams, including medical oncologists, oncologic surgeons, radiation oncologists, rehabilitation physicians, nurses, physical therapists, occupational therapists, social workers, and psychologists, should take an active part in screening for CRF. Physicians have the responsibility of identifying and treating conditions that can mimic or contribute to CRF such as anemia, depression, and recurrent cancer. Physical therapists, occupational therapists, and exercise physiologists are responsibly for designing and optimizing exercise programs, teaching energy conservation techniques, etc. Social workers and psychologists can teach cognitive behavior techniques and other mindfulness techniques (NCCN, 2019h).

Treatments for Cancer-Related Fatigue

Managing fatigue is integral to the comprehensive management of cancer patients. An interdisciplinary approach that includes not only oncology clinicians but those from rehabilitation (physiatry, physical therapy, occupational therapy), nursing, social work, nutrition, psychology, exercise physiology, and other disciplines is often key to optimizing patient outcomes (Escalante et al., 2001; NCCN, 2019h). Multiple pharmacologic and non-pharmacologic treatments for CRF have been tested in trials. A meta-analysis of 11,525 patients in 113 studies demonstrated that non-pharmacologic interventions, specifically exercise and psychosocial interventions, improved CRF (Mustian et al., 2017).

Length of Time to Improvement for Cancer-Related Fatigue

Relatively little is known about the length of time from the start of a treatment until the person's functioning improves to the point where CRF is no longer disabling. Studies investigating CRF have generally ranged from 4 to 12 weeks in duration (Bower, 2014). By contrast, CRF is well known to persist for years following treatment, with approximately 25

percent to 30 percent of patients experiencing symptoms up to 5 years or longer following the successful completion of oncologic treatment (Ebede et al., 2017).

Standard Measures of Outcomes for Cancer-Related Fatigue

As noted above, patients with CRF should be screened at regular intervals throughout cancer treatment and into survivorship. Tools such as the Visual Analogue Fatigue Scale are useful in monitoring patient improvement (Charalambous et al., 2016).

CARDIOTOXICITY

A number of cancer treatments, including anthracyclines, trastuzumab and other HER2 receptor blockers, antimetabolites, alkylating agents, tyrosine kinase inhibitors, angiogenesis inhibitors, checkpoint inhibitors, and thoracic irradiation, are associated with significant cardiotoxicity (Jain et al., 2017). Cardiac problems such as heart failure, pericarditis, coronary heart disease, hypertension, arrhythmias, and valve disease can occur.

Anthracycline-based chemotherapy, specifically the use of doxorubicin, is a common component of many cancer treatment regimens and is associated with significant dose-dependent cardiotoxicity. A prospective study of 2,625 patients receiving anthracycline chemotherapy demonstrated cardiotoxicity in 9 percent, with 98 percent of the cases occurring in the first year following treatment. Only 11 percent of tbe patients recovered fully; 71 percent had only a partial recovery (Cardinale et al., 2015). The HER−2-targeted therapy trastuzumab is also associated with cardiotoxicity. Between 0 and 4.1 percent of patients receiving trastuzumab-containing regimens experienced Common Terminology Criteria for Adverse Events (CTCAE)-grade III/IV heart failure or cardiac-related death.[26] The alkylating agent cyclophosphamide at the therapeutic dose of 170–180 mg/kg causes dose-related cardiotoxicity in from 7 to 28 percent of patients, with 11 to 43 percent of them experiencing mortality (Iqubal et al., 2019). Tyrosine kinase inhibitors can cause cardiac toxicity ranging from asymptomatic subclinical abnormalities such as electrocardiographic changes and reduced left ventricular ejection fraction to life-threatening conditions such as heart failure and acute coronary syndromes (Orphanos et al., 2009). Angiogenesis inhibitors such as the vascular endothelial growth factor inhibitors can cause left ventricular dysfunction, among other issues (Tocchetti et al., 2013). Multiple cases of myocarditis and fatal heart failure have been reported in patients treated with immune checkpoint inhibitors, either alone or in combination (Varricchi et al., 2017). In Hodgkin lymphoma survivors, radiation therapy to the mediastinum is well known to cause a variety of cardiac abnormalities, including coronary heart disease, valvular heart disease, heart failure, and pericarditis (van Leeuwen et al., 2016). Radiation therapy for breast cancer can cause coronary heart disease in a dose-dependent fashion with the risk increasing linearly as the dose to the heart increases (Jacobse et al., 2019). A variety of new radiation techniques have been developed to treat breast cancer, including deep inspiration breath hold, gating, accelerated partial breast irradiation, and the use of modern three-dimensional planning with the intention of avoiding or minimizing radiation cardiac toxicity (Yeboa and Evans, 2016).

Professionally Accepted Diagnostic Criteria for Cardiotoxicity

The evaluation and management of cancer treatment-related cardiotoxicity is an emerging field. Cardiovascular evaluation with radionuclide imaging, advanced echocardiography, and magnetic resonance imaging is helpful in the early detection of cardiotoxicity and the prevention of overt heart failure (Jain et al., 2017). There is limited evidence to guide clinical decision making with respect to the detection and management of cancer treatment–associated cardiotoxicity (Conway et al., 2015). In general, medical management of the various cardiac toxicities resulting from cancer treatment follows the principles used to treat analogous disorders resulting from other etiologies.

Oncology clinicians, including medical oncologists, surgical oncologists, and radiation oncologists, as well as non-oncologic health professionals such as internists, primary care physicians and nurse practitioners, and rehabilitation physicians are instrumental in the identification of cardiac dysfunction in the cancer setting. The medical management generally falls to cardiologists, internists, or primary care physicians. Rehabilitation management is often a combination of efforts between a rehabilitation physician and some combination of physical therapists, occupational therapists, and exercise physiologists (Alfano et al., 2016).

Treatments for Cardiotoxicity

A comprehensive program of cardiac rehabilitation should include risk factor modification and patient education in addition to exercise and strengthening and psychosocial support. The effectiveness of rehabilitation for patients with coronary artery disease in the non-cancer population has been well established (Simon et al., 2018). The emergence of home-based cardiac rehabilitation may improve access and availability. One study demonstrated that women with breast cancer and treatment-related heart failure who participated in a cardiac rehabilitation program had similar gains in VO2peak and similar completion rates to those with coronary disease from other causes (Bonsignore et al., 2017).

Length of Time to Improvement for Cardiotoxicity

There are no data concerning the interval between the onset of treatment and functional improvement. And while cardiac disease is generally more common with advancing age (Strait and Lakatta, 2013), there is little known about whether there are certain ages where improvement is more probable.

Standard Measures of Outcomes for Cardiotoxicity

The expected benefits of a comprehensive cancer rehabilitation program include improvements in exercise tolerance, skeletal muscle strength, psychological status, and quality of life. Though little literature exists for patients with cardiac disease resulting from cancer treatment, it is likely that similar benefits would be conferred by cardiac rehabilitation (Bonsignore et al., 2017). Cardiotoxicity in the cancer setting is often permanent and progressive (Virizuela et al., 2019). However, cardiotoxicity due to HER–2 directed agents is typically reversible (Dong and Chen, 2018).

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Neuropathy, or peripheral neuropathy, is defined as the condition arising from the damage and dysfunction of the peripheral nerves—the motor, sensory, and autonomic nerves that connect the brain and spinal cord to the rest of the body (Stubblefield et al., 2009). CIPN is peripheral neuropathy that is caused by exposure to neurotoxic chemotherapeutic agents. It is one of the most common side effects of cancer treatment, with a prevalence of 19 percent to 85 percent (Zajaczkowska et al., 2009). In addition to the pain and functional limitations it causes, CIPN can be a major dose-limiting toxicity for many chemotherapeutic agents (Stubblefield et al., 2009).

The signs and symptoms of CIPN range from mild to disabling with significant implications for function and quality of life (Stubblefield et al., 2009). Abnormal sensations including tingling, numbness, and pain are common. Weakness, difficulty with gait, and falls can occur. Patients may have trouble with the activities of daily living. Autonomic dysfunction, including bowel and bladder dysfunction and orthostatic hypotension, can be seen in the more severe cases. CIPN may not resolve; one study found that after an average of 6 years following treatment, nearly half (47 percent) of women treated for breast cancer still reported CIPN (Winters-Stone et al., 2017). Among women with CIPN, those with symptoms were 1.8 times more likely to fall than those without (Winters-Stone et al., 2017).

Chemotherapeutic drugs and anticancer biologics that are frequently reported as associated with symptomatic neuropathy include platinum-based antineoplastic agents, vinca alkaloids, epothilones (ixabepilone), taxanes, proteasome inhibitors (bortezomib), and immunomodulatory drugs (thalidomide) (Argyriou et al., 2014; Zajaczkowska et al., 2009). Many of these medications (e.g., paclitaxel and cisplatin) are used to treat a variety of cancers. For most regimens, the severity of the neuropathy increases with dose and duration until the cessation of the treatment. A notable exception is the platinum agents, for which symptoms may progress for weeks to months after treatment completion—a phenomenon known as the *coasting effect* (Stubblefield et al., 2009). Another exception to the typical pattern of CIPN is oxaliplatin, which is unique in that two patterns have been observed: acute transient (cold-induced) and cumulative persistent (dose-limiting) neuropathy. For most drugs the symptoms of CIPN usually subside with time, although long-term sequelae can occur (Stubblefield et al., 2009).

Professionally Accepted Diagnostic Criteria for CIPN

The diagnosis of CIPN is generally made on clinical grounds. When patients develop the expected signs and symptoms of CIPN in the setting of a known neurotoxin, no additional investigation is generally needed. If the signs and symptoms are outside the norm in terms of clinical features, severity, or the temporal relationship to neurotoxin exposure that is expected for a given agent, then electrodiagnostic studies or appropriate laboratory investigations may be indicated (England et al., 2009). Pre-existing or emerging neuropathy from other causes, such as diabetes or B12 deficiency, and disorders that mimic CIPN, such as carpel tunnel syndrome or radiculopathy, should be excluded (Stubblefield et al., 2009). If further evaluation is warranted, the treating oncology clinician will generally request consultation with a neurologist and physical medicine and rehabilitation physician.

The primary functional issues seen in CIPN can be categorized as sensory (pain, tingling, numbness, loss of proprioceptive sense), motor (weakness), autonomic (orthostatic hypotension,

bowel and bladder dysfunction, sexual dysfunction), or a combination of impaired modalities (gait dysfunction, falls, mobility issues, impaired activities of daily living). While older adults are more likely to develop CIPN, they generally report less pain and interference with activity despite having worse light touch and impairment in sensing cold and vibration (Argyriou et al., 2006; Wong et al., 2019). Gender differences in the development of CIPN have not been observed. However, regional studies have found a higher prevalence of CIPN in women than in to men (Molassiotis et al., 2019; Shah et al., 2018). This difference might be because gynecologic and breast cancers often receive neurotoxic chemotherapies (Zanville et al., 2016).

Because CIPN symptoms may worsen with accumulating exposure, close monitoring is necessary during chemotherapy. In severe cases, a dose reduction or treatment discontinuation may be indicated at the discretion of the treating oncologist, but this must be weighed against the oncologic risks (Stubblefield et al., 2009).

All members of the oncology and rehabilitation teams, including medical oncologists, oncologic surgeons, radiation oncologists, neurologists, rehabilitation physicians, nurses, physical therapist, and occupational therapists, should take an active part in screening for signs and symptoms of CIPN. Physicians have the responsibility of identifying and treating conditions that can mimic or contribute to CIPN such as diabetic neuropathy, lumbar polyradiculopathy, and carpal tunnel syndrome, among others. Physicians can also treat neuropathic and other pain disorders with medications, injections, and other modalities. Physical therapists can design custom programs to improve balance, gait, transfers, endurance, and other capabilities with the goal of improving function and quality of life. Occupational therapists can improve hand dexterity, coordination, and the ability to perform the activities of daily living (Stubblefield et al., 2009).

Treatments for CIPN

The treatment of neuropathy is based on the functional issues present. There are no medications to treat motor abnormalities, but pain and other positive neuropathic symptoms (paresthesias, dysesthesias, allodynia, etc.) may improve with certain medications. A comprehensive outpatient assessment by a physician knowledgeable in the evaluation and management of neuropathy should be done to exclude contributing medical issues. The prescription of physical therapy or occupational therapy to improve strength, mobility, gait, and participation in the activities of daily living is indicated unless a safety issue precludes it. Various pharmacologic agents have been evaluated in the prevention and treatment of CIPN. Drugs that have been approved by FDA have been approved largely based on their efficacy in reducing pain and producing other positive neuropathic symptoms in diabetic neuropathy and post-herpetic neuralgia. With the exception of duloxetine, most clinical trials on the use medications to prevent or treat CIPN have failed to yield positive findings (Majithia et al., 2016; Smith et al., 2013). To date, no agent has been approved specifically for treating CIPN (Stubblefield et al., 2009). Table 3-14 lists the medications commonly used off-label to relieve pain and produce positive neuropathic symptoms in CIPN.

TABLE 3-14 Common Agents for Pain Management in Neuropathy

Drug	Starting Dose	Titration	Maximum Dose	Duration of Adequate Trial	Potential Side Effects
Duloxetine	20–30 mg/day	No evidence that higher dose is more effective	120 mg/day	2 week	Nausea, xerostomia, constipation, diarrhea
Gabapentin*	100–300 mg nightly or 100–300 mg 3 times/day	Increase by 100–300 mg 3 times/day, every 1–7 days	3,600 mg (depending on absorption)	1–2 week at max tolerated dose	Somnolence, dizziness, GI symptoms, mild edema, cognitive impairment (elderly), exacerbation of gait problems
5% lidocaine patch	Maximum of 3 patches daily	Non-applicable	3 patches	2 week	Rash/erythema
Opioids (oxycodone, morphine, methadone)	5–15 mg every 4 hour	Convert to long-acting after 1 week, titrate based on breakthrough use	No ceiling effect	4–6 week	Constipation, nausea, vomiting (self-limited), sedation, confusion, respiratory depression
Pregabalin	25–50 mg 3 times/day	Increase by 50 mg/dose after 1 week	200 mg 3 times/day	Unclear (likely 2–4 week)	Dizziness, somnolence, xerostomia, edema, blurred vision, decreased concentration

Tramadol	50 mg 1–2 times/day	Increase by 50–100 mg/day, individual doses every 3–7 days	400 mg/d (100 mg 4 times/day); elderly 300 mg/day	4 week	Dizziness, constipation, nausea, somnolence, orthostatic hypotension, increased risk of seizure, serotonin syndrome
Tricyclic antidepressants (amitriptyline,* nortriptyline,* desipramine)	10–25 mg nightly	Increase by 10–25 mg every 3–7 days	75–150 mg; may increase if blood level of drug plus metabolite <100 ng/mL	6–8 week; 1–2 week at max dose	Cardiovascular disease (needs screening), anticholinergic effects, interact with drugs metabolized by cytochrome P450 2D6 (e.g., cimetidine, phenothiazine)

NOTES: * Negative results in randomized controlled clinical trials on chemotherapy-induced peripheral neuropathy. GI = gastrointestinal.
SOURCE: Stubblefield et al., 2009. Reproduced with permission.

Length of Time to Improvement for CIPN

The length of time from the start of a treatment to when functioning improves to the point of which the condition is no longer disabling has not been defined for CIPN. The duration of intervention and assessment in pain treatment studies ranges from 1 to 8 weeks. Physical therapy intervention durations of 6 weeks have been reported for CIPN, but the time is likely to vary significantly depending on the patient's needs (Kleckner et al., 2018). Signs and symptoms of CIPN can persist for years or indefinitely in many patients (Winters-Stone et al., 2017).

Standard Measures of Outcomes for CIPN

Pain associated with CIPN can be assessed over time using a visual analog scale for pain. Patient-reported outcome measures such as the Karnofsky Performance Scale (KPS) or the CTCAE are commonly used to assess patient function (Kaplow and Iyere, 2017; Miaskowski et al., 2018).

LYMPHEDEMA

Lymphedema is a late or long-term side effect of cancer that is caused by the compromise of lymph nodes or vessels during cancer treatment. The condition is characterized by progressive swelling of one or more body parts. Lymphedema is incurable but can be indefinitely managed with treatment. Left untreated, lymphedema tends to progress leading to pain, disability, and medical morbidities including recurrent cellulitic infections and unhealing wounds. The progression is due to the accumulation of proteinaceous debris in the interstitium, which in turn sequentially produces inflammation, scarring, and worsened lymphatic obstruction. As lymphedema progresses, it is marked by the enlargement and eventual hardening (keratinization) of the affected tissues. Lymphedema-related functional loss might impede the ability to work for some patients, depending on the affected body parts, the patient's occupation, and the severity. For example, an inability to stand for extended periods without exacerbating the condition may severely restrict the employment options of patients with leg lymphedema. Additionally, patients

who develop recurrent cellulitis may be unable to hold jobs due to frequent and unplanned medical absences.

While many factors have been associated with the onset and progression of lymphedema, the surgical removal and irradiation of lymph nodes to stage or locally control cancer are its principal cause in the context of cancer treatment (Armer et al., 2019; Nguyen et al., 2017; Rockson, 2018). Cancer survivors develop lymphedema in predictable distributions based on the location and degree of their lymphatic compromise. Because specific lymph node beds are commonly targeted in the treatment of particular cancers, lymphedema occurs in consistent distributions among survivors of breast, prostate, and gynecologic cancers as well as melanoma, lymphoma, and some sarcomas. Secondary lymphedema is also a frequent late effect in patients with head and neck cancer (Deng et al., 2012, 2019; Smith et al., 2015). For example, patients treated for melanoma of the legs typically undergo removal of their inguinal lymph nodes, which places them at risk for lymphedema of the leg and of the external genitalia. The degree to which lymphedema conforms to an anticipated distribution based on cancer type has prognostic significance. Swelling outside the implicated lymph drainage territory suggests an alternative, possibly systemic, etiology and a lower likelihood of response to lymphedema therapy (Sleigh and Manna, 2019).

The current understanding of cancer-related lymphedema's natural history derives largely from observational studies of patients with breast cancer. This subgroup has proven conducive to study because they are numerous and generally have an uninvolved upper extremity for comparison. Incidence rates vary contingent on the lymphedema diagnostic criteria and cancer treatment specifics, ranging from 5 percent, after sentinel node procedures to as high as 25–40 percent following full axillary dissection with radiation (Armer and Stewart, 2005; Norman et al., 2009). Robust reports suggest that lymphedema develops within 3 years of breast cancer treatment, with a majority of patients presenting by 2 years (Garza et al., 2017; Norman et al., 2009). Some patients develop lymphedema during cancer treatment, but for many acute swelling occurs only transiently after surgery, if at all.

Incidence rates also vary by the type and extent of cancer treatment, with the use of radiation and the number of lymph nodes surgically removed being principal risk factors. Many patients, e.g., those with gynecologic and prostate cancers, have undergone removal of their pelvic lymph nodes and are therefore at risk for lymphedema involving both legs, their lower trunks, and genitalia. Accelerated lymphedema progression in legs versus arms is due to the increased demands of vertically transporting metabolic waste from the large lower extremity muscle groups against gravity (Vagas and Ryan, 2003).

Functional morbidity associated with lymphedema following cancer treatment varies considerably and depends on a host of factors. Research has not yet identified lymphedema characteristics that are consistently associated with functional morbidity. As a consequence our current understanding that late-stage lymphedema is more functionally morbid derives from anecdotal clinical experience. Lymphedema of the lower extremities, because of its more rapid progression to advanced stages, causes a higher frequency of cellulitis, wounds, and other morbidities and is therefore assumed to be more disabling. Patients with comorbid vascular insufficiency or obesity are also more likely to develop morbid, late-stage lymphedema and, presumably, disability.

Professionally Accepted Diagnostic Criteria for Lymphedema

Symptoms of heaviness and aching characterize the initial onset of lymphedema, particularly following activity. The symptomatic period that precedes objective swelling is referred to as stage 0 lymphedema and may be exceedingly brief or prolonged. The eventual appearance of soft-tissue swelling indicates progression to stage 1 lymphedema. The swelling initially fluctuates, often with transient periods of complete resolution. It is common for lymphedema to involve limited portions of an affected extremity or body part. Breast cancer-related lymphedema of the arm, for example, often involves the dorsum of the hand and tissue around the elbow with relative sparing of the intervening areas. Ultimately, swelling becomes constant and progresses to stage 2 lymphedema. The transition from stage 1 to stage 2 indicates the presence subdermal fibrosis and scarring and can be discerned by the presence of rubbery tissue deposits that do not alter with changes in swelling. Progression to stage 3, the most advanced, is characterized by keratinized, thickened skin, often appearing first over the most involved portions of a limb (Sleigh and Manna, 2019)

The hallmark of lymphedema is the presence of enlarged or redundant soft tissue overlying the affected body part and associated with skin changes and symptoms of heaviness and aching. Because limb volume is relatively straightforward to measure, volume measurements are a principal means by which lymphedema may be diagnosed. However, absent pre-treatment volume measurements which allow an estimation of change over time, reliance on volume as a sole diagnostic criterion may lead to under-diagnosis. A physical examination by an experienced clinician to screen for changes in tissue texture, pitting, deviation from normal limb contour and architecture, and thickening and hardening of the skin, also referred to as dermal metaplasia, is arguably the most accurate means of diagnosis. Diagnostic testing may include evaluations to identify alternative causes of swelling such as venous obstruction and insufficiency. Lymphoscintigraphy to assess lymph flow is the most widely available means of assessing lymphatic function. An abnormal lymphoscintigram confirms lymphedema in most cases

A higher proportion of women develop cancer-related lymphedema, principally because they develop cancers (i.e., breast and gynecological) whose treatment involves lymph node removal. There is currently no evidence of a gender difference in lymphedema incidence among patients for head and neck cancer or melanoma, malignancies whose treatment also requires lymph node removal. The age of lymphedema onset is tightly linked to the age of the cancer diagnosis. Some reports have associated advanced age with lymphedema risk, but this finding has not been consistent.

Lymphedema treatments are most often delivered by certified lymphedema therapists and physical therapists with lymphedema therapy training. Ideally these individuals should have undergone training and received certification from the Lymphology Association of North America. Physicians may participate in lymphedema management, but specialists are few and generally situated at specialty centers. Most often, the physician's role is restricted to excluding diagnoses that can mimic lymphedema, confirming a diagnosis of lymphedema, and referring patients to therapy. Because lymphedema receives scant attention in medical training, physicians may be unaware of the importance of identifying therapists with complex decongestive therapy training (Garza et al., 2017). A positive notation of lymphedema in a physician's documentation is generally an accurate reflection of the diagnosis. However, an absence of mention or a negative mention does not necessarily rule out a diagnosis of lymphedema. Primary care physicians, physical medicine and rehabilitation physicians, and vascular surgeons as well as cancer care providers may oversee lymphedema management. Some medical centers have

survivorship clinics staffed by cancer care providers, internists, and advanced practice providers, among other clinicians who participate in lymphedema detection and treatment. Apart from lymphedema therapists and physical therapists, clinicians do not generally administer lymphedema treatments. Plastic surgeons who perform lymphovenous bypass and vascularized lymph node transplant surgeries are an exception (Garza et al., 2017).

Treatments for Lymphedema

Lymphedema can be managed but not cured (Shaitelman et al., 2015). The current international standard of care is a two phase treatment system that involves reduction (phase 1) and maintenance (phase 2), which is referred to as complete or complex decongestive therapy (CDT). When it is detected early, survivors' lymphedema may only require maintenance care. Maintenance generally involves the daytime use of compression garments of appropriate type, size, and pressure. Because such garments are not consistently covered by federal and commercial payers, many patients either go without or replace their garments infrequently. Survivors who are initially diagnosed with advanced lymphedema require initial intense lymphedema therapy (i.e., complete decongestive therapy [phase 1]). Although it is remarkably effective when delivered at optimal intensity (1–2 times daily for up to 2 weeks), reductive CDT treatment commonly occurs at less frequent intervals, often only twice per week for up to 4 to 8 weeks. Therefore, while lymphedema, irrespective of the body part, improves with guideline-concordant treatments, these are not available to a majority of patients. Treatment should also include cellulitis prevention which is done by reducing microbial skin growth and, in case of recurrent infections, antibiotic prophylaxis. Various types of pneumatic pumps have been used as adjuncts to CDT. Their use as sole treatment is generally regarded as inappropriate and inferior to CDT. However, pumps may improve CDT outcomes for some patients when used as adjunctive treatments (Aldrich et al., 2016; Szuba et al., 2002). Exercises done against resistance to improve muscle bulk and quality in the affected territory are also a common adjunct.

At present medications are not indicated in the treatment of lymphedema. Diuretics are commonly prescribed to patients, particularly with lower extremity lymphedema, but their use is not guideline endorsed or evidence based. Several microsurgeries, including lymphovenous bypass and vascularized lymph node transplant, have gained traction over the past decade as a means of further temporizing lymphedema. These surgeries do not necessarily cure lymphedema or obviate the requirement that patients wear compression garments (Garza et al., 2017). Long-term surgical outcomes are currently being studies, and these surgeries are not endorsed by current guidelines (Garza et al., 2017).

Lymphedema treatments are most often delivered at physical therapy and occupational therapy facilities, which may or may not be affiliated with larger health systems. Increasingly oncology care providers are mandated to ensure that patients are able to access rehabilitation services (Silver et al., 2018). However, it is not yet clear whether this will lead to an increase in their onsite provision of lymphedema services. Plastic surgeons who perform lymphedema surgeries are often situated in large medical centers to ensure sufficient volume for their specialty practices.

Cancer survivors are identified for treatment through various routes. Some cancer centers screen for lymphedema using volume measurements or patient-reported outcomes, but this is not a standardized practice. Patients with cancer are increasingly educated about the possibility of developing lymphedema. As a consequence, many self-refer to lymphedema specialists if they

note swelling or else bring the swelling to the attention of their primary or oncological care teams.

Length of Time to Improvement for Lymphedema

Volume reduction typically occurs rapidly, over 2–4 weeks, when CDT is appropriately administered at adequate frequency, once to twice daily. The resolution of dermal keratinization and interstitial fibrosis typically lag, but some improvement should be expected within 2–4 weeks of initiating appropriate CDT.

Standard Measures of Outcomes for Lymphedema

Treatment response is typically monitored using changes in limb volume, estimated either by a formula that incorporates serial limb circumference measurements or by optoelectric or water displacement volumetry (Deltombe et al., 2007). Bioimpedance is used to detect and assess lymphedema of the arms and, more recently, the legs. However, the cost of the necessary equipment has been an impediment to broad uptake. A physical examination to characterize normalization of limb contour, improvements in tissue texture, and resolution of dermal metaplasia is essential to a comprehensive assessment. A physical examination may additionally evaluate improvements in wounds, lymphorrhea (seepage of lymph through intact skin), and microbial skin colonization. An additional marker of treatment response is the frequency of cellulitic infections, which should reduce with effective therapy (Al-Niaimi and Cox, 2009).

Several patient-reported outcomes have been validated to assess the function and quality of life in individuals with lymphedema. However, their use has, similarly, not been mainstreamed. When available they may reflect treatment success or failure. Generic and cancer-specific patient-reported outcomes, which are routinely collected in some oncologic and rehabilitation practices, evaluate domains (e.g., pain and function) that may improve with lymphedema treatment. Absent lymphedema-specific tools, these patient-reported outcomes may help to clarify whether a patient has improved with treatment.

PULMONARY DYSFUNCTION

Chronic lower respiratory disease is the fourth-leading cause of death in the United States behind heart disease, cancer, and unintentional injuries (Murphy et al., 2008). Because of this high prevalence, pre-existing pulmonary disease is present in many cancer patients and may develop or worsen during treatment and survivorship. Lung cancer is the second most common cancer for both men and women and the leading cause of cancer-related death for both sexes (ACS, 2019b). Additionally, the lungs are a primary site for metastatic disease. Lung metastases can be seen in 57 to 77 percent of breast cancer patients and nearly half of colorectal cancer patients who succumb to their disease (Kindler and Shulman, 2001).

A number of cancer treatments can cause pulmonary dysfunction with severity ranging from mild to life threatening (Stubblefield, 2018). Toxicity includes bronchospasm, interstitial lymphocytic or eosinophilic pneumonitis, non-cardiogenic pulmonary edema due to increased vascular permeability, and late pulmonary fibrosis. The time course of toxicity is generally divided into early (immediate to 2 months after therapy) and late (2 or more months following completion of chemotherapy) (Garipagaoglu et al., 1999). The best known cause of pulmonary

fibrosis is bleomycin, which causes toxicity in about 10 percent of treated patients with a mortality rate of 1–2 percent (Abid et al., 2001). Tyrosine kinase inhibitors, a relatively new treatment modality for many cancers, are associated with pulmonary toxicity with an incidence ranging from 0.2 percent to 10.9 percent (Peerzada et al., 2011). Radiation therapy can cause extrinsic (kyphoscoliosis, chest wall fibrosis, phrenic nerve paralysis) or intrinsic lung disease. Acute radiation-induced lung injury manifests as radiation pneumonitis. Radiation pneumonitis develops in approximately 5–15 percent of patients who receive high-dose radiation for lung cancer and in 10–20 percent of individuals receiving chest radiation for other tumors (Garipagaoglu et al., 1999; Roach et al., 1995). Late radiation-induced lung injury typically presents as pulmonary fibrosis (Hanania et al., 2019). The incidence of serious radiation-induced pulmonary complications has decreased secondary to advances in radiation delivery techniques. An understanding of the relationship between when and how radiation was delivered and the clinical manifestations will help distinguish radiation-induced injury from other etiologies. The treatment of acute pneumonitis is dependent on its clinical severity, and ut typically responds completely to corticosteroids. Identifying and effectively treating patients who may progress to fibrosis remains a challenge (Hanania et al., 2019).

Professionally Accepted Diagnostic Criteria for Pulmonary Dysfunction

The diagnosis of cancer and treatment-related pulmonary dysfunction is initially based on the patient's history, symptoms, physical examination, and diagnostic testing. An evaluation of blood gases is useful in assessing oxygen and carbon dioxide levels. Imaging, such as chest X-ray and CT, is often helpful for identifying tumors, effusions, and fibrosis. Pulmonary function tests are a non-invasive method of testing such lung functions as volume, capacity, flow rates, and gas exchange, facilitating the diagnosis of obstructive and restrictive disorders. Bronchoscopy allows for a direct visualization and biopsy of lung tissue (NCCN, 2019g).

Oncology physicians, including medical oncologists, surgical oncologists, and radiation oncologists, as well as non-oncologic physicians such as internists, primary care physicians, and rehabilitation physicians are instrumental in the identification of pulmonary dysfunction in the cancer setting. The medical management of pulmonary dysfunction generally falls to pulmonologists, internists, or primary care physicians. Rehabilitation management is often a combination of efforts between a rehabilitation physician and some combination of physical therapists, occupational therapists, and exercise physiologists.

Treatments for Pulmonary Dysfunction

The treatment of cancer and treatment-related pulmonary disease varies considerably by type. A pulmonologist with knowledge and experience in evaluating and managing such complications is generally best equipped to help cancer survivors achieve optimal outcomes. Pulmonary rehabilitation (PR) is an evidence-based, multidisciplinary comprehensive exercise program designed to benefit patients with symptomatic chronic respiratory dysfunction (Rivas-Perez and Nana-Sinkam, 2015). The goal of PR is to optimize pulmonary function and improve a patient's ability to function despite the disease. PR integrates education and exercise that is individualized to the patient's needs. A standard protocol for PR includes three 30- to 90-minute sessions per week of aerobic exercise and strength training carried out for 6–8 weeks. Training modalities may include a treadmill, a stationary bicycle, NU-Step, upper body resistance training, and training in breathing techniques. Evidence suggests that PR is safe and effective

before, during, and after lung cancer treatment (Rivas-Perez and Nana-Sinkam, 2015). While PR has been found to improve exercise capacity and quality of life in idiopathic pulmonary fibrosis patients, the benefits of PR in radiation-induced pulmonary fibrosis have not been well evaluated (X. Yu et al., 2019).

Length of Time to Improvement for Pulmonary Dysfunction

The length of time from the start of treatment for cancer and treatment-related pulmonary disease to where a patient's functioning improves to the point where the condition is no longer disabling has not been specifically evaluated. In many cases, pulmonary disease resulting from cancer and its treatment is permanent and progressive.

Standard Measures of Outcomes for Pulmonary Dysfunction

Pulmonary function tests provide an objective measure of pulmonary function that can be monitored over time. Patients' self-reports of overall function can be measured with the KPS. The CTCAE is also often used by oncologists to monitor patient pulmonary function.

COGNITIVE DYSFUNCTION

Cognitive dysfunction (CD) is a common consequence of cancer and its treatment. CD is often the presenting symptom of a brain tumor (Ozawa et al., 2018). More than 90 percent of patients with gliomas will demonstrate significant cognitive deficits in at least one domain (Tucha et al., 2000). CD can result from direct brain involvement by primary CNS lymphoma, brain metastases, or leptomeningeal disease. In addition, neurologic complications associated with brain cancer, including seizures, increased intracranial pressure, hydrocephalus, and stroke, can cause CD.

It is widely accepted that cancer treatments can also result in CD. The overall incidence of CD in cancer survivors without central nervous system involvement, including breast, prostate, cervical, and colorectal cancers, ranges from 17 to 75 percent (Jean-Pierre and McDonald, 2016). CD in cancer survivors was previously thought to be caused by to psychological distress or by cancer side effects such as fatigue because chemotherapy was not believed to cross the blood–brain barrier. Howver, recent evidence controlling for psychological factors and cancer side effects—and, more recently, functional neuroimaging studies—have found evidence for persistent cognitive changes following chemotherapy and other forms of cancer treatment (Ahles and Saykin, 2007). This phenomenon is known colloquially as "chemo brain." Radiation therapy is also well known to cause CD (Wilke et al., 2018).

Attention, memory, and executive functioning are the most frequently identified cognitive domains affected by cancer and its treatment (Pendergrass et al., 2018). Cognitive symptoms have a profound impact on function, independence, and quality of life and are often cited by patients and caregivers as having the greatest negative impact on quality of life when compared with physical or other neurologic symptoms.

Professionally Accepted Diagnostic Criteria for Cognitive Dysfunction

Following the exclusion and treatment of medical causes of CD, neuropsychological evaluation is helpful in identifying CD, assessing its severity, and determining the specific impairments so that treatments can be targeted effectively

All members of the oncology and rehabilitation teams, including medical oncologists, oncologic surgeons, radiation oncologists, rehabilitation physicians, nurses, physical therapists, occupational therapists, social workers, and psychologists, should take an active part in screening for cognitive dysfunction. Physicians have the responsibility of identifying and treating conditions that can mimic or contribute to cognitive dysfunction, such as cerebrovascular disease, dementia, depression, and brain metastases, among others. Neuropsychologists and others can perform detailed neurocognitive assessments. Rehabilitation programs designed to adapt to cognitive deficits can be performed by neuropsychologists, occupational therapists, speech language pathologists, and social workers.

Treatments for Cognitive Dysfunction

A cognitive rehabilitation program is intended to enhance patients' neurocognitive functioning, specifically their memory, attention, language, visuospatial, and executive function abilities (Weller et al., 2014). Cognitive behavioral therapy and neuropsychological/cognitive training may help improve symptoms of CD in cancer survivors (Fernandes et al., 2019; Sleight, 2016). In addition to neuropsychologists, occupational therapists and speech language pathologists are often trained to evaluate and treat CD in cancer survivors.

Length of Time to Improvement for Cognitive Dysfunction

The time from initiation of treatment until persons with cancer or treatment-related CD improve to where they are no longer disabled has not been defined. Cognitive rehabilitation programs generally run for several weeks and, although generally helpful, might not return a cancer survivor to their pre-treatment level of cognitive functioning.

Standard Measures of Outcomes for Cognitive Dysfunction

A variety of neurocognitive assessments are available to assess improvement or deterioration of cognitive function in cancer survivors (Lange and Joly, 2017). Cognitive functioning can be assessed objectively with cognitive tests and subjectively with self-report questionnaires. Cognitive complaints can be assessed by the FACT–Cognitive Function questionnaire, which was developed from interviews with expert clinicians and oncology patient focus groups. The International Cognition and Cancer Task Force recommends using some neuropsychological tests that assess the most objective impaired cognitive domains in patients with cancer. However, in practice these tests are rarely able to establish the differential diagnosis between chemotherapy-related cognitive impairment and neurodegenerative disease (Lange and Joly, 2017). Another instrument to measure cognitive dysfunction is the physician-reported Everyday Cognition scale (Oh, 2017); this questionnaire has been validated for use in the assessment of dementia, and is not commonly used in cancer research and practice (Farias et al., 2011).

NEW AND DEVELOPING CANCER TREATMENTS

The development of anticancer drugs has changed radically from designing chemotherapies to maximize damage to cancer cells to developing therapeutics based on our greater understanding of tumor biology. Current strategies hope to remove the basic function of the cancer cells while sparing normal cells and limiting toxicities. New approaches for drug discovery now involve immunomodulatory agents and drugs that target proliferation, angiogenesis, and growth-signaling pathways as well as targeted therapies that can be used as single agents or in combination with chemotherapeutic agents and radiation therapy (Ramaswami et al., 2013). The most recent advances in cancer treatment now involve genetic profiling, targeted medicine, and immunotherapy. Contemporary tumor profiling techniques tend to be in the area of "precision" or "personalized" medicine.

Precision Medicine

Breakthroughs in technology have dramatically improved our understanding of many molecular etiologies of cancer including genomic, transcriptional, proteomic, and epigenetic aberrations and immune mechanisms. This research has led to the concept of "precision medicine" based on a personal approach to treatment. Precision medicine, also known as "personalized medicine," allows oncologists to select treatments that are most likely to help patients based on a genetic understanding of their disease. (NCI, 2019c). Specific treatments are designed to individualize care using the genetic changes in a patient's own tumor.

Genetic Therapy

Genomic profiling is increasingly used in the management of cancer. One of the first studies to use personalized medicine for treating cancer was the IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy) Study, a precision medicine program at the University of Texas MD Anderson Cancer Center for patients with advanced cancer (ASCO, 2018). The approach involves the use of tumor molecular profiling and treating patients with matched targeted therapy. Results have been encouraging in terms of the rates of response, progression-free survival, and overall survival compared with non-matched therapy (Tsimberidou, 2017; Tsimberidou et al., 2017). Using next-generation sequencing to profile the tumor, the therapy can be optimized to provide treatment for patients with difficult-to-treat cancers. In the IMPACT study, the targeted therapy resulted in slower cancer growth and prolonged survival across a diverse set of cancer types, including gastrointestinal cancer, gynecologic cancer, breast cancer, melanoma, lung cancer, and thyroid cancer (ASCO, 2018).

Although treatment for breast cancer has evolved significantly in the past several decades, gene therapy has emerged as a promising treatment strategy as research has explored the possibility of correcting defective genes and modulating gene expression (McCrudden and McCarthy, 2014; Stoff-Kahlili et al., 2006). In a review of gene therapy's potential to affect breast cancer research, Bottai and colleagues (2017) noted that further efforts will be required to increase the clinical application of RNA interference-based therapeutics, especially in combination with conventional treatments. Innovative strategies, including genome editing and stem cell-based systems, may contribute to translating gene therapy into clinical practice. Major challenges involving safety, the efficiency of delivery systems, immunogenicity, and functionalization must still be overcome before considering gene therapy as a concrete option for the treatment of cancer patients.

Targeted Therapy

Research in the field of targeted therapy has most frequently involved a very specific tumor type identified for a very specific treatment. For example, targeted therapies for NSCLC have included the gene for epidermal growth factor receptor (EGFR). Therapies targeting genes including EGFR have consistently demonstrated improved response rate (56–83 percent) and progression-free survival (9–14 months) than standard chemotherapy in patients with advanced disease (Maemondo et al., 2010; Mitsudomi et al., 2010; Sequist et al., 2013). It has been suggested that targeted therapies could be used as single agents or, in some cases, in combination with chemotherapeutic agents and radiation therapy (Ramaswami et al., 2013). Ultimately, access to molecular testing and treatment will be the key to realizing the benefits of precision oncology— the premise that treatment choices tailored to individual patients using personalized cancer genomic data may markedly improve outcomes—at a population level (Del Rivero et al., 2016).

To address some of the limitations of targeted gene therapy, including its high toxicity and high cost as well as the genetic heterogeneity of tumors that can lead to drug resistance, efforts have been made to identify broad-spectrum therapies (Block et al., 2015). This involves the development of a low-toxicity "broad-spectrum" therapeutic approach that could simultaneously target many key pathways and mechanisms. While still in development, approaches using natural products and phytochemicals may play an important role in integrative oncology to improve patients' quality of life as well as their lifespan.

Immunotherapy

Immunotherapy, which was briefly described earlier as it is becoming a more common practice, refers to a biological treatment (using substances made from living organisms to treat cancer) which helps an individual's own immune system fight cancer (NCI, 2019d). These treatments can either help the immune system attack cancer directly or stimulate the immune system in a more general way. The National Cancer Institute lists several types of immunotherapies:

- *Checkpoint inhibitors* are drugs that work by releasing the "brakes" that are keeping T cells (lymphocytes that play a central role in immune response) from killing cancer cells, thus interfering with the ability of cancer cells to avoid immune system attack.
- *Adoptive cell transfer* attempts to boost the natural ability of T cells to fight cancer. T cells are removed from a tumor, and the most aggressive ones are grown in the lab to be returned to the patient as an active agent.
- *Monoclonal antibodies*, also known as therapeutic antibodies, are immune system proteins produced in the lab. These antibodies are designed to attach to specific targets found on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system, and this is a type of immunotherapy. Other monoclonal antibodies that are used in cancer treatment do not cause a response from the immune system. Such monoclonal antibodies are considered to be targeted therapy, rather than immunotherapy.
- *Treatment vaccines*, which work against cancer by boosting one's immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.

- *Cytokines*, primarily interferons (IFNα, IFNβ, and IFNγ) and interleukins (IL-2), are proteins that enhance the immune system's ability to respond to cancer. IFNα and IFNβ are involved in innate immune response and increase the resistance of normal cells to natural killer cells and make cancer cells more vulnerable to killing by cytotoxic T cells. Interleukin-2 (IL-2) stimulates activity of T cells to enhance their antitumor activity (Chemoth.com)

Immunotherapy, particularly antibody-based treatments, has revolutionized the medical approach to non-small-cell cancer (NSCLC) therapies for a small number of individuals with curable disease (Corrales et al., 2018; Guillon et al., 2017; Somasundaram and Burns, 2017). Since the first monoclonal antibody was approved in the mid-2000s (Sandler et al., 2006), new therapies have continued to emerge, improving survival for patients (Guillon et al., 2017). In November 2016 the results of the KEYNOTE-024 trial showed for the first time the superiority of immunotherapy over chemotherapy as a first-line treatment for NSCLC (Reck et al., 2016). In this phase 3 trial, a humanized monoclonal antibody against programmed death was tested in patients who had previously untreated advanced NSCLC. The clinical trial was stopped by the safety monitoring committee on the basis of the substantial clinical benefit of the immunotherapy. In addition, two classes of ICIs have been found to be effective against a variety of malignancies (Schvartsman et al., 2016). Another type of drug that shows promise, CAR-T cell therapy, takes the adoptive cell transfer approach. Until recently, the use of CAR-T cell therapy has been restricted to small clinical trials of patients with advanced blood cancers. These therapies have had remarkable responses in patients for whom other treatments proved ineffective. In 2017, two CAR T-cell therapies were approved by FDA—one for adults with advanced lymphomas, and another for children with acute lymphoblastic leukemia (NCI, 2019d).

Immunotherapies have also been shown to be effective in treating melanomas, including disseminated melanoma for which there is currently no single or combination chemotherapy that has been shown to prolong survival. Several studies have found ICIs, particularly the CTLA-4 and PD-1 blocking antibodies, to act by blocking an innate negative regulation of T-cell activation and response, allowing the immune system to attack the tumor, although serious toxicities may occur (Hodi et al., 2010; Larkin et al., 2015; Robert et al., 2015a,b). As there is growing evidence that tumor mutational burden is a strong independent predictive factor for the efficacy of immunotherapies (Hugo et al., 2016; McGranahan et al., 2016; Snyder et al., 2014), researchers are now addressing the effect of immunotherapy regimens in patients with melanoma with specific germlines such as CDKN2A mutations (Helgadottir et al., 2018). Other strategies have been to combine immune checkpoint inhibitors to improve melanoma outcomes (Khair et al., 2019). Similarly, combining immunotherapies with targeted therapies has also been recommended (C. Yu et al., 2019).

Recent advances in immunotherapies, specifically checkpoint-based treatments, have also been made in breast cancer, especially in difficult to treat types. In 2018, the results of the IMpassion130 trial showed a substantial overall survival benefit in patients with PD-L1-positive (PD-L1+) metastatic or inoperable locally advanced triple-negative breast cancer through the addition of the anti-PD-L1 agent atezolizumab to first-line chemotherapy (Schmid et al., 2018). The FDA has approved several new immunotherapies for use in cancer patients in the past year, including atezolizumab combination for lung cancer and triple-negative breast cancer, and pembrolizumab for head and neck cancer, first-line treatment of lung cancer, and pre-surgical treatment for advanced melanoma (Cancer Research Institute, 2020). The success of precision

medicine to date provides the promise of strategies to come that will increase response, remission, survival, and the quality of life for cancer patients.

VARIATIONS IN TREATMENT RESPONSE

The response to treatments and the periods of disability caused by cancer progression or by toxicities of cancer treatment will differ considerably by cancer site, cell subtype, treatment, and individual characteristics. Some patients with cancer will die quickly with a short period of disability. Others will experience disability associated with their treatment or go into remission and not experience symptoms for some period of time. As an example of variation by cancer site, thyroid cancers and skin cancers were given as examples of cancers in the committee's Statement of Task but were not among the committee's selected cancers as they are unlikely to be disabling. Studies show a very low risk of disabling effects for patients with thyroid cancer, a recurrence rate of less than 1 percent, and a low chance of needing treatment. In fact, a paper published by Nikiforov et al. in 2016 recommended renaming "thyroid cancer" to "noninvasive follicular thyroid neoplasms with papillary-like nuclear features." Most people with melanoma, the most disabling type of skin cancer, are cured by their initial surgery. Invasive melanoma accounts for 1 percent of all skin cancers diagnosed (ACS, 2019c). Nonmelanoma skin cancer, also known as keratinocyte carcinoma (KC), is the most common type of skin cancer. The incidence of KC is difficult to estimate because cases are not required to be reported to cancer registries. Almost all cases of KC can be cured (ACS, 2019c). On the other hand, metastatic pancreatic adenocarcinoma is highly lethal and disabling, and was not among the committee's selected cancers as it is unlikely to improve with treatment. Few effective treatments exist for this malignancy, and many patients die within 5 years of diagnosis (Rossi et al., 2014).

Importantly, the originating organ system of the cancer often does not predict the amount or duration of disability an individual patient should experience. Within cancers of a specific organ system, there are differences by specific cancer cell type and by cancer stage. For example, triple-negative[2] invasive breast cancer is much more aggressive and has lower survival rates than other invasive breast cancer cell types. Another example is that although most thyroid cancer is detected at an early stage and the long-term survival is high, anaplastic thyroid cancer is very aggressive with limited treatment options and thus results in a short life expectancy. Other causes of variance are the different treatments available for each cancer and the fact that patients react differently to available treatments for a variety of reasons.

Newer, more effective treatments in the paradigm of precision medicine work on specific subsets of cancer with genomic alterations not shared by all cancers of that category. Three to 5 percent of all NSCLC carry an ALK gene mutation and respond to a targeted agent crizotinib. The committee considered new treatments that may improve life expectancy and functioning. These treatments result in sustained benefit for only a subset of patients.

Variation in Treatment Response by Age

The committee's Statement of Task included an item on "specific ages where improvement is more probable" for the treatments discussed. There is a small literature documenting differences in response to cancer treatment by age. This section describes the few

[2] "Triple negative" refers to cancer tumors lacking the three most common types of receptors related to breast cancer–estrogen, progesterone, and the HER–2/neu gene.

studies that the committee identified related to this topic. One therapy that does show variation in response by age is immunotherapy, which is not surprising, given that aging is associated with profound changes to the immune system (Weyand and Goronzy, 2016). However, the direction of the relationship appears to vary by treatment and cancer site. A study by Kugel and colleagues (2018) found in an analysis of more than 500 patients at different cancer centers with metastatic melanoma treated with the immune checkpoint inhibitor pembrolizumab that older people with melanoma appeared to respond more efficiently to treatment than younger people. More people aged 62 or older had tumor shrinkage or stable disease after pembrolizumab treatment than did people younger than 62. For every decade of age, the probability that a patient was resistant to pembrolizumab dropped by 13 percent, with no difference by gender. The researchers then followed up with a study in mice to observe the physiologic pathways. The results of the mouse study mirrored that of the observational study in human patients and suggested that the pattern might be in part due to an age-related shift in the types of immune cells found in melanoma tumors (Kugel et al., 2018). Another team of researchers (Sceneay et al., 2019) used mouse models to study the implications of age on the results of immune checkpoint blockade therapy in patients with triple-negative breast cancer. The study found that age had a significant effect on response to immunotherapy—young mice experienced greater reduction in tumor growth and better overall survival rates in response to treatment than those who did not receive the treatment; on the other hand, the immunotherapy treatment did not significantly benefit the aged mice compared with the aged mice who did not receive treatment.

A study by Lee and colleagues (2019) observing patients in the National Cancer Database with stage II and III rectal adenocarcinoma (not one of the selected cancers) treated with neoadjuvant chemoradiation found a strong stepwise relationship between age and response to treatment. Younger patients had a lower rate of treatment response, specifically of pathologic complete response and nodal clearance. Researchers Shah and Boucai (2018) studied the effects of age on response to therapy in 320 patients with thyroid cancer at high risk of recurrence. The patients had a median age of 49 years and were receiving thyroid-stimulating hormone-suppressive therapy and had at least one neck ultrasound during the first 2 years of follow-up. They found that age did affect response to therapy, with patients younger than 55 years significantly more likely to have an excellent response to the treatment than older patients.

These studies suggest that the directionality of treatment response variation by age depends on the cancer site and treatment, among other factors. Additional research would need to be conducted to draw more conclusive inferences.

RETURN TO WORK AFTER CANCER

While this chapter addresses the effect of cancer treatments on disease status and functional ability, there is not a clear linkage to return to work. This section reviews reports studying the effects of surviving cancer on long-term employment and return to work. The committee found a few papers on this topic that studied individuals with breast cancer. Cocchiara and colleagues (2018) performed a systematic review of papers on return to work after breast cancer. Of the 26 articles they reviewed, they found that the studies primarily addressed factors affecting return to work, interventions to enhance return to work, qualitative data on experiences of cancer survivors returning to work, and the economic aspects of cancer survivors returning to work. A 2019 systematic review performed by McLennan and colleagues analyzed 47 studies of prostate patients, comprising 20,083 individuals with a mean age of 61 years, and found a high

overall return-to-work rate, with lower rates among those with physically demanding or low-paid jobs, comorbid conditions, and poor physical functioning.

Several studies reviewed return-to-work data across cancer survivors of multiple cancer sites. Moran and colleagues (2011) analyzed data from the Penn State Cancer Survivor Study and compared that with data from a comparison group drawn from the Panel Study of Income Dynamics, which focused on younger workers (ages 28 to 54 years). The researchers found that as long as 2 to 6 years after diagnosis, cancer survivors have lower employment rates and work fewer hours than other similarly aged adults. The difference in employment rate, averaged across survivors who remain cancer-free and those with new cancers, was 7–8 percentage points. The average reduction in usual hours per week was about 3.5 hours for female survivors and about 5.5 hours for male survivors, including those who stopped working. The reappearance of cancer added considerably to the long-term effects of the disease on the employment of survivors, and younger male survivors were particularly hard hit by recurrences and second cancers.

A 2013 study by Mehnert and colleagues summarized return-to-work data from several review articles analyzing U.S. and European cancer survivors and found that return-to-work rates averaged 64 percent among the studies, with a range of 24 percent to 94 percent, noting that a meta-analysis by de Boer et al. (2009) found that the unemployment risk was 1.48 times higher in the United States than in European countries. Overall, Mehnert et al. noted that studies indicate a steady increase in return to work with increasing time intervals after a cancer diagnosis, based on data from populations with early-stage breast cancer, gynecologic cancers, and gastrointestinal, blood, and urologic cancers. The percentage of patients with these cancers returning to work at 6 months after diagnosis averaged 40 percent, increasing to 89 percent at 24 months after diagnosis. Mehnert et al. (2013) also reported that, based on results from six studies, a risk of unemployment was associated with extensive surgery and advanced tumor stage.

Roelen and colleagues (2011) found, in a study of employees with breast cancer, genital cancer, gastrointestinal cancer, lung cancer, skin cancer, and blood cancers in the Netherlands, that 2 years after a cancer diagnosis the highest percentage of patients who fully returned to work were those with female genital cancer, male genital cancer, skin cancer, and breast cancer. The lowest percentage of patients returning to work were those with lung cancer and gastrointestinal cancer. Advanced cancer stages and palliative treatment intention were associated with lower return-to-work rates.

A 2008 study by Short and colleagues analyzed data from the Penn State Cancer Survivor Study and the Health and Retirement Study data to quantify the increase in work disability attributable to cancer in a cohort of adult survivors who were an average of 46 months post-diagnosis. The sample included 647 survivors of ages 55–65, diagnosed at four medical centers in Pennsylvania and Maryland, and 5,988 similarly aged subjects without cancer in the Health and Retirement Study. The study found that even for cancer-free survivors, the disability rate was significantly higher than in adults with no chronic conditions (female odds ratio [OR]=1.94; male OR=1.89).

SUMMARY AND CONCLUSIONS

Cancer is the second leading cause of death in the United States and a major cause of disability. In recent years, because of the development of new treatments such as immunotherapy and CAR T-cell therapy, there has been an increase in the overall survival of patients with

cancers that would historically have had a poor prognosis. The committee notes the following cancers are likely to be disabling for a length of time (usually around the time of diagnosis) but might improve with treatment, particularly with recent developments in cancer therapy: breast cancer (excluding ductal carcinoma in situ), melanoma, renal cancer, head and neck cancers, advanced epithelial ovary cancer, non-small-cell lung cancer, and diffuse large B-cell lymphoma. The committee acknowledges that other cancers might also fit the criteria.

In addition to the effects of the medical condition itself, cancer treatments are well known to cause morbidity in cancer survivors. Although treatments have generally improved to the point that they are both more effective and less debilitating, treatment-related impairments are still common and, in many instances, expected. Studies show that most types of cancers result in decreased work ability in patients, at least during active treatment or in its terminal phase, and that the decreased work ability is often associated not with the progression of the cancer itself, but rather with treatment, treatment-related side effects (also known as toxicities), and comorbidity with other health conditions. The adverse effects of some treatments can be profound, with serious implications for function and quality of life. At the core of cancer treatments are surgery, systemic therapy, and radiation therapy. Each of these modalities has evolved significantly in recent years. Systemic therapy, for instance, which historically centered on various combinations of cytotoxic chemotherapeutics, now includes hormonal and biologic (targeted, immune, and gene) therapies. The addition of these new agents has revolutionized the treatment of many types of cancer but has also introduced new types of morbidity. Treatment-related impairments include pain, fatigue, cardiotoxicity, peripheral neuropathy, lymphedema, pulmonary dysfunction, and cognitive dysfunction. The residual effects of cancer treatments can present decades after treatment. Studies have shown that the majority will improve after treatment completion although the time course is patient specific.

The most significant recent advance in our understanding of cancers that are likely to improve with treatment has been achieved through an influx of promising new pharmaceuticals. Improved prognoses for some cancers have been realized through the integration of novel, targeted immune checkpoint and PARP inhibitors (pharmacological inhibitors of the enzyme poly ADP ribose polymerase), among others. The impact of these agents has been nothing short of revolutionary for some cancers (i.e., achieving durable remissions in cancers that were previously considered imminently mortal). Their effects on metastatic melanoma have been particularly remarkable, for instance. The effective practice of precision medicine permitted by these agents is exciting and will doubtlessly expand precipitously as it is extended across different types and stages of cancer as well as being expanded through the addition of new agents to an already formidable arsenal. However, much uncertainty remains regarding the toxicities of these treatments, and only patients whose tumors express targetable molecules are eligible for these therapies. Common, functionally morbid toxicities with the potential to affect all body systems have been attributed to these agents. Consequently, the body of evidence regarding their harms and benefits continues to evolve. Additional advances in cancer care that have improved treatment outcomes include enhanced imaging, earlier detection capabilities, and enhanced supportive care, among others.

Cancers are a very heterogeneous class of medical conditions, with impairments and recovery that are hard to generalize over the course of the disease. The committee developed three overall conclusions regarding their review of specific selected cancers. First, variation in the ability of a cancer to improve with treatment exists within cancers of a particular organ system, not only by stage, but also by cancer cell type and molecular and genomic

characteristics. Prognosis and treatment decisions are likewise based on the cancer site, stage, cell type, and molecular and genomic characteristics. For example, triple-negative invasive breast cancer (breast cancer with tumors lacking estrogen, progesterone, and the HER–2 gene) is much more aggressive and has lower survival than many other invasive breast cancer cell types. Another example is that recent phase III trials show that targeted therapies demonstrate superior efficacy to chemotherapy in non-small-cell lung cancer patients with an activating EGFR (epidermal growth factor receptor) mutation and in patients with ALK (anaplastic lymphoma kinase) rearrangements. Patients' ultimate survival varies dramatically based on the treatments available for their specific cancer sites, stage of disease, cell types, and molecular and genomic markers as well as their individual characteristics, including comorbid disease, functional status, and the social determinants of health. Additionally, a few studies suggest that for certain combinations of cancer site and treatment, response varies by age; however, the direction of the relationship varies among the studies reviewed.

Second, success in cancer treatment does not predict improved functional outcomes. Long-term cancer survivors often experience multiple comorbidities and impairments related to the toxic effects of cancer therapies, including surgery, radiation, and systemic therapy (chemotherapy, biologic therapy). These impairments, which are a major cause of morbidity, have their own trajectories, treatments, and treatment response considerations. They can be acute side effects that develop during treatment but are transient, long-term side effects that develop during treatment but are chronic, late effects that develop after completion of the treatment, or secondary effects that result from acute and long-term side effects. The committee suggests that the following common cancer-related impairments can be disabling for a period of time, but managed, though not necessarily cured, with treatment: pain, cancer-related fatigue, cardiotoxicity, chemotherapy-induced peripheral neuropathy, lymphedema, pulmonary dysfunction, and cognitive dysfunction. Additionally, the committee notes that improved functional outcomes do not predict return to work.

Finally, it is important to consider the recursive nature of cancer, cancer treatments, and impairments. Cancer is a dynamic process, and as cancer patients survive longer, they experience a higher probability of disease relapse which can reset an episode of treatment. Given that cancer treatments commonly result in functional impairment, and disease relapse is highly probable, the question of how long it takes from initiation of cancer treatment until functioning improves is a complex one. The committee suggests that the length of time from the start of cancer treatment until a person's functioning improves to the point at which the condition is no longer disabling involves two timeframes: (1) the time to remission of the cancer, and (2) the time to recovery from the toxicities, symptoms, and functional impairments caused by either the cancer or the treatment. The committee notes that a cancer patient's disease status, more so than the cancer site and stage, is an appropriate indicator of whether the patient's functional status should be assessed for improvement. If a patient's cancer achieves complete remission, functional status improvement is probable, and it is reasonable to reevaluate the patient's functional status 12 months after achieving complete remission. If a patient's cancer achieves a stable partial remission, functional status improvement is possible, and it is reasonable to reevaluate the patient's functional status 12 months after achieving stable partial remission. If the patient has no response to treatment or experiences a progression of the disease, then functional improvement is unlikely.

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4

Mental Health Disorders

Mental health disorders affect a person's thinking, feeling, mood or behavior and include conditions such as depression, anxiety, bipolar disorder, and schizophrenia (CDC, 2018). The *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5), defines mental disorder as "a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychologic, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities" (APA, 2013, p. 20).

The committee selected mental health disorders, for inclusion in the report, in accordance with the stipulations in the statement of task—that is, that the committee consider conditions that last 12 months or longer and can be disabling for a period of time but that may not result in permanent disability. The decision on which specific mental health disorders to include was based on the prevalence of the disorders in the United States and on their potential responsiveness to treatment. The committee selected the mental disorders listed in Table 4-1, recognizing that others might also meet its criteria.

TABLE 4-1 Selected Mental Health Conditions

SSA Listing	DSM-5 Diagnosis	DSM-5 Classification
Depressive, bipolar, and related disorders	Major depressive disorder	Depressive disorders
	Bipolar I disorder	Bipolar and related disorders
	Bipolar II disorder	
Anxiety and obsessive compulsive disorders	Panic disorder	Anxiety disorders
	Generalized anxiety disorder	
	Social anxiety disorder (social phobia)	
	Obsessive compulsive disorder	Obsessive compulsive and related disorders
Trauma and stress-related disorders	Posttraumatic stress disorder	Trauma and stress-related disorders

The chapter begins with a description of the prevalence of mental disorders in the United States, followed by a discussion of cross-cutting issues that affect individuals with the selected

mental health disorders. The remainder of the chapter consists of discussions of the issues noted in the statement of task and ends with a summary and conclusions.

The committee collected information from a variety of sources. The DSM-5 (APA, 2013) provides the professionally accepted diagnostic criteria for mental health disorders used by health care professionals in the United States and was the source for the diagnostic criteria described in this chapter. Pertinent modifications to those criteria that occurred over time are noted where relevant. Selected clinical practice guidelines from professional organizations were used to identify evidence-based treatments for each disorder. The guidelines used were selected based on their comprehensiveness and relevance to the questions, their transparency and clarity about literature search strategies and approaches to evidence-based decisions, recently updated information, and whether the guideline had had an external peer review. See tables A-1 through A-5 in Appendix A for details on the guidelines used for each disorder. Other sources of scientific information include recent systematic reviews, meta-analyses, and notable publications.

It is estimated that in in 2018, 19.1 percent of U.S. adults experienced mental illness (47.6 million people), and 4.6 percent experienced serious mental illness (11.4 million people) (SAMHSA, 2019). For the specific disorders of interest, the best data available suggest that the 12-month prevalence for anxiety disorders is 18.1 percent among U.S. adults (estimated 23 million people) (Kessler et al., 2005a); for major depressive episode, 7.2 percent (17.7 million people) (SAMHSA, 2019); for posttraumatic stress disorder, 3.5 percent (7 million people) (Kessler et al., 2005a); for any bipolar disorder, 2.8 percent (estimated 6 million people) (Merikangas et al., 2007); and for obsessive compulsive disorder, 1.2 percent (estimated 2.5 million people) (Ruscio et al., 2010).

CROSS-CUTTING ISSUES FOR SELECTED MENTAL HEALTH DISORDERS

Cross-cutting issues include the types of medical professionals involved in mental health treatment, responses to treatment in the context of disability, and the complexity of measuring the improvement from treatment in terms of functional outcomes, as required by the Social Security Adminstration (SSA) in determining entitlement. Pain is also a cross cutting feature in the mental health conditions discussed. Chapter 2 includes a discussion of approaches to pain and pain treatment in general.

How People Are Identified for Treatment and the Types of Medical Professionals Involved in Care

People are identified for mental health treatment through a number of different mechanisms. Some people self-refer because they or their family members or friends become concerned about certain behaviors; some people are identified through screenings in a given health care setting; others are referred through medical professionals during an encounter for another condition. Less commonly, people may be identified as needing mental health care because of a risk to self or others. Individuals are then directed to a specific treatment depending on the treatment guidelines, their treatment history, patient preference, and treatment availability, among other factors.

Non-mental health specialists may be involved in the treatment of people with mental health disorders. However, for those individuals with severe, persistent, and treatment-resistant

disease, which might be disabling, the expectation is that they would be receiving psychiatric services from a variety of mental health professionals, including a prescriber (e.g., psychiatrist, advanced practice nurse), psychologist, or licensed clinician with a social work, counseling, or rehabilitation degrees. For some populations (e.g., those in rural areas or small towns), however, care from qualified mental health professionals (e.g., specialized in evidence psychotherapy) might not be available.

Response to Treatments for Mental Health Disorders in the Context of Disability

Most of the mental disorders under consideration can occasionally result in Social Security–defined disability. Individuals meeting the criteria for disability are likely to have a severe form of the disorder or a significant comorbidity that affects response to treatment and the potential for remission. Thus, the applicability of usual treatment algorithms is uncertain. It is very possible that individuals who are determined to be disabled by SSA may require second- and third-line treatment or even be non-responders to treatment. Additionally, most of the mental health disorders being considered can be chronic and relapsing. Although an individual could respond to treatment in the acute phase and remain well (with ongoing treatment or even in the absence of treatment) for a period of time, episodes of illness can recur, sometimes with greater severity and reduced response to treatment. Finally, the presence of comorbidities may limit treatment choices because of the presence of or risk for side effects.

Measuring Improvement of Functional Outcomes

The SSA definition of disability requires that a person have limitations in function that prevents that person from engaging in substantial gainful activity (SGA). Under SSA's Medical Improvement Review Standard, benefits may not be stopped unless there is medical improvement related to the ability to perform SGA, as determined in the disability decision that entitled the person to benefits. Determining how impairments affect occupational function has been a longstanding challenge. Because of its importance within the SSA review standard, the SSA asked the committee to describe time to improvement in functioning to the point where the condition is no longer disabling.

In response to that issue, the committee acknowledges important challenges, which are common to the mental health disorders discussed in the chapter. First, the treatments in research and in clinical practice guidelines for mental health disorders target symptoms and do not clearly focus on occupational function as an outcome. Second, psychiatric disorders are often recurrent and, therefore, the time until improvement is not adequately captured as a linear process. Third, psychiatric disorders are often comorbid with other psychiatric disorders, pain, and other medical conditions, and thus the time to improvement will depend on those and other factors. Any estimates of time to improvement need to consider the fact that clinical trials generally exclude participants with comorbidities. Fourth, symptom improvement and functional improvement may represent separate aspects of recovery, and one cannot assume that improvement in symptoms results in improvements in functioning. For the mental health conditions described in this chapter, the discontinuity between symptoms and functioning as well as the multiple, inter-related domains that measure function are not well understood. The 2019 National Academies report *Functional Assessment for Adults with Disabilities* found that when assessing the functional abilities of individuals with mental health disorders, the following domains are

important: general cognitive/intellectual ability, language and communication, learning and memory, attention and vigilance, processing speed, executive functioning, adaptability, and work-related personal interactions. The report concluded that because of the fluctuating nature of the disease course, it is important to understand the relationship between mental illness and functioning and to perform frequent assessments of disability in applicants with mental health disorders. The report also concluded that there is no single measure that captures all important aspects of the mental abilities needed for work. Only some measures include occupational functioning as one of the domains to measure improvement for psychiatric disorders. Some of the measures developed for assessing the occupational domain, which are described further in the 2019 National Academies report and in the 2016 Canadian Network of Mood and Anxiety Treatments (CANMAT) guidelines, are the Multidimensional Scale of Independent Functioning, the World Health Organization (WHO) Disability Assessment Schedule 2.0, the Social and Occupational Functioning Assessment Scale, the Work Disability Functional Battery Mental Health Measures, the University of California, San Diego (UCSD) Performance-Based Skills Assessment, and the Occupational Functioning Scale.

Bearing in mind those challenges, the committee now discusses the limited research base related to treatment and functional improvement within each mental health disorder section.

Mental Health Conditions and Pain

It is well known that mental conditions and chronic pain often occur together, but the causal pathway or direction of the association is still debated. Chronic pain may contribute to mental conditions, and, vice versa, mental conditions may result in an increased risk of chronic pain (Velly and Mohit, 2018). According to data from the World Mental Health Survey Initiative, individuals with mental conditions comorbid with chronic pain conditions (back or neck pain) were more likely to be among the most disabled, as measured by the WHO Disability Assessment Schedule, than those with neither mental disorder nor chronic pain (Scott et al., 2009). As reported by Velly and Mohit (2018) and Gureje et al. (1998), individuals with chronic pain are four times more likely to have anxiety or depression than those without chronic pain (Gureje et al., 1998).

Regardless of the causal pathway, mental conditions with comorbid chronic pain result in more work-loss days than do the individual conditions by themselves. The effect is additive except for chronic back pain, where the interaction with mental conditions has been found to be synergistic with respect to work loss (Buist-Bouwman, 2005; NASEM, 2019) Additionally, a systematic review found no evidence of a difference in return-to-work rates between patients with chronic back pain and mental comorbidities (depression, bipolar disorder, panic disorder) and chronic back pain patients without mental comorbidities (Baumeister et al., 2012). The same review, however, reported more work absence and more work-related disability in depressed chronic back pain patients than in patients without depression.

The types of chronic pain that commonly co-occur with mental conditions include migraine headaches (Fishbain et al., 2017; Goldstein, 2009; Katzman et al., 2014), neck and back pain (Fishbain et al., 2017; Goldstein, 2009; Katzman et al., 2014; Kroenke et al., 2013; Velly and Mohit, 2018), fibromyalgia (Fishbain et al., 2017; Kroenke et al., 2013; Velly and Mohit, 2018), rheumatoid arthritis (Goldstein, 2009; Katzman et al., 2014; Velly and Mohit, 2018), and abdominal pain (Velly and Mohit, 2018). The treatment of comorbid chronic pain and mental conditions varies by the type of chronic pain and the specific mental condition. The treatment for both conditions should be managed by a team of specialists and monitored cautiously to avoid

adverse outcomes or addictions (see Chapters 2 and 5 for further discussion of treatments for chronic pain management).

MAJOR DEPRESSIVE DISORDER

The adult depressive disorders listed in the DSM-5 have common features, such as sad, empty, or irritable mood, and they include: major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. The disorders differ from each other in their duration, timing, and presumed etiology

This section focuses on major depressive disorder. It is both the most prevalent mental health disorder in the United States and a major cause of disability, and it exhibits many of the common features noted above. Major depression affects multiple domains which result in important economic burdens for individuals and countries (Salomon et al., 2015). Its adverse effects can be observed in physical health problems and include heart disease, arthritis, asthma, back pain, chronic pulmonary disease hypertension, and migraine. In addition, as with other mental disorders, major depressive disorder is associated with negative functional outcomes such as social and occupational dysfunction (Deschenes et al., 2015) and reduced quality of life (Burgel et al., 2013; Faller et al., 2015; Schowalter et al., 2013). WHO reported that depression accounts for over 5 percent of population illness-related productivity loss. Major depressive disorder is associated with 65.5 excess lost days per worker with depression and with $31 billion to $51.5 billion in annual workplace costs. In the areas of social and work functioning, the impairments range from the mild to complete incapacity, and three factors are associated with higher work disability: the severity of the illness, concurrent medical conditions, and anxiety as a comorbidity (Kessler et al., 2005a).

Professionally Accepted Diagnostic Criteria for Major Depressive Disorder

The DSM-5 describes major depressive disorder as involving discrete episodes of at least 2 weeks' duration involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions (i.e., when the symptom severity is within the normal, nondepressed range). In the most common presentation of major depression, a single episode is typically longer than 2 weeks, and recurrent episodes are frequent. According to the DSM-5 there is no specific age of onset, but puberty seems to be a critical period, and the incidence is highest at approximately age 20. Table 4-2 includes criteria for the diagnosis of major depressive episode. A more chronic form of depression, persistent depressive disorder (defined as dysthymia and chronic major depression in DSM-IV), is diagnosed when the mood disturbance continues for at least 2 years in adults.

TABLE 4-2 DSM-5 Criteria for Major Depressive Disorder and Severity Specification

Criterion/Symptom Description
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Insomnia or hypersomnia nearly every day. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). Fatigue or loss of energy nearly every day. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode. Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Severity Specification	
Mild	Few, if any, symptoms in excess of those required to make the diagnosis are present; the intensity of the symptoms is distressing but manageable; and the symptoms result in minor impairment in social or occupational functioning.
Moderate	The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for “mild” and “severe.”
Severe	The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable,

and the symptoms markedly interfere with social and occupational functioning.

Developmental Course, Gender Distribution, and Comorbidities

Major depressive disorder (MDD) presents in various ways, and it is recommended that a diagnosis be accompanied by "specifiers" that can guide the selection of an approach to management and monitoring tools. These specifiers might include the presence of anxiety, melancholic features, atypical features, psychotic features, catatonia, peripartum onset, and seasonal pattern. Often the severity, which is an important aspect of a disability determination, is also included in the diagnosis as a specifier (see Table 4-2).

Although each person will experience major depression differently, Figure 4-1 is widely recognized as a representation of the typical course of major depressive disorder. Because of its episodic nature, a patient's remission status needs to be included as a specifier when diagnosing, managing, and monitoring the disease. For example, a patient in remission might consider an adjuvant treatment to minimize the risk of relapse. This course, where an acute episode is followed by a maintenance phase and a continuation phase, corresponds chronologically with the treatment phases that have been proposed, and it has implications for how to identify improvements in functioning.

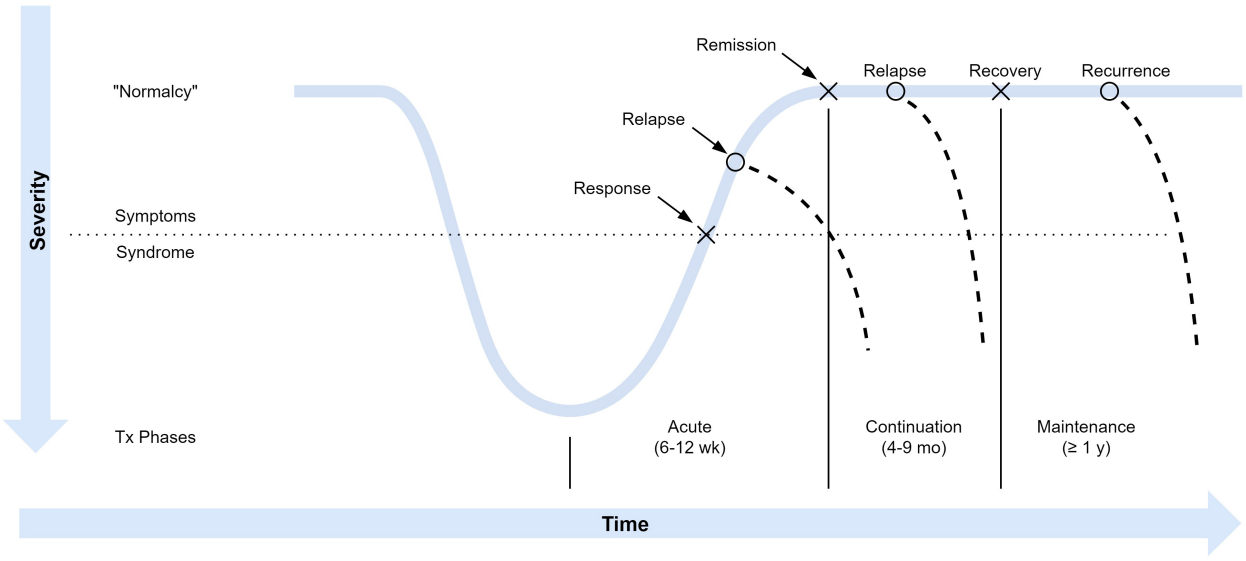

FIGURE 4-1 Phases of treatment of major depression.
NOTE: Response represents a clinically significant reduction in symptom severity relative to baseline status (usually 50 percent). Remission is when symptom severity is within the normal, nondepressed range. Relapse is the reemergence of symptoms of major depression following some level of remission, but preceding recovery. Recovery is a prolonged period of remission that marks the end of the index episode (e.g., 6–12 months). Recurrence is the onset of a new episode of depression following recovery.
SOURCE: Kupfer, 1991.

The DSM-5 states that although the 12-month prevalence of MDD in the United States is about 7 percent, females experience it at a much higher rate, specifically 1.5–3 times more frequently than in males. Major depressive disorder often occurs with other medical or mental health comorbidities. In one study almost 75 percent of individuals with lifetime major

depressive disorder met the criteria for another psychiatric disorder (Kessler et al., 2003), especially an anxiety disorder (59 percent). Moreover, 31.9 percent of the persons with major depressive disorder had at least one other International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis, and 24 percent had at least one substance use disorder. With regard to medical comorbidities, depression can be either a primary condition or due to another medical condition. Some medical conditions with high rates of comorbid depression include cancer, cardiovascular disease, multiple sclerosis, traumatic brain injury, HIV, epilepsy, migraines, Parkinson's disease, hepatitis C, and chronic pain.

Standard Measures of Outcomes for Major Depressive Disorder

The field still lacks reliable and valid biomarkers for depression, recovery, and prognosis. The most recent systematic review of predictors of depression treatment outcomes concluded that despite a vast literature on the topic, there are still no reliable or valid biomarkers or other predictors that can be recommended for use in the clinic (Perlman et al., 2019).

This section describes two sets of patient-reported outcome measures, symptom measures and functional measures. Measures of depression symptom severity are the most widely used types of outcome assessment.

The Hamilton Depression Rating Scale (HDRS, also known as HAM-D) is one of the oldest and most widely used depression symptom severity measures, though it has declined in use in recent years (Bagby et al., 2004). The original HDRS is a multidimensional 21-item clinician-rated measure with variable item scaling that covers symptom severity over the past week (Hamilton, 1967). However, items do not correspond to DSM criteria, limiting the validity of the measure (Furukawa, 2010). Although the original HAM-D has only adequate internal and inter-rater reliability (Furukawa, 2010), it has been the benchmark to which other measures are compared in term of sensitivity to change, clinically significant response to treatment, and remission (Reeves et al., 2012). The Montgomery Asberg Depression Rating Scale (MADRS) is a clinician-rated measure designed to be sensitive to antidepressant-versus-placebo effects rather than following DSM criteria (Furukawa, 2010). It has excellent inter-rater reliability, good concurrent validity compared with the HDRS, and sensitivity to change similar to the HDRS (Furukawa, 2010). The Quick Inventory of Depressive Symptomology is a measure that covers DSM-IV and DSM-5 criteria. It has good internal consistency, high correlations with the HDRS, and a sensitivity to change similar to the HDRS. The Beck Depression Inventory II (BDI-II) contains most DSM major depressive disorder criteria. It has good internal consistency and good test–retest reliability. The sensitivity to change of the BDI-II is comparable to that of MADRS (Furukawa, 2010). The Patient Health Questionnaire-9 (PHQ-9) parallels DSM-IV and DSM-5 major depressive disorder criteria. It has excellent internal consistency and test–retest reliability (Furukawa, 2010). In contrast with most other measures, it is a valid screener for MDD with a pooled sensitivity of 0.80 and a pooled specificity of 0.92, generally using a cutoff of 10 or higher (Gilbody et al., 2007). The PHQ-9 is at least as sensitive to change as other measures (Furukawa, 2010).

Historically, response to treatment (typically defined as at least a 50 percent reduction in symptom severity compared with baseline) has been the most widely used standard for judging symptomatic outcomes by clinicians and researchers. However, remission (the virtual absence of depressive symptoms as defined by the measures described above) has been adopted as the target of treatment because patients who achieve it have better functioning, better prognosis, and a

more stable state (Frank et al., 1991; Paykel et al., 1995) and are less likely to relapse into another MDD episode (Rush et al., 2006a).

Although reduced depression symptom severity can be associated with improved functioning, there is not always improvement even with adequate depression treatment (McKnight and Kashdan, 2009; Sheehan, 2017; Trivedi, 2013). Clinicians have recommended that measures of daily functioning be included in depression treatment trials (Rush et al., 2006a). The topic of measuring functional outcomes is complicated by the fact that major depressive episodes can have both acute and chronic effects on cognition. A recent review by Summit Consulting, commissioned by SSA (Mosbach et al., 2018), found that depression can significantly affect attention, concentration, learning, and memory as well as executive functioning (Lee et al., 2012; Rocca et al., 2015; Rock et al., 2014; Snyder et al., 2013). There is evidence that impaired cognition can begin with the first depressive episode (Lee et al., 2012) and that cognitive deficits continue even after remission (Bhalla et al., 2006). A high-enough degree of residual cognitive impairments can result in work disability.

Treatments for Major Depressive Disorder

Depression treatment can be divided into two phases. The goal of the acute phase, which typically lasts 8–12 weeks, is to achieve symptom remission. The goals of the maintenance phase, which can last 6–24 months or longer, are to restore full functioning and prevent relapse. Detailed treatment algorithms are available to help guide clinical decision making. An example of such an algorithm for managing depression is presented in Figure A-1 of Appendix A.

Table 4-3 lists the first- and second-line psychologic and pharmacologic treatments both for acute episodes and for maintenance, based on the CANMAT[1] guidelines and the U.S. Department of Veterans Affairs/U. S. Department of Defense (VA/DoD) guidelines.[2] Complementary and alternative medicine treatments are not included in the table because of the more limited clinical evidence regarding their effectiveness.

TABLE 4-3 Treatments for Major Depressive Disorder

Treatment	Psychotherapy	Pharmacotherapy
First-line	Cognitive behavioral therapy (CBT) Interpersonal therapy (IPT) (for acute) Behavioral activation (for acute) Mindfulness-based cognitive therapy (for maintenance)	Agomelatine, bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mianserina, mirtazapine, paroxetine, sertraline, vortioxetine
Second-line	IPT (for maintenance) Behavioral activation (for maintenance) Mindfulness-based cognitive therapy (for acute) Cognitive behavioral analysis system of psychotherapy	Amitriptyline, clomipramine, levomilnacipran, moclobemide, quetiapine, selegiline transdermala, trazodone, vilazodone

[1] The Canadian Network for Mood and Anxiety Treatments (CANMAT) is a network of academic and clinical experts dedicated to improving clinical care for people with mood and anxiety disorders.

[2] The 2016 U.S. Department of Veterans Affairs and U.S. Department of Defense *Clinical Practice Guideline for the Management of Major Depressive Disorder* provide evidence-based recommendations that have been peer reviewed. The committee assumes those guidelines are applicable to the civilian population.

	Problem-solving therapy (acute)
	Short-term psychodynamic psychotherapy (acute)
	Telephone-delivered CBT and IPT (acute)
	Internet-and computer-assisted therapy (acute)

SOURCE: CANMAT, 2016; VA/DoD, 2016.

The overall effectiveness of antidepressants and of evidence-based psychotherapies are equivalent (Cuijpers et al., 2014a). An initial treatment with anti-depressant medication results in remission in 30–50 percent of cases (Rush et al., 2006b; Thase et al., 2005, 2010). Treatment may take as long as 10–12 weeks to be effective (Rush et al., 2006b). The overall remission rate associated with psychotherapies is 43 percent versus 27 percent for all control groups (Cuijpers et al., 2014a). Psychotherapy, especially cognitive behavioral therapy and interpersonal therapy, results in persistent benefit after the treatment is over, whereas with anti-depressant medications the benefits of treatment are often lost once the drug is stopped (APA, 2010; Parikh et al., 2009). It is important to note that combined anti-depressant medication and psychotherapy is more effective than either treatment alone (Cuijpers et al., 2009a,b). The U.S. Department of Veterans Affairs and the U.S. Department of Defense (VA/DoD) (2016) or CANMAT (2016) guidelines recommend a combination of antidepressant medication and a psychologic intervention for moderate to severe major depression (Cuijpers et al., 2009a,b).

Studies have shown that combining medical treatments with psychotherapy is effective for treatment-resistance depression. However, less than 50 percent of patients respond to first-line antidepressant treatment or psychotherapy. A meta-analysis and meta-regression analysis conducted to investigate the effectiveness of psychotherapy for treatment-resistant depression found that adding psychotherapy (cognitive behavioral therapy, interpersonal therapy, mindfulness-based cognitive therapy, and cognitive behavioral analysis) to treatment as usual had a moderate effect on treatment-resistance depression (van Bronswijk et al., 2019). A 2018 meta-analysis reported that there was moderate-quality evidence that adding psychotherapy to usual care significantly increased remission from treatment-resistant depression (Ijaz et al., 2018). Finally, a meta-analysis of treatment augmentation showed that adding mood stabilizers, antipsychotics, and N-methyl-D-aspartate (NMDA) targeting drugs to current treatment significantly reduced symptom severity (Strawbridge et al., 2019). Augmentation, however, is not always acceptable to the patient, given the potential for added interactions and side effects.

Alternative medications represent another option for treating treatment-resistance depression. The VA/DoD guideline (VA/DoD, 2016) on treating depression recommends monoamine oxidase inhibitors (MAOIs) (e.g., isocarboxazid, phenelzine, and tranylcypromine) and tricyclic antidepressants (e.g., amitriptyline, imipramine, desipramine, nortriptyline) for people who have failed first-line treatments. However, MAOIs require dietary restrictions on tyramine. Both MAOIs and tricyclics have worse adverse-effect profiles than first-line antidepressant medications. Lithium and triiodothyronine can be used to augment selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). The VA/DoD guideline also recommends neurostimulation for treatment-resistance depression. Electroconvulsive therapy (ECT) is an effective treatment for persons with severe MDD or treatment-resistance depression. Indications for ECT include catatonia, psychosis, and severe suicidality as well as poor response to multiple medical treatments. Repetitive transcranial magnetic stimulation is also potentially effective for treatment resistance depression.

Finally, a recent systematic review and network meta-analysis[3] of the comparative efficacy and tolerability of pharmacologic and somatic interventions for treatment-resistant depression found that ketamine demonstrated superior efficacy for treatment-resistant depression when compared with other pharmacologic and somatic treatments at 2 weeks after treatment began (Papadimitropoulou et al., 2017). Data comparing ketamine to other treatments beyond 2 weeks are limited. At 4, 6, and 8 weeks, quetiapine augmentation and risperidone augmentation were found to be the first and second best treatments, respectively.

Because symptomatic recovery from depressive illness does not guarantee recovery of function, including occupational functioning, investigators have increasingly advocated for the use of combined treatments that target both depressive symptoms and functional impairments, including work disability (Adler et al., 2015; Trivedi, 2018). That combined treatment approach parallels what has been used to reduce work disability in other populations, such as those suffering from chronic pain (Costa-Black et al., 2010). Furthermore, there is mixed evidence concerning whether adding work-focused interventions (e.g., assisting the depressed person with return to work) to a standard depression treatment improves work-related outcomes (Adler et al., 2015; Hellstrom et al., 2017; Lerner et al., 2012; Nieuwenhuijsen et al., 2014). However, the science of using cognitive rehabilitation strategies to treat cognitive dysfunction in persons with major depression is still being explored, and findings are inconclusive (Porter et al., 2014).

More pertinent to this report is the limited treatment literature on fostering return to employment in persons who are already on SSDI due to mental illness. Drake and colleagues (2013) randomized 2,059 SSDI recipients with depression, schizophrenia, or bipolar disorder to a multifaceted intervention consisting of individual placement and support, medication management, other behavioral health services, health insurance coverage with no copay, and the suspension of disability reviews compared with usual services. The treatment group achieved greater paid employment (60.3 versus 40.2 percent) as well as improved mental health and quality of life relative to the controls. However, according to the authors, only 14 percent of eligible beneficiaries joined the study (perhaps because of fears about potential loss of benefits). Moreover, among those who returned to work, less than 3 percent earned at or above the threshold for substantial gainful activity established by the Social Security Administration.

Length of Time to Improvement for Major Depressive Disorder

Estimating time to symptom improvement is complicated by numerous factors, including undertreatment, the need for multiple sequential treatment episodes to achieve remission of symptoms, treatment-resistance depression, the presence of comorbidities, and the chronic relapsing course of major depression. Additionally, the resolution of functional impairments likely lags behind the remission of depressive symptoms. For example, depression-related cognitive impairment might persist despite depression remission or recovery. Residual functional and cognitive impairments might require supplementary cognitive- or work-focused treatments to optimize improvement.

The American College of Neuropsychopharmacology recommends that clinical trials last 12–20 weeks to optimize the detection of remission (Rush et al., 2006b). However, the STAR*D4 study, a trial that includes patients with medical and psychiatric comorbidities,

[3] Network meta-analyses uses all available data from randomized clinical trials to estimate the effect of each intervention relative to other interventions, even those that have not been compared directly.

reported less optimistic results. The trial, which included a sample of 4,000 adults receiving various successive treatments for their current depression, found that only 36.8 percent of the patients remitted within the first 12- to 14-week treatment phase and that even the overall cumulative remission rate which included all four acute treatment steps, was 67 percent over 48–56 weeks. In the overall group of remitters, 33–50 percent relapsed within the 1-year study follow-up period. The trial also found that even in cases when the second, third, or fourth step resulted in remission, the outcome might be temporary and that remission was less likely for those with a comorbid anxiety disorder.

On the other hand, among SSA beneficiaries, improvement in employment rate began within 6 months and peaked at 19 months post treatment initiation (Drake et al., 2013). However, almost no one achieved the threshold for substantial gainful employment; functional improvement is thought to occur more slowly than symptom improvement (McKnight and Kashdan, 2009; Mintz et al., 1992). Thus, the expected times for improvement mentioned above are likely underestimates for the purpose of predicting functional improvement. In addition, the course of major depression is not linear and residual symptoms during a temporary period of remission may lead to relapse (Conradi et al., 2011; Judd et al., 2000; Nierenberg et al., 2010). Given the evidence about predicting final response to treatment (Steidmann et al., 2013; Wagner et al., 2017), assessing early response (after 4 to 8 weeks) during the course of treatment could be helpful in predicting the likelihood of improvement.

Finally, there appears to be the potential for depression improvement among adults of any age. A recent systematic review of predictors of antidepressant efficacy reported that antidepressants are effective across a broad age range and that any age effects were inconsistent and depended on the type of treatment (Perlman et al., 2019) Systematic and other reviews of psychosocial treatments for depression in older adults indicate they are effective (Huang et al., 2015; Renn and Arean, 2017).

BIPOLAR DISORDERS

Bipolar disorders are mood disorders that manifest as episodes of mania, hypomania, and major depression (APA, 2013). They include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder. This section includes discussions of bipolar I and bipolar II disorders.

The diagnostic guidelines indicate that as many as 30 percent of individuals diagnosed with bipolar I disorder have been estimated to exhibit occupational impairments. The DSM-5 indicates that bipolar II disorder can be as severe and disabling as bipolar I disorder because those individuals with bipolar II disorder experience more depression, sometimes co-occurring with hypomanic symptoms (APA, 2013). In addition, although bipolar I disorder has more severe symptoms, individuals with bipolar II disorder experience episodes with more frequency and with higher rates of comorbidities and recurrent suicidal behaviors (Vieta and Suppes, 2008). Furthermore, their executive functioning can be as impaired or more so (Dickinson et al., 2017) compared with those with bipolar I disorder. Even the functional consequences of individuals with cyclothymia can be significant as a result of the mood disturbances. Patients with bipolar disorder have the potential to be impaired in all functional domains (e.g., social, occupational, and general function) (Baune and Malhi, 2015; Dickinson et al., 2017; Gitlin and Miklowitz,

2016; Raucher-Chene et al., 2017; Szmulewicz et al., 2017), although the factors that cause impairment have not been clearly specified.

Professionally Accepted Diagnostic Criteria for Bipolar Disorders

Bipolar disorder can be experienced in various forms and is typically accompanied by serious impairments in work and social functioning. Individuals with bipolar I disorder may experience manic episodes with inflated self-esteem and a decreased need to sleep, for example. The majority of those individuals also experience major depressive episodes during the course of their lives. Individuals diagnosed with bipolar II disorder present with at least one major episode of depression and one of hypomania, but not manic episodes.

According to the DSM-5 there is no specific age of onset for bipolar I disorder and bipolar II disorder, although the average age of onset is earlier for bipolar I disorder—specifically, around 18 years of age for bipolar I and the mid-20s for bipolar II disorder (APA, 2013). Women with bipolar II appear to be more likely than those with bipolar I disorder to experience hypomania with mixed depressive features and a rapid-cycling course. Table 4-4 lists criteria for the diagnosis of bipolar I disorder and bipolar II disorder as described in DSM-5.

TABLE 4-4 DSM-5 Criteria Bipolar I Disorder and Bipolar II Disorder

Diagnosis	Criterion/Symptom Description
Bipolar I disorder	For a diagnosis of bipolar I disorder it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary). B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity). 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.
Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Bipolar II disorder

For a diagnosis of bipolar II disorder it is necessary to meet the following criteria for a current or past hypomanic episode *and* the following criteria for a current or past major depressive episode:

Hypomanic Episode
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable), represent a noticeable change from usual behavior, and have been present to a significant degree:
1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment).

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Major Depressive Episode
(see Table 4-2 under Depression section)

Specifiers to Help with Diagnosis and Treatment (CANMAT, 2018).

Specifier	Manic Episode	Depressive Episode	Illness Course
Anxious distress	X	X	
Mixed features	X	X	
Rapid cycling			X
Melancholic features		X	
Atypical features		X	
Psychotic features	X	X	
Catatonia	X	X	
Peripartum onset	X	X	
Seasonal pattern			X
Remission	X	X	
Current episode severity	X	X	

Developmental Course, Gender Distribution, and Comorbidities

Recent studies confirm that bipolar disorder is a recurrent disorder, with more than 90 percent of individuals having recurrent mood episodes. There is a great variability in the presentation, sequence, and length of episodes in bipolar disorders, but patterns are repeated for a given patient. For example, some patients tend to experience a manic episode followed by a depressive episode, whereas the reverse pattern is typical for other patients. A manic episode with psychotic features is more likely to be followed by more episodes with psychotic features (APA, 2013).

In patients undergoing usual care for bipolar I disorder, the median length of mood episodes (manic or depressed) is 13 weeks, and 75 percent recover within 1 year (Solomon et al., 2010). Although depressive episodes vary, they typically last longer than manic episodes, as depicted in Figure 4-2. For example, one study found that patients spent longer periods in depression (on average three times longer) than in the mania/hypomania states (Baldessarini et al., 2010). Despite the episodic nature of the disease, which implies periods with no symptoms and normal functioning, studies have shown that bipolar patients experience symptoms the majority of the time (Judd et al., 2002, 2003). People with rapid cycling bipolar disorder I or II will experience a minimum of four episodes of mania/hypomania or depression each year (Carvalho et al., 2014).

The National Comorbidity Survey–Replication study (NCS-R), a nationally representative survey of mental disorders in adults in the United States, found that the 12-month prevalence of bipolar I disorder was 0.6 percent, with no difference by gender. For bipolar II disorder, the 12-month prevalence was 0.8 percent in the United States, with some indication of higher rates in females (Merikangas et al., 2007). There are also gender-related differences in the presentation of bipolar disorders. Females experience the depressive symptoms more frequently

than males as well as rapid cycling and mixed states as specifiers. Lifetime eating disorders and a higher risk of alcohol use disorder are often comorbid with bipolar disorder (APA, 2013).

Several factors can modify the course of the disorder. For those with psychosis or severe psychosocial impairment at an episode's onset, the probability of recovery is diminished (Solomon et al., 2010). Those with more total years spent in manic or depressed episodes are less likely to recover. Each year spent in a major or minor depression episode reduces the likelihood of recovery from subsequent major depressive episodes by 7 percent (Solomon et al., 2013). As the number of mood disordered episodes increase, there is greater risk of recurrence, longer duration of episodes, increased symptom severity during episodes, decreasing threshold for developing recurrent episode, and increased likelihood of dementia.(Kessing and Andersen, 2017).

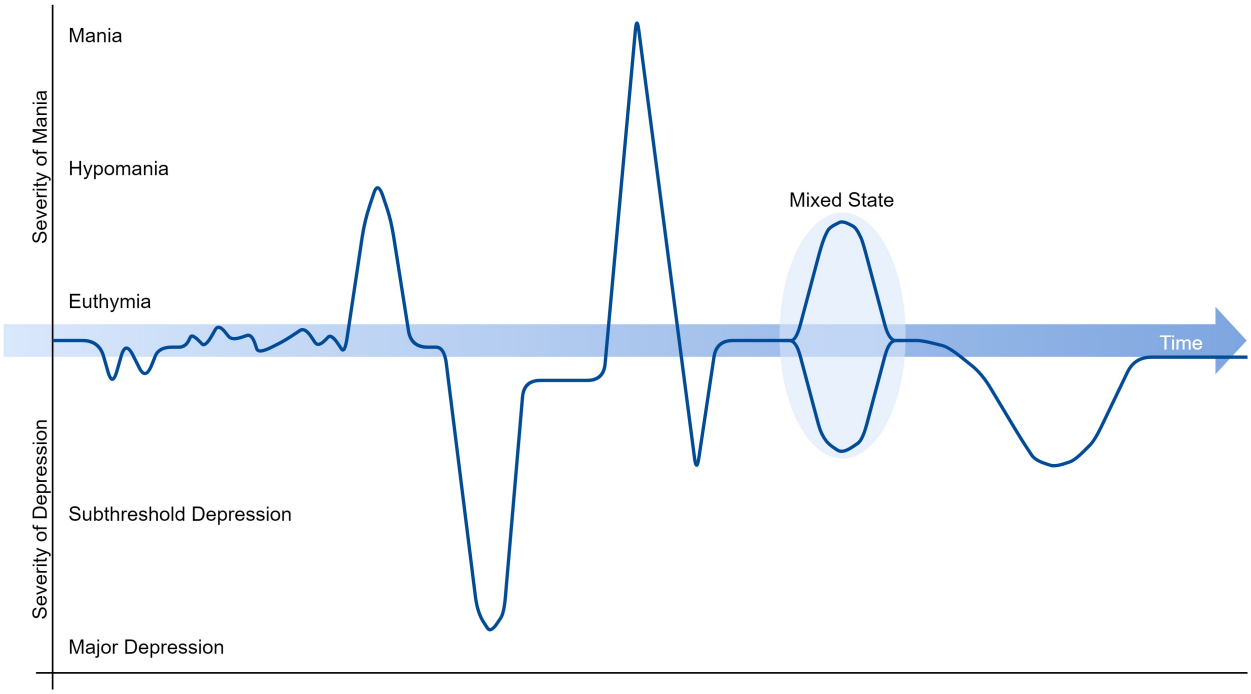

FIGURE 4-2 Longitudinal course of bipolar disorder.
NOTE: As explained in the text, patients with bipolar I disorder experience mania while those with bipolar II disorders experience hypomanic and depression episodes, and patients with cyclothymia do not experience mania or major depression episodes.
SOURCE: Grande et al., 2016.

Bipolar disorder often co-occurs with comorbidities that complicate the course of the disorder. The existence of comorbidities is an important consideration when making decisions about a treatment plan. The most frequent comorbid psychiatric disorders are anxiety disorders, obsessive compulsive disorder, attention deficit hyperactivity disorder (ADHD), substance use disorder, eating disorders, and personality disorders. Common medical comorbid disorders include metabolic syndrome and migraine headache.

Standard Measures of Outcomes for Bipolar Disorder

A recent systematic review examined the clinical utility of patient-reported and clinician-rated measures of mania and depression for the management of bipolar disorder (Cerimele et al., 2019). The authors found that the Altman Self-Rating Mania Scale[5] had high clinical utility in that it is brief, easy to score, and has good reliability and validity. No clinician-rated measure of mania had clinical utility that was as good or better. With regard to depression measures, the researchers concluded that the self-report and clinician-observed version of the Quick Inventory of Depressive Symptomatology both had high clinical utility scores. The five-item version of the Hamilton Depression Rating Scale, a clinician-rated measure, also had high clinical utility scores. The Internal State Scale and the Affective Self-Rating Scale had moderately good clinical utility scores for patient-reported measures. Two measures that clinicians use to rate both mania and depression, the Bipolar Inventory of Symptoms and the Life Chart Methodology—Clinician version, had moderately high clinical utility scores.

In addition to symptom measures, measures of daily functioning and cognition are also pertinent to people with bipolar disorder. Correspondingly, a few tools have been developed and used to measure the functional outcomes of bipolar disorder. Some of the most widely used tools were developed for the general measurement of function (e.g., the Global Assessment of Functioning, Functioning Assessment Short Test, and the WHO Disability Assessment Schedule [WHODAS 2.0], which is directly linked to the *International Classification of Functioning, Disability and Health*). Those tools have been adapted and validated with core sets for bipolar disorder. In the domain of cognitive functioning, the International Society for Bipolar Disorders' Targeting Cognition Task Force recommends the Battery for Assessment of Neurocognition composite (Yatham et al., 2010); an alternative measure that has been validated in bipolar disorder is the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (Burdick et al., 2011).

Treatments for Bipolar Disorders I and II

The first step in deciding on a treatment for bipolar disorder is to determine whether the patient is experiencing mania, hypomania, or depression as the therapeutic plan will vary depending on the state of the individual. Other factors that will require assessment are the presence of comorbidities, previous treatments, and the patient's response to and adverse effects of prior treatments. As with other mental disorders, the patient's preferences for treatment need to be taken into consideration.

As with major depression and other mental disorders, guidelines recognize the need to treat both the acute and maintenance phases (Bauer and Gitlin, 2016). Treating the acute phase, which typically lasts 6–12 weeks, involves establishing the correct diagnosis; initiating treatment; monitoring efficacy, safety, and tolerability; and achieving symptom remission as well as functional improvements. If remission is achieved, the patient enters the maintenance phase, which lasts 6–24 months or longer. During that period the focus is on returning to baseline functioning and quality of life, treating comorbidities, and preventing relapse or recurrence. Though most studies have been short term and have been conducted in individuals experiencing

[5] The Altman Self-Rating Mania Scale is a short, five-item self-assessment questionnaire that can be used in assessing the presence and severity of manic or hypomanic symptoms. This scale is compatible with other diagnostic scales and the DSM-IV diagnostic criteria.

acute episodes, the same therapies are typically recommended for both the acute and the maintenance phases. An example of an algorithm that clinicians use to guide decisions, depending on the patients' status (i.e., whether the patient is in a mania/hypomania, depressive, or mixed episode) can be found in Figure A-2 in Appendix A.

Pharmacotherapy recommendations for bipolar I related depression are summarized in Table 4-5. The CANMAT guideline states that the general principles for assessing depression in patients with bipolar I disorder also apply to patients with bipolar II disorder. The evidence-based treatments for mania are exclusively pharmacologic and not psychologic. For clarity and efficiency, only first- and second-line treatments for mania are listed in Table 4-6.

TABLE 4-5 Pharmacologic Treatments for Acute Bipolar Depression: Level of Evidence[a] and Line of Treatment[b]

Treatment	Level of Evidence and Line of Treatment				
	Acute	**Maintenance**			**Acute**
	Acute Depression	Prevention of Any Mood Episode	Prevention of Depression	Prevention of Mania	Acute Mania
First-line treatments					
Quetiapine	Level 1	Level 1	Level 1	Level 1	Level 1
Lurasidone + Li/DVP	Level 1	Level 3	Level 3	Level 4	
Lithium	Level 2	Level 1	Level 1	Level 1	Level 1
Lamotrigine	Level 2	Level 1	Level 1	Level 2	Negative evidence
Lurasidone	Level 2	Level 4	Level 4	Level 4	nd
Lamotrigine	Level 2	Level 4	Level 4	Level 4	Negative evidence
Second-line treatments					
Divalproex	Level 2	Level 1	Level 2	Level 3	Level 1
SSRIs/bupropion	Level 1	nd	Level 4	nd	
ECT	Level 4	Level 4	Level 4	Level 4	Level 3
Cariprazine	Level 1	nd	nd	nd	Level 1
Olanzapine-fluoxetine	Level 2	nd	nd	nd	nd

NOTES:
[a] Level 1 and 2 evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3.
[b] First line: Level 1 of evidence or Level 2 plus clinical support; Second line: Level 3 or higher plus clinical support; Third line: Level 4 or higher, plus clinical support. Clinical support refers to the application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence maybe downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.
ECT = Electroconvulsive Therapy; Li/DVP = Lithium/Divalproex; nd = No Data; SSRI = Select Serotonin Reuptake Inhibotor.

TABLE 4-6 Pharmacologic Treatments for Acute Mania: Level of Evidence[a] and Line of Treatment[b]

	Level of Evidence and Line of Treatment by Phase				
	Acute	**Maintenance**			**Acute**
	Acute Mania	Prevention of Any Mood Episode	Prevention of Depression	Prevention of Mania	Acute Depression
First-line treatments: Monotherapies					
Lithium	Level 1	Level 1	Level 1	Level 1	Level 2
Quetiapine	Level 1	Level 1	Level 1	Level 1	Level 1
Divalproex	Level 1	Level 1	Level 3	Level 2	Level 2
Asenapine	Level 1	Level 2	Level 2	Level 2	nd
Aripiprazole	Level 1	Level 2	Level 2	nd	Negative evidence
Paliperidone	Level 1	Level 2	Level 2	nd	nd
Risperidone	Level 1	Level 4	Level 4	nd	nd
Cariprazine	Level 1	nd	nd	nd	Level 1
First-line treatments: Combination therapies					
Quetiapine + Li/DVP	Level 1	Level 1	Level 1	Level 1	Level 4
Aripiprazole + Li/DVP	Level 2	Level 2	Level 2	nd	Level 4
Risperidone + Li/DVP	Level 1	Level 4	Level 4	nd	Level 4
Asenapine + Li/DVP	Level 3	Level 4	Level 4	nd	Level 4
Second-line treatments					
Olanzapine	Level 1	Level 1	Level 1	Level 1	Level 1
Carbamazepine	Level 1	Level 2	Level 2	Level 2	Level 3
Olanzapine + Li/DVP	Level 1	Level 4	Level 4	Level 4	nd
Li + DVP	Level 3	Level 3	Level 3	nd	nd
Ziprasidone	Level 1	Level 4	Level 4	nd	Negative evidence
Haloperidol	Level 1	nd	Level 4	Negative evidence	nd
ECT	Level 3	Level 4	Level 4	Level 4	Level 4

NOTES:

[a] Level 1 and 2 evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiologic or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3.

[b] First line: Level 1 evidence or 2 plus clinical support; Second line: Level 3 or higher plus clinical support; Third line: Level 4 or higher, plus clinical support. Clinical support refers to application of

expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence maybe downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.
Ect = Electroconvulsive Therapy; Li/DVP = Lithium/Divalproex; nd = No Data.

Bipolar disorders cause a wide range of functional impairments which can be lasting and which merit treatment in an effort to improve overall outcomes. Persistent functional impairment is predicted by the number of manic/hypomanic episodes and is even more strongly correlated with subsyndromal mood symptoms, especially mood instability and mild depressive symptoms (Gitlin and Miklowitz, 2017). Cognitive impairment can be caused by depression, mania, or hypomania and also persists after symptomatic recovery. Cognitive impairment represents an independent impediment to functional recovery (Baune and Malhi, 2015; Gitlin and Miklowitz, 2016). Cognitive impairment may stem from medication side effects and experiencing psychosis during mood episodes (Gitlin and Miklowitz, 2016). Psychosocial stress (e.g., deterioration of social and financial supports) as well as personality factors and substance dependence can play a role in functional outcomes (Gitlin and Miklowitz, 2017). A number of other factors are associated with worse functional outcomes, such as lower education, being unmarried, poor sleep quality, receiving multiple psychiatric medications, and hospitalization (APA, 2013; Bonnin et al., 2019).

Bipolar-related impaired ability to work is especially pertinent to this report. As is the case with other mental disorders, functional recovery, including return to work, may lag behind or not occur despite a recovery from symptoms (Gitlin and Miklowitz, 2017). As a result, multiple investigations have examined the efficacy of treatments that combine medical management and psychosocial treatments in order to improve residual functional outcomes, including cognitive impairment and work disability. There is some evidence that work-focused interventions such as Vocational Case Management, a multi-faceted supported employment intervention (Abdel-Baki et al., 2013; Drake et al., 2013), and cognitive remediation plus supported employment (Ikebuchi et al., 2017) improve work outcomes in people with severe mental illness, including bipolar disorder. Evidence indicates that for persons on SSDI, robust return-to-work efforts rarely result in substantial gainful employment (Drake et al., 2013).

Length of Time to Improvement for Bipolar Disorders

The committee could not find any evidence to indicate clearly what the time to functional improvement in bipolar disorders is. In one large, longitudinal study of bipolar disorder under usual care conditions, 25 percent of individuals recovered from the onset of a mood episode within 5 weeks, 50 percent recovered within 13 weeks, 75 percent recovered within 38 weeks, and 85–89 percent recovered within 2 years (Solomon et al., 2010). Functional recovery is thought to lag behind symptomatic recovery and potentially depends on additional specific treatments to promote improved functioning in bipolar disorder (Gitlin and Miklowitz, 2017). Therefore, the rates of recovery suggested by Solomon and colleagues likely underestimate the time to functional improvement. Finally, a study of Social Security beneficiaries with bipolar, schizophrenia, or depression found that in the treatment arm of the study, employment increased from 5 to 30 percent by the end of 16 months, but the results may not be representative of these populations because of the low participation (Drake et al., 2013).

Both pharmacologic and psychologic treatments have a role in managing bipolar disorders. The 2018 CANMAT guideline on managing bipolar disorder concludes that despite limited research on treatment efficacy in older adults, medications that are efficacious in adults are likely to be efficacious in older adults (Yatham et al., 2018); that conclusion was thought to be true for managing acute mania, bipolar depression, and maintenance therapy. Therefore, improvement should be possible across all adult ages. With regard to psychologic treatments for bipolar-related depression, there is research demonstrating the efficacy of cognitive behavioral therapy for treating depression in both the acute and the maintenance phases of bipolar I disorder. Psychoeducation is considered to be an evidence-based treatment only for the acute phase (see CANMAT guidelines).

OBSESSIVE COMPULSIVE DISORDER

Obsessive compulsive disorder (OCD) is a relatively common and potentially highly disabling disorder with substantial impacts on multiple domains of functioning. The illness is generally characterized by the presence of unwanted, recurring thoughts (obsessions) that generate compulsions which are thoughts or acts performed to reduce distress or prevent an undesirable outcome related to the obsessions.

According to the NCS-R, OCD has a lifetime prevalence of 2.3 percent and a 12-month prevalence of 1.2 percent (Ruscio et al., 2010). The mean age of onset is 19.5 years old, and new onset rarely occurs after age 30 (Ruscio et al., 2010). The NCS-R study also found that males are more likely to develop early onset, with almost a quarter of males developing the illness before age 10. In contrast, females tend to have higher rates of onset during adolescence. Overall, several epidemiologic studies of children and adolescents reported equal rates in boys and girls (Flament et al., 1988; Heyman et al., 2001). The disorder is evenly distributed across socioeconomic strata in most studies (Karno et al., 1988).

Almost 30 percent of individuals without OCD report experiencing obsessions or compulsions at some point in their lives. That finding underscores the general problem in obtaining an accurate understanding of the epidemiology of OCD. Prevalence estimates have varied widely, perhaps due to the differing definitions of the disorder and shifts in understanding of the threshold for having a diagnosis as opposed to subsyndromal symptoms (Ruscio et al., 2010). Notably, diagnoses of OCD obtained in the Epidemiological Catchment Area Study[6] were found to have poor validity (Nelson and Rice, 1997), leaving estimates of the prevalence of OCD uncertain at that time. The NCS-R study found that individuals with lifetime OCD who had symptoms within the past year reported spending an average of 5.9 hours each day coping with obsessions and 4.6 hours per day engaging in compulsions (Ruscio et al., 2010). Such intense engagement would likely interfere with functioning.

The disability and reduced quality of life associated with a diagnosis of OCD is substantial. WHO has ranked OCD as the 10th leading cause of disability of all health conditions in the industrialized world. Specifically, the NCS-R found that nearly two-thirds (65.3 percent) of people who had been diagnosed with OCD and who had experienced symptoms for 12 months reported severe impairment. Just over half (53.6 percent) reported any work-related impairment

[6] The Epidemiologic Catchment Area (ECA) program of research was initiated in response to the 1977 report of the President's Commission on Mental Health. The purpose was to collect data on the prevalence and incidence of mental disorders and on the use of and need for services by the mentally ill.

(Ruscio et al., 2010). In a large study of outpatients, Yaryura-Tobias and colleagues (2000) found that increased OCD symptoms were associated with reduced occupational functioning. A loss of work, reduction to part-time status, or work in occupations unrelated to professional training (i.e., nonprofessional work when trained for professional career) were common.

Professionally Accepted Diagnostic Criteria for OCD

The diagnostic criteria for OCD changed to some extent between the *Diagnostic and Statistical Manual for Mental Disorders, 4th Edition* (DSM-IV), which was used before 2013, and DSM-5. Table A-6 in Appendix A shows the differences between DSM-IV and DSM-5. In DSM-IV, OCD was considered in the class of anxiety disorders. In DSM-5 it was considered in the class of obsessive-compulsive and related disorders. DSM-5 also allows the specification of the presence of a current or a past tic disorder.

The professionally accepted current diagnostic criteria for OCD are described within the most recent DSM-5 and listed in Table 4-7.

TABLE 4-7 DSM-5 Criteria for Obsessive-Compulsive Disorder

Criterion/Symptom Description
A. Presence of obsessions, compulsions, or both: Obsessions are defined by (1) and (2): 1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress. 2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion). Compulsions are defined by (1) and (2): 1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly. 2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive. Note: Young children may not be able to articulate the aims of these behaviors or mental acts.
B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The obsessive compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and

other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:
With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.
With poor insight: The individual thinks obsessive compulsive disorder beliefs are probably true.
With absent insight/delusional beliefs: The individual is completely convinced that obsessive compulsive disorder beliefs are true.
Tic-related: The individual has a current or past history of a tic disorder.

Developmental Course, Gender Distribution, and Comorbidities

OCD is often chronic if left untreated. Remission rates for treated individuals are more promising. In a meta-analysis examining long-term remission in adults with OCD, remission rates were found to be 53 percent (Sharma et al., 2014). In that study, remission was defined as a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) rating of less than 16 at the longest follow-up. The meta-analysis included 17 studies with a mean follow-up time of 4.91 years and was composed primarily of naturalistic studies. Being of female gender, experiencing a shorter duration of untreated illness, having had an onset in late adolescence or early adulthood, and having a lower baseline symptom severity were associated with better outcomes. Poorer insight has been linked to worse long-term outcome (APA, 2013). The DSM-5 also includes gender differences on symptomatology (APA, 2013) for OCD.

OCD can be comorbid with other psychiatric disorders. The most common comorbidities are depression (41 percent) and anxiety disorders, such as panic disorder, generalized anxiety disorder, specific phobias, or social anxiety disorder (76 percent) (DSM-5). Childhood onset is associated with high rates of ADHD, oppositional defiant disorder, and tic disorders (Janardhan Reddy, 2017). Tic disorder is most common in males with childhood onset (APA, 2013).

Additional comorbidities may include bipolar disorder, with a prevalence of 17 percent (Amerio et al., 2014), and schizophrenia, with a prevalence of 12.1 percent (Achim, 2009; Janardhan Reddy, 2017). Prevalence estimates for comorbid OCD and bipolar disorder are higher in children and adolescents than in adults (24.2 to 13.5 percent, respectively) (Amerio et al., 2014). OCD that is comorbid with bipolar disorder tends to be episodic in nature, with worsening symptoms during depressive periods and improvement in symptoms during manic or hypomanic periods (Janardhan Reddy, 2017). Mood symptoms influence the type of treatment used because the SSRIs commonly used to treat OCD might induce mania or lead to rapid cycling (Janardhan Reddy, 2017). OCD symptoms are reported in approximately one-third of schizophrenia patients (Janardhan Reddy, 2017). Antipsychotics such as clozapine, risperidone, and olanzapine may cause or worsen obsessive compulsive symptoms (Janardhan Reddy, 2017).

Standard Measures of Outcomes for OCD

The primary outcome measure used to evaluate improvements in symptoms is the Y-BOCS; there are versions for children and adults (Janardhan Reddy, 2017; Sharma et al., 2014). The Y-BOCS is a 10-item scale measuring symptom severity during the previous week. Scores greater than or equal to 16 are considered clinically significant (Janardhan Reddy, 2017). The Y-BOCS asks about time spent dealing with compulsions, impact on functioning, distress, and resistance against and degree of control over both obsessions and delusions. The Y-BOCS scores

are correlated with the Quality of Life scale, and Y-BOCS scores greater than 20 have an impact on functioning (as cited in Sharma et al., 2014). The Y-BOCS functioning items are listed in Box 4-1.

BOX 4-1
Functioning Items in the Yale–Brown Obsessive Compulsive Scale

Interference Due To Obsessive Thoughts Score
How much do your obsessive thoughts interfere with your work, school, social, or other important role functioning? Is there anything that you don't do because of them?
0 = None
1 = Slight interference with social or other activities, but overall performance not impaired
2 = Definite interference with social or occupational performance, but still manageable
3 = Causes substantial impairment in social or occupational performance
4 = Incapacitating

Interference Due To Compulsive Behaviors Score
How much do your obsessive thoughts interfere with your work, school, social, or other important role functioning? Is there anything that you don't do because of them?
0 = None
1 = Slight interference with social or other activities, but overall performance not impaired
2 = Definite interference with social or occupational performance, but still manageable
3 = Causes substantial impairment in social or occupational performance
4 = Incapacitating

A positive response to treatment that lasts for a week is indicated by a 35 percent or greater reduction in Y-BOCS scores and a Clinical Global Impression–Improvement (CGI-I) score of 1 or 2 (1=very much improved, 2=much improved) (Janardhan Reddy, 2017). Remission is present when a patient no longer meets the DSM criteria for the disorder or has a score of 12 or less on the Y-BOCS and a Clinical Global Impression-Severity (CGI-S) score of 1 or 2 (1=normal, not at all ill, 2=borderline mentally ill) for 1 week (Janardhan Reddy, 2017). During that time, residual obsessive-compulsive symptoms might be present, but they are not time consuming or life interfering. To be considered to be in recovery, patients must meet those same criteria for remission for at least 1 year (Janardhan Reddy, 2017).

Treatments for OCD

To the extent that the Y-BOCS, which covers both symptom severity and functioning, has been used in studies on which the practice guidelines are based, the treatments should have implications for both symptom reduction and functioning. At the same time, because functioning is embedded in the Y-BOCS, an overall score might not provide specific information about functioning. Scores of 3 or 4 on Y-BOCS items 2 and 7 would be most associated with functional impairment. The committee did not find evidence suggesting that treatment recommendations vary by age in adults.

Psychotherapy for OCD

The American Psychiatric Association (APA) practice guidelines indicate that cognitive behavioral therapy (CBT) consisting of exposure response prevention (ERP) should be a first-

line treatment for patients who are not too severely ill, anxious, or depressed to comply with treatment (Koran et al., 2007). The recommended duration includes 13–20 weekly sessions or daily sessions for 3 weeks (Koran et al., 2007). Successful treatment should be followed by monthly boosters for 3–6 months to prevent relapse (Janardhan Reddy 2017; Koran et al., 2007).

Although the APA guidelines recommend ERP as a first line treatment, the Canadian Clinical Practice Guidelines for Management of Anxiety, Post Traumatic Stress, and Obsessive Compulsive Disorders suggest that outcomes are similar between interventions that focus on exposure and those that focus on cognitive interventions (Katzman et al., 2014). In one study, a cognitive intervention (danger ideation reduction therapy) without exposure was found to be more effective than the intervention with exposure (as cited in Katzman et al., 2014). Katzman and colleagues (2014) suggest that cognitive interventions may be more helpful for patients without overt compulsions, since exposure is more difficult with these patients. A review article on OCD (Grant, 2014) found that approximately 60–85 percent of patients have a reduction in symptoms after exposure therapy and that the improvement in symptoms is maintained for up to 5 years after treatment discontinuation. After cognitive therapy, about 60–80 percent of patients improve, but there is a 20–30 percent dropout rate (Grant, 2014).

With new advances in technology, there is a question regarding whether technology-delivered CBT is as effective as in person CBT. The British Association for Psychopharmacology (BAP) guidelines indicate that although internet-delivered CBT is better than online supportive therapy, therapist-led CBT is more effective than computerized CBT (Baldwin, 2014). A recent meta-analysis (Dèttore et al., 2015), examining the effectiveness of technology-delivered CBT versus control and therapist-administered CBT, found technology-delivered CBT was better than control on OCD symptoms but not on comorbid depression. The differences between the two methods of delivering treatment were not significant, even though there was a trend favoring therapist-administered CBT.

The effectiveness of individual versus group CBT is unknown (Baldwin et al., 2014). However, the National Institute for Health and Care Excellence (NICE) 2013 guidelines indicate that more people have clinical remission with group CBT rather than with sertraline medication. If patients are non-responsive to CBT, it is recommended that SSRIs or CBT plus SSRIs be used (Janardhan Reddy, 2017). Combined psychological and pharmacologic treatment has been shown to be superior to medication alone, but not to CBT alone (Katzman et al., 2014).

Medications for OCD

Serotonin reuptake inhibitors (SRIs) are recommended for patients who are unable to comply with CBT, prefer medication, or have previously responded well to medication (Koran, 2007). Sertraline, clomipramine, fluoxetine, fluvoxamine, and paroxetine are approved by the U.S. Food and Drug Administration (FDA) for the pharmacologic treatment of OCD (Koran et al., 2007). Although research suggests that clomipramine may have greater efficacy than other SSRIs, it is not typically recommended because of its side effects; therefore other SSRIs are recommended as a first-line treatment (Baldwin et al., 2014; Bandelow et al., 2008; Koran et al., 2007). Clomipramine and other SSRI treatments result in a 20 to 40 percent symptom improvement in about 40 to 65 percent of patients (Grant, 2014).

During SRI treatment, APA guidelines recommend increasing the dosage on a weekly basis to the maximum tolerated and FDA-approved dosage during the first month of treatment and continuing at that dose for at least 6 weeks (Koran et al., 2007). Other guidelines, such as those from NICE and the British Association for Psychopharmacology, recommend starting at

lower doses and only increasing the dose if there is an insufficient response (Baldwin et al., 2014; NICE, 2006). It is recommended that effective treatment should be continued for at least 12 months to prevent relapse. APA guidelines recommend continuing successful medication treatment for 1–2 years before tapering by 10–25 percent every 1–2 months (Koran et al., 2007). Relapse rates are 25–40 percent if treatment is discontinued after 2 years and as high as 80 percent if treatment is discontinued earlier (Grant, 2014). The probability of full remission with pharmacotherapy alone is 11 percent (Grant, 2014). An early age of onset, severe OCD, tics, or hoarding symptoms are associated with poor response to pharmacotherapy (Grant, 2014).

The British Association for Psychopharmacology guidelines also suggest that increasing the dose of an SSRI beyond formulary limits may be helpful or, alternatively, considering the augmentation of an SSRI or clomipramine with an antipsychotic (Baldwin et al., 2014). That is supported by evidence from a meta-analysis comparing antipsychotic augmentation and placebo augmentation in treatment-resistant OCD (Dold et al., 2013). In that study the antipsychotics aripiprazole, haloperidol, and risperidone were significantly more effective than placebo at reducing Y-BOCS scores (Dold et al., 2013). However, olanzapine, paliperidone, and quetiapine were not significantly different from placebo. Another potential treatment is electroconvulsive therapy, but the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines state that this should be limited to treatment-refractory OCD (Bandelow et al., 2008).

Other Treatments

Most guidelines, such as those from NICE and WFSBP, indicate that transcranial magnetic stimulation (TMS)[7] might not be an effective treatment for OCD (Bandelow et al., 2008; NICE, 2013). However, the Canadian clinical practice guidelines suggest that it may be helpful for improving comorbid depressive symptoms (Katzman et al., 2014). TMS is typically used when other depression treatments have not been effective. Deep high-frequency TMS was found to be more effective than sham TMS for individuals whose OCD did not satisfactorily respond to pharmacologic and psychologic interventions.

The Canadian clinical practice guidelines also indicate that deep brain stimulation might improve symptoms and functioning in up to two-thirds of patients with treatment-refractory OCD, based on data from small studies (Katzman et al., 2014). A meta-analysis of 31 deep brain stimulation studies for severe treatment-resistant OCD in 116 adults found a Y-BOCS reduction of 45.1 percent after treatment (Alonso et al., 2015). Better response was associated with an older age at onset and the presence of sexual or religious obsessions and compulsions.

Brown et al. (2016) conducted a systematic review of the literature and found supporting evidence for the efficacy of both dorsal anterior cingulotomy and anterior capsulotomy in highly treatment-refractory populations. Other experimental treatments that may improve symptoms include adjunctive moderate intensity aerobic exercise and herbal therapies such as milk thistle, valerian root, and St. John's wort (Katzman et al., 2014).

Length of Time to Improvement for OCD

According to the Canadian clinical practice guidelines, the optimal duration and intensity of treatment is a persistent question (Katzman et al., 2014). An intensive exposure and response

[7] Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression.

prevention therapy (ERP) program provides 15 2-hour sessions delivered daily (5 days per week) over 3 weeks (Foa et al., 2005; Kuzak and Foa, 2004). Interestingly, a comparable twice-weekly program was similarly effective as the intensive 5 days/week strategy (Abramowitz et al., 2003). Another study which provided a step-care approach consisting of 6 weeks of low-intensity counseling with ERP bibliotherapy (i.e., reading materials relevant to the individual with OCD) and standard ERP for those who did respond was generally as effective as an initial therapy with standard ERP (17 sessions twice weekly) (Tolin et al., 2011). Accordingly, the APA practice guidelines indicate that the number of treatment sessions, their length, and the duration of an adequate trial have not been firmly and consistently established; nevertheless, expert consensus is that for most patients treatment should consist of 13–20 weekly sessions. A number of studies that followed patients longitudinally have found that the benefits of cognitive behavioral therapy (CBT) may last from 1 to 5 years (Braga et al., 2010; Jaurrieta et al., 2008; van Oppen et al., 2005).

In contrast to psychotherapy, psychopharmacologic treatments will not produce substantial improvement until patients have received 4–6 weeks of medication. Further, in some patients treatment for as much as 10–12 weeks is necessary to see meaningful improvement.

Relapse prevention and naturalistic follow-up studies have provided information about the long-term benefits of therapy. Generally speaking, such studies compare patients who have responded to medication and who are then randomized to placebo or continued active treatment. Overall, a meta-analysis of six relapse-prevention studies provided support for the ongoing benefits of treatment in reducing risk of relapse with SSRIs over 6 to 12 months (Donovan et al., 2010). A number of medications have shown benefits in randomized controlled trials (RCTs), including escitalopram (Fineberg et al., 2007), paroxetine (Hollander et al., 2003), sertraline (Koran et al., 2002), and high-dose fluoxetine. (Romano et al., 2001). In addition, studies that have tested mirtazapine (Koran et al., 2005) and clomipramine (Katz et al., 1990) have demonstrated continued improvement compared with placebo in RCT discontinuation studies over approximately 6 to 12 months. Other studies provide evidence that fluoxetine, fluvoxamine XR, and sertraline are efficacious of over 6 to 24 months (Bergeron et al., 2002; Koran et al., 2010; Rasmussen et al., 1997; Ravizza et al., 1996)

It is notable that complete relief from all OCD symptoms is uncommon with first treatments. If 13–20 weeks of weekly outpatient CBT treatment, 3 weeks of daily CBT, or 8–12 weeks of SRI treatment (including 4–6 weeks at the highest comfortably tolerated dose) does not produce an adequate response, it is reasonable for the clinician to consider, with the patient, whether to enhance or alter the treatment (see APA guidelines).

Given that OCD can be a relapsing disorder, another set of challenges and decisions confronts patients who have responded to treatment and their clinicians: How long should such treatments should be continued? APA guidelines suggest that successful medication treatment should be continued for 1–2 years. At that point it is reasonable to consider a gradual taper by decrements of 10–25 percent every 1–2 months with close monitoring of the possibility of symptom return or exacerbation. Regarding ERP, it is recommended that patients receive monthly booster sessions for 3–6 months following an initial successful course of ERP. Follow-up could be more intensive for individuals who have achieved only a partial improvement. It is difficult to know the relapse rates in discontinuation trials of medications because of methodologic differences across studies. Thus, a continued treatment of some form is recommended for most patients. The benefits of ERP may be more durable than those of some

SRIs after discontinuation, but it is also possible that the observed differences in relapse rates across the two treatment types could be explained by other factors.

Relationship Between Symptomatic and Functional Improvement in OCD

As previously mentioned, the treatment for OCD very likely improves functional outcomes based on improvements in the Y-BOCS. However, there is scant information from treatment trials on the specific impact of different treatments on occupational functioning. A recent randomized trial comparing cognitive behavioral therapy (exposure and ritual prevention [EX/RP]) to risperidone and pill placebo found greater functional improvements among patients receiving EX/RP than among those who received risperidone or the pill placebo (Asnaani et al., 2017). Steketee (1997) noted that few treatment outcome studies have examined functional outcome; a few studies of ERP did establish improvement in occupational functioning with treatment and 1 one year after treatment completion. A review evaluating the impact of in vivo exposure in treatment of individuals with anxiety disorders did find some benefits of such exposure on work-related outcomes for individuals with OCD (Noordik et al., 2010). Specifically, the authors found low- to high-quality evidence that exposure in vivo can reduce adverse work-related outcomes with a medium to large effect in different modalities and comparisons (group CBT versus SSRIs, group CBT plus SSRIs versus SSRIs, clinician-guided CBT versus systematic self-relaxation, exposure homework combined with clomipramine versus clomipramine with anti-exposure homework). They also found moderate evidence that exposure in vivo failed to improve adverse work-related outcomes in workers with OCD in three other modalities and comparisons (computer CBT at home via telephone versus systematic self-relaxation, exposure at home versus response prevention, and exposure at home plus response prevention versus response prevention). Additionally, Noordik et al. (2010) summarized a meta-analysis of two OCD studies representing the net contribution of exposure in vivo; their overall conclusion from those meta-analyses is that there is moderate evidence that anxiety treatments, including exposure in vivo, can improve work-related outcomes in workers with OCD.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder, or PTSD, is a potentially chronic and disabling condition associated with significant morbidity and mortality as well as with disruptions in family, work, and social relationships (APA, 2013). Extensive research has documented the negative consequences of PTSD, including presence of other forms of psychophathology (Brown et al., 2001; Gradus et al., 2015a; Kessler et al., 1995; O'Donnell et al., 2004; Pietrzak et al., 2011); poor physical health (Gradus et al., 2015a, 2017; Hoge et al., 2007; Pacella et al., 2013; Schnurr and Jankowski, 1999); poor health-related quality of life (Fang et al., 2015: Goldberg et al., 2014; Schnurr et al., 2006, 2009); and mortality, specifically death by suicide (Boscarino, 2006; Gradus et al., 2015a,b, 2018; Kessler et al., 1999a). Thus, it is not surprising that PTSD has been described as conferring an important burden to individuals and society (Kessler, 2000).

Professionally Accepted Diagnostic Criteria for PTSD

The professionally accepted diagnostic criteria for PTSD are described within the DSM-5 (APA, 2013) and listed in Table 4-8. It is critical to note that the diagnostic criteria for PTSD

have changed in significant ways in the last few years (VA/DoD, 2017). Prior to the current diagnostic criteria in the DSM-5, from 2004 to 2013, the 4th edition DSM-IV was used to diagnose PTSD (APA, 2000). One of the more substantive changes is its new classification as a trauma- and stress-related disorder (versus an anxiety disorder in the DSM-IV). In addition, the definition of trauma has been clarified and narrowed. The number of symptom groups increased from three to four, and the number of symptoms increased from 17 to 20. Furthermore, acute and chronic PTSD specifiers were eliminated in the DSM-5, and the concept of "delayed-onset PTSD" was replaced with "delayed expression." These changes have the potential for significant impact on the screening and diagnosis of PTSD. One study has estimated that a significant number of people (~50 percent) would be diagnosed under one set of criteria but not the other (Hoge et al., 2016), while other experts do not support that conclusion (Friedman et al., 2016). An additional important implication, particularly with regard to our understanding of the effect of available treatments, is that almost all research to date on recommended treatments for PTSD was performed among persons meeting the criteria for the previous DSM-IV definition and not the current DSM-5 definition of PTSD. Until more is known about the implications of the change in diagnostic criteria on PTSD screening, diagnosis, and treatment, this report must be read and interpreted with appropriate caution.

TABLE 4-8 DSM-5 Criteria for Posttraumatic Stress Disorder

Criterion/Symptom Description
Note: The following criteria apply to adults, adolescents, and children older than 6 years.
A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains: police officers repeatedly exposed to details of child abuse).
Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.
B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
Note: In children, there may be frightening dreams without recognizable content.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
Note: In children, trauma-specific reenactment may occur in play.
4. Intense or prolonged psychologic distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:
With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder and, in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:
1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:
With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Developmental Course, Gender Distribution, and Comorbidities

According to the National Comorbidity Survey, the lifetime prevalence of PTSD in the U.S. general population is 8 percent, making it the fifth-most prevalent mental disorder in the United States (Kessler et al., 1995). The 12-month prevalence is 3.5 percent (Kessler et al., 2005a). More recent data from the National Epidemiologic Survey on Alcohol and Other Related Conditions reported a PTSD prevalence of 6.4 percent overall in the United States, with a prevalence of 8.6 percent in women and 4.1 percent in men (Pietrzak et al., 2011). PTSD is a common issue among U.S. veterans—approximately 10 percent of VA health care users have a PTSD diagnosis (Bernardy and Friedman, 2017). According to the DSM-5, PTSD can occur at any point from 1 year of age onward (APA, 2013).

Almost all people who experience a trauma will experience at least some symptoms consistent with PTSD in the immediate aftermath of the event. For many people the symptoms will resolve over time, usually in 1 to 3 months (APA, 2017). A recent meta-analysis of the natural course of PTSD remission found that without specific treatment, 44 percent of individuals with PTSD at baseline no longer met criteria for the diagnosis at approximately 10 months (Morina et al., 2014). Persons with PTSD symptoms that do not resolve over time, or that worsen, become eligible for a diagnosis of PTSD. While most people with PTSD experience an onset of symptoms immediately after a trauma and it is the lack of the resolution of these symptoms that ultimately leads to a diagnosis, research has shown that a significant proportion (approximately 15–25 percent) of the population may experience delayed onset PTSD in which the diagnostic criteria are not met until 6 months after the traumatic event (VA/DoD, 2017). The symptoms of PTSD can cause significant distress and impairment in functioning, yet many people with PTSD do not present for treatment for months or sometimes years after the symptoms begin (likely owing at least in part to the nature of the disorder, which involves avoidance of reminders of the event). Studies have shown that approximately 42.6 percent of adults with PTSD do not seek treatment and that the treatment is often inadequate among those persons who do seek treatment (Forman-Hoffman et al., 2018). According to a 2014 systematic review and meta-analysis of 42 observational prospective studies including 81,642 persons, 44 percent of individuals with PTSD no longer met criteria for the diagnosis after 10 months, but overall PTSD remission rates varied greatly across studies (from 8 to 89 percent) (Morina et al., 2014). It is important to note that the previous work was based on observational research and, in these studies, remission was not linked to any specific treatment. Therefore, an average remission rate cannot be implied because the remission rates in individual studies are not comparable.

Diagnoses of comorbid psychiatric disorders and physical health conditions are common among persons with PTSD (Forman-Hoffman et al., 2018). According to the APA publication *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder in Adults* (2017),

commonly co-occurring psychiatric disorders and conditions include substance use and abuse, depression, anxiety, dissociation and dissociative disorders, personality disorders, psychosis, cognitive impairment, violence toward self and others, non-suicidal self-injury, and suicide. PTSD has also been shown to be associated with poorer physical health, morbidity, and increased health care use (VA/DoD, 2017). While PTSD itself is in part defined by compromised functional status, the co-occurrence of other disorders with PTSD can lead to further functional challenges and a decreased quality of life (VA/DoD, 2017). The adverse consequences of PTSD and comorbid disorders can be seen over the life course with impacts on many domains of functioning, including educational attainment, work stability, marriage, and family life. Although comorbidity should not prevent patients from receiving PTSD treatment (VA/DoD, 2017), complications due to multiple comorbidities can make PTSD difficult to treat (APA, 2017).

Standard Measures of Outcomes for PTSD

In almost all studies of PTSD treatment, the main outcome of interest is PTSD symptom reduction (other secondary outcomes typically assessed include the loss of the PTSD diagnosis or improvement in functioning) as a marker of treatment efficacy (Forman-Hoffman et al., 2018). Both clinician-administered and patient-rated diagnostic instruments can be used for measuring outcomes. Among the clinician-administered measures, the Clinician-Administered PTSD Scale (CAPS) is a commonly used 30-item scale that assesses past-week, past-month, or lifetime PTSD and PTSD severity (Weathers et al., 2001). Versions of the CAPS have been developed that correspond to both the DSM-IV and the DSM-5 diagnostic criteria. Other clinician-administered PTSD scales include the PTSD Symptom Scale Interview, the Posttraumatic Diagnostic Scale, and the Structured Interview for PTSD (Forman-Hoffman et al., 2018). Among patient-rated or self-report measures, the PTSD checklist (PCL-5), is a commonly used a 20-item measure (note: a previous version of the PCL that corresponded with the 17 items of the DSM-IV diagnostic criteria for PTSD was also commonly used, particularly in the research that generated the treatment results described below) (Weathers et al., 1993). Furthermore, a four-item primary care PTSD screening tool is often recommended and has demonstrated good reliability and validity (Spoont et al., 2015). Other patient-rated PTSD measures include: the PTSD Symptom Scale Self-report Version and the Impact of Events Scale (Forman-Hoffman et al., 2018).

Because compromised functioning is an essential criterion of PTSD diagnosis, scales related to the assessment of functioning have also been used in PTSD treatment studies. Outcome scales in this domain include the Global Assessment of Functioning, the Sheehan Disability Scale, and the Work and Social Adjustment Scale (Forman-Hoffman et al., 2018).

Treatments for PTSD

Although often thought of as a chronic condition, PTSD is treatable, even many years after a traumatic event. The committee did not find evidence suggesting that treatment recommendations vary by age in adults. As with many disorders, an early diagnosis and appropriate treatment of PTSD are crucial to ameliorating its symptoms and shortening the course of the disorder, as well as reducing functional impairment (Forman-Hoffman et al., 2018). Despite this, there is no one universally preferred method for treating PTSD, and the various treatment guidelines that exist offer somewhat contradictory recommendations (Forman-Hoffman et al., 2018). Combine that with treatment complications that arise as a result of high levels of comorbid psychiatric disorders and variability in PTSD presentation, and it becomes

clear why clinical uncertainty remains about which treatment to select for patients. A recent report from the Agency for Healthcare Research and Quality (AHRQ) provides the following broad guidance on the length of adequate treatment: "receiving either appropriate pharmacotherapy for 2 or more months for the focal disorder plus more than four visits to any type of physician or eight or more psychotherapy visits with any health care or human services professional lasting an average of 30 minutes or more" (Forman-Hoffman et al., 2018). Manualized trauma-focused psychotherapies for PTSD (described below) mostly involve 8 to 16 sessions with a therapist (VA/DoD, 2017).

Below is summary of the PTSD treatment recommendations from three clinical practice guidelines—specifically, the APA, the International Society for Traumatic Stress Studies, and the VA and DoD (APA, 2017; VA/DoD, 2017)—and the 2018 systematic review from the AHRQ (Forman-Hoffman et al., 2018). These recommendations fall broadly within two categories: psychologic and pharmacologic interventions.

Psychotherapy for PTSD

According to the Department of Veterans Affairs and Department of Defense (VA/DoD) joint document Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder, the first-line recommendation for PTSD is psychotherapy with treatments that involve cognitive restructuring or exposure (as compared with non-trauma-focused psychotherapy or pharmacotherapy) (VA/DoD, 2017). The recommendation of trauma-focused psychotherapy as preferable to pharmacotherapy was based on the results of two meta-analyses which demonstrated that psychotherapy has greater and longer-lasting benefits on PTSD symptoms than pharmacotherapy (Lee et al., 2016; Watts et al., 2013). The trauma-focused psychotherapies generally recommended in the VA/DoD guideline include cognitive processing therapy (CPT), prolonged exposure (PE), and eye movement desensitization therapy (EMDR), specific cognitive behavioral therapies for PTSD, brief eclectic psychotherapy (BEP), narrative exposure therapy (NET), and written narrative exposure. According to the VA/DoD guideline, the strongest evidence is shown for CPT, PE, and EMDR, with evidence of efficacy on amelioration of PTSD symptoms across trials and under varying methods and settings, while the other therapies listed above have sufficient (although potentially less strong) evidence to warrant their use. Within the VA/DoD guideline, second-line psychotherapy treatments include non-trauma focused interventions such as stress inoculation training, present-centered therapy (PCT), and interpersonal psychotherapy (IPT). In general, those treatments are described as likely not having as large an effect as trauma-focused psychotherapy, but they are useful options when trauma-focused therapy is not available or when preferred by the patient (VA/DoD, 2017).

The VA/DoD guideline is generally consistent with the International Society for Traumatic Stress Studies (ISTSS) Posttraumatic Stress Disorder Prevention and Treatment Guidelines, which strongly recommends CBT, cognitive therapy, EMDR, PE, and trauma-focused CBT (Hoskins et al., 2015). The guideline further provides a recommendation of non-trauma-focused CBT, NET, and PCT (Hoskins et al., 2015). In contrast, guidelines from the APA do not distinguish any form of psychotherapy as a first-line treatment for PTSD, relative to pharmacotherapy, likely due to the few studies comparing the effectiveness of psychotherapy and pharmacotherapy for PTSD directly (APA, 2017). Overall, the APA treatment guidelines strongly recommend CBT, CT, and PE for the treatment of PTSD (APA, 2017). Those recommendations were largely upheld by a more recent (2018) systematic review from the AHRQ (Forman-Hoffman et al., 2018). Although the term "first line treatments" was purposely

omitted from the APA guidelines, CBT, CPT, cognitive therapy, and PE were recommended more strongly than other forms of psychotherapy. (APA, 2017).

Medications for PTSD

`Within the VA/DoD guideline (2017), pharmacotherapy is recommended as a second-line treatment only, when trauma-focused psychotherapy is either unavailable or unwanted by the patient. The VA/DoD guideline recommends three SSRIs—sertraline, paroxetine, and fluoxetine—and one SNRI—venlafaxine—as second-line treatments for PTSD (VA/DoD, 2017). Evidence for the efficacy of those medications comes from both systematic reviews and meta-analyses showing that these have a larger impact on PTSD symptoms than do other SSRIs and SNRIs (Davidson et al., 2006a; Lee et al., 2016; Watts et al., 2013).

While the recommendations about psychotherapy vary somewhat among the VA/DoD, ISTSS, and APA guidelines, the recommendations for pharmacotherapy are more consistent with two important exceptions. First, the APA guidelines describe insufficient evidence for considering pharmacotherapy as a second-line treatment to psychotherapy, based on insufficient evidence from studies that directly compare the two (APA, 2017). However, when pharmacotherapy will be used for the treatment of PTSD, the APA guidelines recommend fluoxetine, paroxetine, sertraline, and venlafaxine, consistent with the VA/DoD guidelines, and describe these medications as all having moderate evidence for a small effect on PTSD symptom reduction (APA, 2017). The AHRQ systematic review generally corroborates this viewpoint, with the exception of sertraline, for which the strength of evidence was reported as low (Forman-Hoffman et al., 2018). This is consistent with the ISTSS treatment guidelines, in which fluoxetine, paroxetine, sertraline, and venlafaxine are all described as having a "low" effect (Hoskins et al., 2015). The APA guidelines further recommend topiramate as having moderate evidence for a medium to large effect on symptoms (APA, 2017), but this finding was not mirrored in the AHRQ systematic review or the ISTSS treatment guidelines, which described the strength of the evidence for topiramate as limited (Forman-Hoffman et al., 2018; Hoskins et al., 2015).

Other Treatments

Various treatments have been used for PTSD that have insufficient evidence for their efficacy in treating PTSD symptoms. In psychotherapy, dialectical behavior therapy, skills training in affect and interpersonal regulation, acceptance and commitment therapy, and Seeking Safety need further research before use in the treatment of PTSD (VA/DoD, 2017). Additionally, the ISTSS treatment guidelines include couples trauma-focused CBT, group trauma-focused CBT, reconsolidation of trauma memories, single session CBT, written exposure therapy, and the medication quetiapine as treatments with emerging evidence (Hoskins et al., 2015).

Length of Time to Improvement for PTSD

People with PTSD may face functional deficits related to education, socioeconomic status, social relationships, and employment (APA, 2017). Studies of specific psychotherapy modalities, such as CT, PE, CBT, BEP, and IPT, have examined improvement in functioning as an outcome. For CT and CBT, the evidence generally indicates that these therapies are associated with an improvement in functioning over approximately 8 to 16 weeks of treatment (Forman-Hoffman et al., 2018). The evidence is less clear for improvements in functioning associated

with PE, BEP, or IPT (Forman-Hoffman et al., 2018). Two studies have documented a benefit of venlafaxine on functioning, while other comparative effectiveness studies of venlafaxine and sertraline have found that sertraline may be more effective, but neither drug had a large impact on functioning outcomes (Forman-Hoffman et al., 2018). Similarly Forman-Hoffman et al. (2018) have found that paroxetine may improve functional status over a period of 12 weeks, while studies of other SSRI's have provided little evidence of efficacy with regard to improving functioning (Forman-Hoffman et al., 2018).

Relationship Between Symptoms and Functional Improvement in PTSD

A 2019 National Academies report reviewed the literature on PTSD and work-related functioning specifically (NASEM, 2019). Although research in this area is more limited, the report states that PTSD may reduce work functioning, particularly if the trauma occurred in the workplace. The few studies that exist have generally found that increased PTSD symptomatology is associated with unemployment and have also documented, more specifically, that the hyperarousal and reexperiencing symptoms of PTSD were most associated with receiving PTSD-related disability benefits. No studies have examined the impact of the specific PTSD treatments described above on improvements in work functioning specifically.

ANXIETY DISORDERS

This section focuses on the three most common clinically presented anxiety disorders: social anxiety disorder (SAD), generalized anxiety disorder (GAD), and panic disorder (PD) (Andrews et al., 2018). Although there is considerable overlap between effective therapies for those anxiety disorders, there are also differences and, for the most part, separate evidence-bases for treating each disorder. For these reasons the committee addresses each of those anxiety disorders separately.

The treatment effectiveness for anxiety disorders is evaluated in terms of symptomatic improvement (McKnight et al., 2016). Generally, treatment response is operationalized in terms of a certain magnitude of improvement (e.g., 30 to 50 percent) on symptom measures, and remission is judged in terms of a predetermined cutoff score (which focuses primarily on the frequency and severity of symptoms specific to each diagnosis). Thus, in keeping with the nature of the treatment literature for anxiety disorders, the committee describes anxiety disorder treatments that improve clinical outcomes (e.g., symptom response or remission) and time to improvement in clinical outcomes, which is generally the duration of effects for a specific intervention in clinical trials. The complexity of the relationship between symptomatic and functional improvement cuts across anxiety disorders and is discussed at the end of this section.

Social Anxiety Disorder

Professionally Accepted Diagnostic Criteria for Social Anxiety Disorder

SAD, also known as social phobia, is a mental disorder characterized by excessive and persistent fears of scrutiny, embarrassment, and humiliation in social or performance situations, leading to significant distress or impairment in functioning. Individuals with SAD avoid feared social situations or endure them with intense distress. They often experience anticipatory anxiety, worrying for hours or days prior to a feared event. In social or performance situations, persons

with SAD may also experience physical manifestations of anxiety, such as blushing, sweating, trembling, and palpitations, which sometimes can take the form of a full panic attack. People with SAD often fear that others will notice that they are irrationally anxious.

The DSM-5 criteria for SAD are listed in Table 4-9. Compared with the DSM-IV-TR, changes to the diagnostic criteria for SAD have been minimal. The DSM-5 includes SAD and a performance-only subtype (APA, 2013). This replaces the DSM-IV-TR subtypes of generalized and nongeneralized SAD. Persons with performance-only SAD have performance fears that are most impairing in their professional lives; they do not fear or avoid nonperformance social situations. Persons diagnosed with SAD not limited to performance situations have more severe symptoms and impairment than individuals with the performance-only subtype of SAD (Baldwin et al., 2014; Bögels et al., 2010). SAD that is not limited to performance situations is the more relevant disorder to general psychiatric clinical work and thus is considered for this statement of work. Furthermore, clinical trials of treatments for SAD were based on samples primarily composed of patients with the generalized form of the disorder.

TABLE 4-9 DSM-5 Criteria for Social Anxiety Disorder

Criterion/Symptom Description
A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech). Note: In children, the anxiety must occur in peer settings and not just during interactions with adults.
B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing: will lead to rejection or offend others).
C. The social situations almost always provoke fear or anxiety. Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.
D. The social situations are avoided or endured with intense fear or anxiety.
E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The fear, anxiety, or avoidance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental

disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.

J. If another medical condition (e.g., Parkinson's disease, obesity, disfigurement from bums or injury) is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive.

Specify if:
Performance only: If the fear is restricted to speaking or performing in public.

Developmental Course, Gender Distribution, and Comorbidities

SAD is one of the most common types of anxiety disorder, with a 12-month prevalence of about 7 percent and a lifetime prevalence of about 12 percent in the United States (Ruscio et al., 2008). SAD typically begins in childhood or adolescence (median age of onset is 13 years), although it can occur as early as age 5 years (Grant et al., 2005; Kessler et al., 2005b). It often arises as an intensification of non-impairing shyness, although some patients will identify an unusually stressful social experience as a precipitant. New onset after age 30 years is uncommon (Beesdo et al., 2007). Left untreated, SAD has a chronic and unremitting course (Wittchen and Fehm, 2003). Risk factors for SAD include female gender (the female-to-male ratio is approximately 2:1), a family history of SAD, and early childhood shyness or behaviorally inhibited temperament (Grant et al., 2005; Hirshfeld-Becker et al., 2008; Kessler et al., 2005b; Low et al., 2008). SAD is associated with low socioeconomic status and being single or divorced (Acarturk et al., 2009; Schneier et al., 1992). SAD can be associated with extensive functional impairment, economic burden, and reduced quality of life (Katzman et al., 2014; Ruscio et al., 2008). Despite its early onset and the extent of distress and impairment, many individuals with SAD never seek treatment, and those who do generally only seek treatment after 15–20 years of symptoms (Wang et al., 2005). Among those presenting for clinical care, SAD tends to be particularly persistent (APA, 2013).

SAD generally co-occurs with other psychiatric disorders (Grant et al., 2005; Kessler et al., 2005b). Rates of comorbidity with depressive (30–50 percent) and other anxiety disorders (50–60 percent) are particularly high (NICE, 2013). Comorbidity with other anxiety disorders may reflect shared diagnostic features and possibly shared higher-order traits, such as harm avoidance, anxiety sensitivity, or neuroticism. SAD also increases the risk of other mental disorders, including depression and substance use disorders (Beesdo et al., 2007; Schneier et al., 2010). In patients with severe SAD, symptoms are pervasive and overlap with those of avoidant personality disorder (Friborg et al., 2013). About 15 percent of those with schizophrenia also have SAD (Achim et al., 2011). Persons with medical conditions that include highly visible symptoms, such as tremulousness from Parkinson's disease, stuttering, facial disfigurement, and hyperhidrosis, may develop excessive social anxiety and meet DSM-5 criteria for SAD (Schneier et al., 2001).

Standard Measures of Outcomes for Social Anxiety Disorder

The Liebowitz Social Anxiety Scale (LSAS) was the first instrument developed specifically for SAD (Liebowitz, 1987). The original clinician-administered version and the self-report version have comparable and strong psychometric properties (Baker et al., 2002; Fresco et al., 2001). The other commonly used clinician-administered scale for SAD symptom assessment

is the Brief Social Phobia Scale (Davidson et al., 1997). A 2015 systematic review of the psychometric properties of 22 self-report measures (including shortened derivatives) found that there was no "gold standard" trait social anxiety self-report measure (Modini et al., 2015). Furthermore, other than the LSAS (Mennin et al., 2002), it is unknown which measures of outcome in SAD are commonly used in routine care. To evaluate outcome, clinicians may use measures of anxiety that are not specific to social phobia, such as the Hamilton Anxiety Scale (Hamilton, 1959) or global measures of improvement such as the 7-point Clinical Global Impression of Change (CGI) scale (Guy, 1976). Previous meta-analyses have shown that changes in the CGI among patients with anxiety disorders are broadly similar to changes in the other clinician-rated and patient-rated instruments (e.g., Bandelow et al., 2007).

Treatments for Social Anxiety Disorder

All clinical treatment guidelines for SAD recommend CBT, medications (usually antidepressants), or their combination for optimal management (Andrews et al., 2018; Baldwin et al., 2014; Bandelow, 2012; Katzman et al., 2014; NICE, 2013). There is no consistent evidence that the efficacy of pharmacotherapy or psychotherapy for SAD varies by age (Davis et al., 2014; Eskildsen et al., 2010; Schneider et al., 2015). Fifty to 70 percent of patients respond to treatments for SAD in clinical trials (Andrews et al., 2018; Eskildsen et al., 2010); however, remission rates are lower (e.g., Leichsenring et al., 2013). Response and remission rates may be even lower in routine practice settings where patients, therapists, and clinical support systems are more variable. In general, clinical trials have not found one modality to be superior to the other (Canton et al., 2012). The onset of symptom response may be faster with pharmacotherapy, although CBT results in a more durable improvement (Baldwin et al., 2014; Canton et al., 2012; Haug et al., 2003; Liebowitz et al., 1999). In most studies, combined medications and psychotherapy have not resulted in improved patient outcomes relative to first-line monotherapy (Baldwin et al., 2014; Katzman et al., 2014; Mayo-Wilson et al., 2014). D-cycloserine, a partial agonist at the glycine recognition site of the glutamatergic NMDA receptor, seems to accelerate treatment response when used as an adjunct to exposure therapy for SAD—but within a narrow therapeutic window and only when exposure sessions are successful (Hofmann, 2014). The 2013 NICE guideline recommends CBT over pharmacologic interventions for SAD and the combination of psychotherapy and pharmacotherapy for individuals who are partial responders to either monotherapy after an adequate treatment course (Baldwin et al., 2014; NICE, 2013).

Psychotherapy for Social Anxiety Disorder

CBT developed for SAD is the best studied and most efficacious of the psychotherapies (Canton et al., 2012; Katzman et al., 2014). In CBT tailored for SAD, the therapist works with the patient to identify and challenge maladaptive cognitions associated with social situations and to confront these feared situations through in vivo exposure. A network meta-analysis including 101 clinical trials found CBT to be superior to no treatment, to pill placebo, to psychologic control conditions, and to several psychotherapies including psychodynamic psychotherapy, interpersonal psychotherapy, mindfulness, and supportive therapy (Mayo-Wilson et al., 2014). Network meta-analyses use all available data from randomized clinical trials to estimate the effect of each intervention relative to other interventions, even those that have not been compared directly. A 2019 meta-analysis concluded that CBT maintained superiority to control conditions for SAD beyond the 12-month period following treatment (van Dis et al., 2019).

CBT for SAD can be provided in individual or group formats. In the above-referenced network meta-analysis, individual CBT for SAD was the most effective psychotherapy (Mayo-Wilson et al., 2014), and the NICE (2013) guideline recommends individual over group CBT for SAD. However, no statistical difference was reported between group and individual therapy for SAD, and a 2016 meta-analysis of 36 RCTs reported equivalence between group and individual therapies for SAD (Barkowski et al., 2016). Evidence is also accumulating to support self-administered (e.g., Internet-based or through printed material) CBT for SAD (e.g., Andrews et al., 2011; Hedman et al., 2011). It is, however, unclear whether therapist contact and guidance is a necessary component of self-administered CBT for SAD (Katzman et al., 2014), and effect sizes are generally larger for therapist-assisted self-help than for pure self-help (Andrews et al., 2018).

Exposure therapy is as effective as CBT for SAD at post-treatment, but evidence suggests that CBT results in better maintenance of treatment gains (Hofmann et al., 2004). Other therapies that have been found to be more effective than waitlist control[8] but less effective than CBT include manual-based psychodynamic psychotherapy for SAD (NICE, 2013), interpersonal therapy (Stangier et al., 2011), and mindfulness-based therapy (Koszycki et al., 2007). Those therapies, therefore, may be useful for patients who do not want, cannot access, or do not fully benefit from CBT. Attention retraining, an intervention that modifies the attentional bias underlying many forms of psychopathology by training patients to attend to non-threatening rather than threatening stimuli, may have benefits for individuals with SAD (Katzman et al., 2014; Li et al., 2008; Schmidt et al., 2009), though more robust trials are needed.

Cognitive behavioral therapy has shown evidence of persistent benefits for as long as 5 years after treatment (Mörtberg et al., 2011; Powers et al., 2008), although some patients require longer-term treatment or subsequent "booster" sessions to maintain gains. A meta-analysis of RCTs of variants of CBT found that significant effects at posttreatment were maintained at follow-up, with no drop in effect sizes. However, less than half of SAD patients achieve remission from SAD even with CBT (Springer et al., 2018). Furthermore, many patients do not have access to quality CBT or are hesitant to enter psychotherapy (Wolitzky-Taylor et al., 2015).

Medications for Social Anxiety Disorder.

Table 4-10 lists recommendations for pharmacotherapy for SAD from the 2014 Canadian clinical practice guidelines (Katzman et al., 2014). Those recommendations are largely consistent with other clinical guidelines (Baldwin et al., 2014; Bandelow, 2012). There is, however, a paucity of studies examining pharmacotherapy for SAD in individuals with comorbid mental disorders, including substance use disorders.

SSRIs and the SNRI venlafaxine extended release (XR) are considered first-line treatments for SAD. Systematic reviews and a network meta-analysis confirmed that the classes of drugs that include SSRIs and SNRIs have a greater effect on outcomes than placebo (Mayo-Wilson et al., 2014). A 2017 Cochrane systematic review of 66 RCTs of medications versus placebo in the treatment of SAD found that SSRIs were the only medications that proved effective in reducing relapse based on moderate quality evidence and the only medication that demonstrated evidence of a reduction in functional disability (Williams et al., 2017).

[8] Waitlist control group in psychotherapy research is a group of participants who do not receive the experimental treatment, but who are put on a waiting list to receive the intervention after the active treatment group does.

Second-line medications that show efficacy in SAD have side-effect profiles (MAOIs and benzodiazepines) or show less consistent effects (fluoxetine; moclobemide) in comparison with placebo (Katzman et al., 2014). Evidence for the effectiveness of adjunctive medications in partial responders and nonresponders comes from open trials and case series (Katzman et al., 2014). Third-line agents are recommended for patients who have been found to be refractory to first- and second-line monotherapies and adjunctive therapies.

The findings of randomized placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment for SAD reveal a significant advantage for staying on active medication for at least 6 months (Baldwin et al., 2014; Blanco et al., 2013; NICE, 2013). Most people who respond to a SSRI will relapse within a few months if the drug is discontinued, and about 25 percent of those who continue will relapse within 6 months (e.g., Montgomery et al., 2005).

TABLE 4-10 Recommendations for Pharmacotherapy for Social Anxiety Disorder

First-line[a]	Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line[b]	Alprazolam, bromazepam, citalopram, clonazepam, gabapentin, phenelzine
Third-line[c]	Atomoxetine, bupropion SR, clomipramine, divalproex, duloxetine, fluoxetine, mirtazapine, moclobemide, olanzapine, selegiline, tiagabine, topiramate
Adjunctive therapy	Third-line: pregabalin Not recommended: clonazepam, pindolol
Not recommended[d]	Atenolol, buspirone, imipramine, levetiracetam, propranolol, quetiapine
Biological and alternative emerging therapies for which more data are needed	Repetitive transcranial magnetic stimulation, herbal preparations such as silexan, *Galphimia glauca* extract, passiflora, valerian; resistance training (weightlifting), aerobic exercise, acupuncture, meditation, and yoga-based treatments

[a] First-line treatment recommendations derived from Level 1 and Level 2 evidence plus clinical support for efficacy and safety.
[b] Second-line treatment recommendations derived from Level 3 evidence or higher plus clinical support for efficacy and safety.
[c] Third-line treatment recommendations derived from Level 4 evidence or higher plus clinical support for efficacy and safety.
[d] Not recommended treatments derived from Level 1 or Level 2 evidence for lack of efficacy.
CR = ; SR = ; XR =
Adapted from Katzman et al., 2014.

Length of Time to Improvement for Social Anxiety Disorder

Improvement in social anxiety symptoms, not function, is the primary outcome in clinical trials of interventions for SAD. Specific domains of functioning may be included as secondary outcomes, but functional outcomes are not reviewed or summarized in clinical treatment guidelines, systematic reviews, and meta-analyses of treatments for SAD. Furthermore, most studies assess only short-term outcomes and do not provide information on the durability of the treatment effects. Initial improvements in symptoms may not be maintained over time (Baldwin

et al., 2014) and may not translate into improved functioning and reduced disability. Those characteristics of the extant literature presented a significant challenge for an evaluation of time to improvement in functioning in SAD. However, on average the duration of treatment in both medication and psychotherapy trials is 12 weeks (Mayo-Wilson et al., 2014).

A standard course of CBT for SAD involves approximately 14 1.5-hour sessions delivered over 3 to 4 months (Baldwin et al., 2014; NICE, 2013). Psychodynamic psychotherapy for SAD is of longer duration—it consists of 25 to 30 50-minute sessions over 6 to 10 months (Leichsering et al., 2013). However, the time to improvement in functioning may be considerably longer in routine practice due to various factors, including the characteristics of the patients, the skills of the therapists, and logistic considerations that preclude scheduling sessions at the same frequency used in RCTs.

Generally, a response to antidepressants is seen within 12 weeks of beginning treatment, which is the limit of most studies (Baldwin et al., 2014; Canton et al., 2012; Ipser et al., 2008). However, non-responders at 8–12 weeks may become responders with continuation of the same medication for 6 to 12 months (Ipser et al., 2008).

There is no consistent evidence that the efficacy of pharmacotherapy or psychotherapy for SAD varies by age (Davis et al., 2014; Eskildsen, et al., 2010; Schneider et al., 2015).

Panic Disorder

Professionally Accepted Diagnostic Criteria for Panic Disorder

PD refers to the experiencing of recurrent panic attacks, with one or more attacks followed by at least 1 month of fear of another panic attack or significant maladaptive behavior related to the attacks. The DSM-5 criteria for PD are listed in Table 4-11. It should be noted that agoraphobia (i.e., where an individual avoids situations for fear of developing a panic attack) was considered to be a complication of panic disorder in DSM-IV. The unlinking of PD and agoraphobia in DSM-5 reflects the current conceptualization that agoraphobia is a distinct disorder (APA, 2013; Wittchen et al., 2010). Because that change occurred relatively recently, much of the existing literature is based on mixed samples (i.e., those diagnosed with agoraphobia with or without panic attacks). Research suggests that agoraphobia in the absence of panic disorder is relatively rare in treatment-seeking samples (Wittchen et al., 2010). PD frequently co-occurs with agoraphobia (Bienvenu et al., 2006), particularly in treatment-seeking samples (APA, 2010; Weissman et al., 1997).

TABLE 4-11 DSM-5 Criteria for Panic Disorder

Criterion/Symptom Description
A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and during which time four (or more) of the following symptoms occur:
Note: The abrupt surge can occur from a calm state or an anxious state.
1. Palpitations, pounding heart, or accelerated heart rate.

2. Sweating.
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heat sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself).
12. Fear of losing control or "going crazy."
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming, or crying) may be seen. Such symptoms should not count as one of the four required symptoms.

B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:
1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

Developmental Course, Gender Distribution, and Comorbidities

In the general U.S. population, the 12-month prevalence of PD approaches 3 percent when using the DSM-IV criteria (Kessler et al., 2005c, 2006; Grant et al., 2006). PD is approximately twice as common in women as in men (Kessler et al., 1994). Panic attacks (which can occur in disorders other than PD) are much more common than PD, occurring in up to one-third of individuals at some point in their lifetime (Kessler et al., 2006). Rates of PD gradually increase during adolescence, particularly among females, and peak during adulthood. Rates also decline in older (> 60 years of age) adults (Kessler et al., 2005c). The median age of onset is 24 years old (Kessler et al., 2005c). Generally, PD is a recurrent or chronic disorder with a waxing and waning course (APA, 2013; Batelaan et al., 2010).

Comorbidity with other anxiety, PTSD, depressive disorders, and substance use disorders is common (Grant et al., 2006; Kessler et al., 2006). The presence of agoraphobia in individuals with PD is associated with increased severity and worse outcomes (Bruce et al., 2005; Kessler et al., 2006; Porter and Chambless, 2015). PD is also more prevalent in individuals with medical conditions, including thyroid disease, hypoglycemia, seizure disorders, chronic pain, and cardiac conditions, among others (APA, 2010; Katzman et al., 2014). Some evidence suggests that the presence of medical comorbidity is associated with a greater severity of PD symptoms and functional limitations (Marshall et al., 2008).

Standard Measures of Outcomes for Panic Disorder

A complete psychiatric examination, including a medical history, thorough physical and neurologic examination, and standard laboratory testing, is needed to rule out organic causes of the symptoms and establish an accurate diagnosis of PD. Medical conditions such as angina, arrhythmias, asthma, chronic obstructive pulmonary disease, pulmonary embolus, thyroid disease, and, very rarely, temporal lobe epilepsy or pheochromocytoma may mimic panic attacks. Excessive caffeine or the use of other stimulants may trigger or worsen panic disorder.

Clinician-administered and patient self-assessment instruments can be used to monitor changes in severity of PD. These measures assess the frequency of panic attacks and panic-related distress or impairment. The gold standard instrument for the disorder in the United States is the Panic Disorder Severity Scale, which has both clinician-administered and self-report versions (Shear et al., 1997, 2001; Wuyek et al., 2011). Each of seven items in that scale (attack frequency, attack intensity, anticipatory anxiety, phobic avoidance, avoidance of internal bodily sensations, relationship impairment, work impairment) covers a key clinical aspect of the syndrome. To monitor treatment response, clinicians may use other interview or self-report scales specific to PD, general anxiety measures, or global rating scales that are not specific to any one type of psychiatric disorder.

Treatments for Panic Disorder

Clinical practice guidelines indicate that PD can be effectively treated with psychotherapy, medications (usually antidepressants), or a combination of the two (Andrews et al., 2018; APA, 2009; Katzman et al., 2014, NICE, 2011). A 2016 Cochrane systematic review concluded that there was no evidence of a difference between psychologic therapies and medications used to treat panic disorder in terms of short-term remission, short-term response (defined as substantial improvement), or treatment acceptability as measured using dropouts for any reason (Imai et al., 2016). Therefore, the initial selection between anti-depressant medication and therapy for most patients can be made on the basis of patient preference, motivation, and ability to engage in the treatment; prior treatment response; comorbidities; and treatment availability. Notably, there is wide variation across the United States in the availability of therapists trained to provide evidence-based psychotherapies for anxiety disorders (APA, 2009; Weissman et al., 2006), and a significant proportion (about 40 percent) of U.S. patients diagnosed with anxiety disorders remain untreated (Kroenke et al., 2007). Age is not associated with improvement in PD from CBT (Porter and Chambliss, 2015). However, improvement may be related to age at the onset of PD. Specifically, a late age of onset of panic disorder but not agoraphobia may be associated with improvement. Relatedly, a shorter duration of panic disorder, but not agoraphobia, predicts greater improvement at post-treatment.

Psychotherapy for Panic Disorder

Among the psychosocial treatments for PD, CBT is most extensively supported by research. While there is no high-quality, unequivocal evidence to support one psychologic therapy over the others for the treatment of PD with or without agoraphobia, a 2016 network meta-analysis concluded that CBT is often superior to other psychotherapies (Pompoli et al., 2016). A 2019 meta-analysis concluded that CBT was superior to control conditions for PD until 12 months following treatment, after which it was equivalent to active comparison conditions (van Dis et al., 2019).

The central focus of CBT for PD is teaching patients a set of cognitive and somatic coping skills in an effort to manage anxiety as repeated exposures to feared situations and sensations are presented. Through repeated exposures patients learn that panic-related sensations are not harmful, that panic and anxiety can be managed or tolerated, and that they are able to accomplish tasks that were previously avoided.

CBT for PD can be effectively delivered in group or individual format as well as via self-help books, virtual reality, and Internet-based programs (Katzman et al., 2014). CBT treatment sessions are accompanied by homework assignments, usually daily, to be conducted between sessions. Thus, the individuals for whom CBT works best are generally highly motivated and value a problem-solving approach. Not all patients are able or willing to do the homework associated with CBT for PD (APA, 2010).

Other psychotherapies may also improve PD symptoms, although their efficacy is less well established. In the 2016 network meta-analysis (Pompoli et al., 2016), psychodynamic psychotherapies and supportive psychotherapy were found to have promising results, although further research is needed, particularly for supportive psychotherapy. Newer therapies for which evidence is accruing include third-wave therapies,[9] which include features of CBT but focus on mindfulness, acceptance, and patients' values. There were fewer dropouts in psychodynamic therapy and third-wave therapies than in CBT, suggesting that people with PD may tolerate these therapies particularly well compared with other forms of psychotherapy (Pompoli et al., 2016).

Clinical trials have generally found CBT's effects to be sustained over time, although relapse can occur (APA, 2009). A 2006 review of meta-analyses for CBT across disorders concluded that the evidence for the maintenance of treatment gains was particularly strong for panic disorder, where the rate of relapse was almost half the rate of relapse following pharmacotherapy (Butler et al., 2006).

Chronic life stress, or episodic stressful events, can interfere with CBT for panic disorder/agoraphobia. Relationship problems, job stress, financial hardship, and medical problems are examples of stressful situations that can both exacerbate panic symptoms and make it difficult for patients to engage in therapy (Sanderson and Bruce, 2007). A 2015 systematic review found that functional impairment at baseline was consistently related to decreased improvement in CBT for panic disorder and agoraphobia (Porter and Chambless, 2015).

Medications for Panic Disorder

Table 4-12 lists recommendations for pharmacotherapy for panic disorder from the 2014 Canadian clinical practice guidelines (Katzman et al., 2014). These recommendations are largely consistent with other clinical guidelines for PD. SSRIs and SNRIs are considered first-line agents

[9] Third wave therapies prioritize the promotion of psychologic and behavioral processes associated with health and well-being over the reduction or elimination of psychologic and emotional symptoms, which can be a "side-benefit.

for panic disorder. Second-line treatments were those that are less well tolerated and have higher discontinuation rates (as is the case with tricyclic antidepressants), present a risk for dependence (as is the case with benzodiazepines), or are less well researched (as in the case with mirtazapine). Although benzodiazepines are second-line options in this guideline because of their addiction potential, they may be useful for the short-term management of acute or severe agitation or anxiety or at the initiation of SSRI treatment to hasten response (Katzman et al., 2014). The NICE Clinical Guideline for Generalized Anxiety Disorder and Panic Disorder in Adults (2011) recommends against the use of benzodiazepines for panic disorder, noting less favorable long-term outcomes.

Patients who do not respond to first- or second-line agents are considered to have treatment-refractory illness. Third-line agents, adjunctive therapies, and biological and alternative therapies may be useful when patients fail to respond to first- and second-line therapies used alone and in combination.

Most studies that have examined maintenance effects report continued benefits of ongoing pharmacotherapy for panic disorder (Katzman et al., 2014). Adding CBT to pharmacotherapy either from the start or at some later point in treatment may enhance long-term outcomes by reducing the likelihood of relapse when pharmacologic treatment is stopped (APA, 2009; Bruce et al., 1999; Katzman et al., 2014; Otto et al., 2010).

TABLE 4-12 Recommendations for Pharmacotherapy for Panic Disorder

First-line[a]	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, paroxetine CR, sertraline, venlafaxine XR
Second-line [b]	Alprazolam, clomipramine, clonazepam, diazepam, imipramine, lorazepam, mirtazapine, reboxetine
Third-line[c]	Bupropion SR, divalproex, duloxetine, gabapentin, levetiracetam, milnacipran, moclobemide, olanzapine, phenelzine, quetiapine, risperidone, tranylcypromine
Adjunctive therapy	Second-line: alprazolam ODT, clonazepam Third-line: aripiprazole, divalproex, olanzapine, pindolol, risperidone
Not recommended[d]	Buspirone, propranolol, tiagabine, trazodone, carbamazepine
Biological and alternative emerging therapies for which more data are needed	Non-invasive brain stimulation using a radioelectric asymmetric conveyor, repetitive transcranial magnetic stimulation, capnometry-assisted respiratory training, acute aerobic exercise

[a] First-line treatment recommendations derived from Level 1 and Level 2 evidence plus clinical support for efficacy and safety.
[b] Second-line treatment recommendations derived from Level 3 evidence or higher plus clinical support for efficacy and safety.
[c] Third-line treatment recommendations derived from Level 4 evidence or higher plus clinical support for efficacy and safety.
[d] Not recommended treatments derived from Level 1 or Level 2 evidence for lack of efficacy.
Adapted from Katzman et al., 2014.

Length of Time to Improvement for Panic Disorder

CBT PD protocols usually involve 12–14 weekly sessions and sometimes include booster sessions following treatment. However, briefer treatment courses and compressing the duration

of therapy by administering multiple sessions per week have also been shown to be effective (Katzman et al., 2014). Some evidence suggests that the less intensive protocols do not work as well with patients with more severe PD (Dow et al., 2007). The 2011 NICE clinical guideline specifies that for most people CBT should take the form of weekly sessions of 1–2 hours and should be completed within a maximum of 4 months of commencement.

Although the time to onset of clinically meaningful action for a pharmacologic agent varies by patient, the treatment is often associated with a delay of about 2–8 weeks in the onset of symptom relief, with full response taking up to 12 weeks or more (Katzman et al., 2014). Longer-term therapy has been associated with continued symptomatic improvement and the prevention of relapse. Clinical guidelines for PD recommend that pharmacotherapy be continued for 6–24 months or more after the desired level of improvement (Andrews et al., 2018; APA, 2009; Bandelow et al., 2012; Katzman et al., 2014; NICE, 2011).

Despite promising findings in clinical trials, a substantial minority of patients who receive evidence-based medications for panic disorder or agoraphobia, or both, fail to show significant symptom improvement. In clinical trials, about one-third of patients are classified as non-responders (Taylor et al., 2012; Westen and Morrison, 2001). Evidence from naturalistic follow-up studies of patients in a tertiary-care setting suggests that at 4–6 years posttreatment about 30 percent of individuals are well, 40–50 percent are improved but symptomatic, and the remaining 20–30 percent have symptoms that are the same or slightly worse (Katschnig et al., 1996; Roy-Byrne and Cowley, 1994).

Age has not been not associated with improvement in studies of CBT for PD (Porter et al., 2015). However, improvement may be related to age of onset of PD; specifically, a late age of onset of PD—but not agoraphobia—may be associated with improvement. Relatedly, shorter duration of panic, but not of agoraphobia, predicts greater improvement post treatment.

Generalized Anxiety Disorder

Professionally Accepted Diagnostic Criteria for Generalized Anxiety Disorder

GAD refers to excessive anxiety and worry for more days than not regarding multiple events or activities and lasting for at least 6 months. That apprehension is associated with somatic symptoms. Since its introduction into the DSM classification in 1980, the conceptualization of GAD has evolved. However, there was not a major change in the diagnostic criteria for GAD in the DSM-5 compared with the DSM IV-TR (APA, 2000). The DSM-5 (APA, 2013) criteria for GAD are listed in Table 4-13.

TABLE 4-13 DSM-5 Criteria for Generalized Anxiety Disorder

Criterion/Symptom Description
A. Excessive anxiety and worry (apprehensive expectation) occurring more days than not for at least 6 months about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): Note: Only one item is required in children.
1. Restlessness or feeling keyed up or on edge.

2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Developmental Course, Gender Distribution, and Comorbidities

In the general population in the United States, the 12-month prevalence of GAD is approximately 3 percent (Kessler et al., 2005c). GAD is approximately twice as common in women as in men (Kessler et al., 1994). The age of onset is variable, with a median of approximately 31 years (Kessler et al., 2005b). There is an increase of new onset cases in older adults, often in the context of chronic physical health conditions (Byers et al., 2010; Mackenzie et al., 2011). GAD is frequently underrecognized (Baldwin et al., 2014).

GAD is associated with high rates of psychiatric comorbidity, particularly with other anxiety disorders, depression (Grant et al., 2005; Kessler et al., 2005c) and substance use disorder (Robinson et al., 2011). The risk of co-occurring medical conditions is also elevated, including pain syndromes, hypertension, cardiovascular and gastric conditions (Comer et al., 2011). Comorbidity with depression or depression and pain is associated with a more severe and prolonged course of illness and with greater functional impairment (Kessler et al., 1999b). GAD has a low likelihood of spontaneous remission (Lenze et al., 2005). A longitudinal study found that the likelihood of recovery from GAD is significantly less than that of recovering from major depression (Yonkers et al., 2000). Among those who do recover, relapse is common. Based on data from the Harvard/Brown Anxiety Disorders Program, Bruce and colleagues (2005) found that nearly half of patients with GAD who recovered had a recurrence over a 12-year follow-up period.

Standard Measurement of Outcomes in Generalized Anxiety Disorder

An in-depth, structured interview by a medical specialist is the first step in establishing the diagnostic features and details of associated behaviors in GAD. An instrument such as the

Anxiety Disorders Interview Schedule for DSM-5 (Brown and Barlow, 2014) can be used to collect data on the domains of worry and the somatic symptoms.

Clinician-administered and patient self-assessment instruments can be used to monitor changes in severity of GAD. These measures assess the cognitive and somatic symptoms of anxiety. Clinical trials often use the Hamilton Anxiety Rating Scale, which is a clinician-rated 14-item measure (Hamilton, 1959). Psychotherapists most commonly use self-report measures to assess GAD symptoms over the course of treatment (Szkodny et al., 2014). The Generalized Anxiety Disorder 7-item scale is a commonly used brief self-report measure (Spitzer et al., 2006). Global measures are also used, such as the Clinical Global Impressions (CGI) scale (Guy, 1976), which consist of two items, one assessing illness severity and the other assessing change from the initial treatment. In practice, clinicians often base their assessments of improvement on subjective impressions rather than on validated measures.

Treatments for Generalized Anxiety Disorder

Clinical practice guidelines indicate that GAD can be effectively treated with psychotherapy or medications (usually antidepressants) (Andrews et al., 2018; Baldwin et al., 2014; Katzman et al., 2014; NICE, 2011). Although few studies have compared psychotherapy and pharmacotherapy in the same trial, the magnitude of benefit appears comparable (Katzman et al., 2014). Few data are available on the use of combined psychologic and pharmacologic treatment for GAD. A meta-analysis concluded that combination pharmacotherapy and CBT was more effective than CBT alone at posttreatment but not at the 6-month follow-up (Hofmann et al., 2009). There is no current evidence to support the routine combination of CBT and pharmacotherapy (Baldwin et al., 2014; Katzman et al., 2014). Age does not appear to moderate treatment effects in individuals with GAD. A systematic review and meta-analysis of the efficacy of controlled interventions for GAD in adults 55 years and older concluded that older adults with GAD benefited from both pharmacologic and psychotherapeutic interventions (Goncalves and Byrne, 2012). A separate 2017 meta-analysis comparing the efficacy of CBT for GAD between working-age and older adults found that there was no statistically significant difference in the effect size for outcomes between the two groups (Kishita and Laidlaw, 2017).

Psychotherapy for Generalized Anxiety Disorder

A 2014 meta-analysis concluded that psychotherapies, especially CBT, are effective in the treatment of GAD in adults and in reducing depression symptoms in individuals with GAD (Cuijpers et al., 2014b). Because of the strength of the evidence, CBT is considered the first-line psychotherapy for GAD (Katzman et al., 2014). CBT for GAD is based on evidence that shows that individuals with GAD tend to overestimate the likelihood of negative events, have low confidence in their problem-solving abilities, and have low tolerance of uncertainty as well as other maladaptive cognitions. CBT for GAD involves challenging and disrupting the misconceptions that maintain worry; actively testing the validity of erroneous beliefs; improving skills to manage worry and anxiety; and developing more adaptive ways of responding to neutral and ambiguous situations. (Katzman et al., 2014; Szkodny et al., 2014).

CBT for GAD can be effectively delivered in both individual and group format. However, individual CBT may lead to earlier improvements (see Katzman et al., 2014). Internet- and computer-based CBT programs have also been found to be effective for relieving GAD symptoms (Cuijpers et al., 2014b; Olthuis et al., 2016).

Other psychotherapies may also improve GAD symptoms, though their efficacy has been less well established. These include applied relaxation therapy (Siev and Chambless, 2007), psychodynamic psychotherapy (Leichsenring et al., 2009), and third-wave CBT including acceptance-based behavioral therapy (Roemer et al., 2008) and metacognitive therapy (van der Heiden et al., 2012). The 2011 NICE clinical guideline recommends applied relaxation along with CBT for individuals with GAD and marked functional impairment.

Meta-analyses suggest that the benefits of psychologic treatments for patients with GAD are maintained after treatment (Covin et al., 2008; Cuijpers et al., 2014b). On average, approximately 50 percent of individuals who undergo treatment for GAD meet the criteria for responder status at 6- and 12-month follow-ups (Szkodny et al., 2014). CBT is associated with moderate GAD symptom reduction relative to control conditions beyond 12 months following treatment (van Dis et al., 2019). Relapse rates may also be lower with CBT than with other forms of psychologic treatment (Baldwin et al., 2014).

Medications for Generalized Anxiety Disorder

Table 4-14 lists recommendations for pharmacotherapy for GAD as presented in the Canadian clinical practice guidelines (Katzman et al., 2014). These recommendations are largely consistent with other clinical guidelines. SSRIs, SNRIs, and pregabalin are first-line agents (Bandelow et al., 2012; Katzman et al., 2014). Response rates to these medications range from 30 to 56 percent (Kapczinski et al., 2003). Some agents, such as benzodiazepines, imipramine, and quetiapine XR, have demonstrated efficacy for the treatment of GAD but have been classified as second-line agents because of their risk profiles. Third-line agents are those with limited data or significant side effects. Adjunctive therapies can be considered for patients with treatment-resistant GAD. Biological and alternative therapies are emerging treatments for which more data are needed. One other clinical guideline specifies that benzodiazepines should only be offered as a short-term measure during crises (NICE, 2011).

Relapse prevention studies indicate an advantage for responders to staying on active medication for at least 6 months, although the benefit of treatment continuation beyond 1 year (Donovan et al., 2010; Mochovitch et al., 2017). It is common in clinical practice for both the doctor and patient to agree to maintain medication across the lifespan. Adjunctive CBT was shown to facilitate benzodiazepine tapering (Gosselin et al., 2006) and may reduce relapse rates (Baldwin et al., 2014).

TABLE 4-14 Recommendations for Pharmacotherapy for Generalized Anxiety Disorder

First-line[a]	Agomelatine, duloxetine, escitalopram, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line[b]	Alprazolam, bromazepam, bupropion XL, buspirone, diazepam, hydroxyzine, imipramine, lorazepam, quetiapine XR, vortioxetine
Third-line[c]	Citalopram, divalproex chrono, fluoxetine, mirtazapine, trazodone
Adjunctive therapy	Second-line[b]: pregabalin Third-line[c]: aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone Not recommended: ziprasidone
Not recommended[d]	Beta blockers (propranolol), pexacerfont, tiagabine
Biological and alternative emerging therapies for which more data are needed	Repetitive transcranial magnetic stimulation, herbal preparations such as silexan, *Galphimia glauca* extract, passiflora, valerian; resistance training (weightlifting), aerobic exercise, acupuncture, meditation and yoga-based treatments

NOTES:
[a] First-line treatment recommendations derived from Level 1 and Level 2 evidence plus clinical support for efficacy and safety.
[b] Second-line treatment recommendations derived from Level 3 evidence or higher plus clinical support for efficacy and safety.
[c] Third-line treatment recommendations derived from Level 4 evidence or higher plus clinical support for efficacy and safety.
[d] Not recommended treatments derived from Level 1 or Level 2 evidence for lack of efficacy.
SOURCE: Adapted from Katzman et al, 2014.

Length of Time to Improvement for Generalized Anxiety Disorder

The optimal duration of treatment for GAD has not been determined. CBT for GAD protocols usually involve 10–16 weekly 1-hour sessions and sometimes include booster sessions over the phone or in person following treatment. More sessions may be required for partial responders or after relapse.

Although the time to onset of clinically meaningful action for a pharmacologic agent varies by patient, signs of improvement may begin within 4 weeks and continue to increase through months 4–6 of treatment. Longer-term therapy has been associated with continued symptomatic improvement and the prevention of relapse (Montgomery et al., 2005).

Relationship Between Symptomatic and Functional Improvement in Anxiety Disorders

The available literature does not permit making strong conclusions about the influence of treatments for anxiety disorders on functioning or work-related disability, let alone about the length of time to treatment-related improvement in functioning to the point where the condition is no longer disabling. In general, evidence-based anxiety disorder treatments target the core

symptoms of the specific anxiety disorder, and symptomatic improvement is the primary endpoint and focus of meta analyses and systematic reviews of treatments. Thus, there is much less evidence on the functional outcomes associated with psychologic and pharmacologic treatments than on clinical response and remission. Furthermore, because the relationship between anxiety disorder symptoms and functioning appears to be weak, one cannot draw conclusions about functioning based on information about symptom improvement. A systematic review of the relationship between symptoms and functioning in individuals with common anxiety disorders found a modest overall relationship (McKnight et al., 2016) which was smaller than had been observed between symptoms of depression and functioning in an earlier study (McKnight and Kashdan, 2009). Of particular relevance to SSA, the average correlations for GAD, SAD, and PD symptoms and occupational functioning were 0.20, 0.12, and 0.01, respectively.

The finding of weak correlations between symptoms and functioning in individuals with anxiety disorders is consistent with research demonstrating that remission in anxiety disorders does not necessarily translate into the levels of functioning seen in healthy controls. Iancu and colleagues (2014) studied trajectories of functioning after remission from anxiety disorders and found that while anxiety disorders' symptom remission was accompanied by improvements in functioning, impairments persisted in all functional areas except self-care. Furthermore, the magnitude of improvement varied by domain—those with remitting anxiety disorders had moderate improvement in interpersonal functioning, participation in society, and cognition but not in work or household functioning. Possible reasons for the persistence of functional impairment among those with remitting anxiety disorders include comorbidities, premorbid functional limitations that are not eradicated through mental health treatments, and subthreshold symptoms that affect functioning (Iancu et al., 2014). Mental scarring in which the psychiatric disorder causes irreversible damage may also affect postmorbid functioning in those with a history of severe or recurrent anxiety disorders (Schopman et al., 2018). Importantly, impaired functioning appears to predispose individuals for an onset or recurrence of anxiety disorders (Rodriguez et al., 2005; Saris et al., 2017; Scholten et al., 2013; Schopman et al., 2018). In sum, even after treatment response or remission from anxiety disorder, individuals may continue to have significant functional impairments which in turn may predispose them to a relapse of the anxiety disorder.

SUMMARY AND CONCLUSIONS

The committee selected eight mental health disorders for inclusion in the report: major depressive disorder, bipolar I disorder, bipolar II disorder, OCD, PTSD, PD, GAD, and SAD. Those mental health disorders are highly prevalent, are associated with significant functional impairment, and may respond to treatment. Professionally accepted diagnostic criteria for these conditions are detailed in the DSM-5.

People diagnosed with a mental health disorder are directed to a specific treatment depending on clinical practice treatment guideline recommendations, their treatment history, their treatment preference, and treatment availability, among other factors. The committee expects that most patients who are disabled by psychiatric disorders are receiving psychiatric services by combinations of mental health professionals, including a prescriber (e.g. psychiatrist, advanced practice nurse), psychologist, licensed clinician social workers, and individuals with counseling or rehabilitation degrees. The conclusions here, however, should be interpreted with

the caveat that for some populations (e.g., those in rural areas or small towns) care from qualified mental health professionals (e.g., specialized in evidence psychotherapy) might not be available. Importantly, the committee cautions that even under ideal treatment, full remission of mental health disorders, particularly when already determined as disabling, is seldom achieved. Disorder-specific clinical practice guidelines detail evidence-based treatments for the eight disorders that the committee reviewed. Generally, those mental health disorders can be treated effectively with psychotherapy, pharmacotherapy or other biologic treatments, or a combination of both. There is no indication that improvement varies with age. However, some individuals do not improve after receiving evidence-based treatments, and among those who do improve, some will relapse. Furthermore, it is uncertain whether the rates of remission and response observed in the scientific literature can be generalized to those receiving SSDIs or SSIs on the basis of a mental health disorder.

For the most part, in the clinical trials of treatments for mental health disorders improvement is defined in terms of disorder-specific symptoms, not functioning. Work-related disability is rarely assessed as an outcome. Furthermore, because there are no evidence-based laboratory tests for mental health disorders, mental health outcomes are assessed using patient self-report measures or clinician assessments.

There is a dearth of data on the length of time from start of treatment until the person's functioning improves to the point where the mental health disorder is no longer disabling. Attempting to accurately describe time to functional improvement by drawing from the existing data has important limitations. First, as mentioned above, treatment efficacy in research trials is generally defined in terms of symptomatic improvement, not functional outcomes, and time to symptomatic improvement is restricted to the duration of the trials. Second, psychiatric disorders are often recurrent, so time until improvement cannot be adequately captured as a linear process. Thus, individuals may have periods of remission during which they no longer meet the criteria for disability and later have an exacerbation of illness and associated functional limitations during which they again meet the criteria for disability. Third, the relationship between changes in symptoms and functioning is complex, and symptomatic improvement may not correspond to contemporaneous improvements in functioning. Fourth, psychiatric disorders generally occur with other psychiatric disorders, chronic pain, and medical conditions, and time to improvement will depend on those and other factors. Any estimates of time to improvement needs to consider the fact that clinical trials generally exclude participants with comorbidities. Fifth, the mental health disorders discussed in the report are under-recognized and effective treatments, particularly evidence-based psychotherapies, are often unavailable. That is particularly true for OCD. However, based on the limited evidence, the committee made the following conclusions regarding time from the start of treatment to improvement in functioning:

With regard to major depression disorder, functional improvement may lag behind or not occur even when a person is in symptomatic remission and may require rehabilitation that targets a return to work. Even then, recovery of occupational functioning, if it occurs, may take 1–2 years and may be limited by environmental contingencies. Early response to treatment might predict likelihood of improvement.

For bipolar I disorder, the acute phase of treatment lasts 6–12 weeks, while the maintenance phase treatment, which focuses on functional recovery, lasts 6–24 months. Caveats include the fact that improvement in social and occupational functioning may be limited or delayed and require targeted rehabilitation efforts. High-quality research shows that even with

the addition of vocational rehabilitation, the potential for return to gainful employment may be limited due in part to financial and other environmental disincentives.

Time to improvement can range from 12 to 24 weeks in OCD. Individuals requiring higher doses of medication or more complex cases may take a year or more to receive the full treatment benefit. For PTSD, there is some evidence from clinical trials indicating that general functioning improves in response to psychotherapy modalities. The length of time to improvement in functioning varies across psychotherapy modalities and usually corresponds to clinical trial follow-up endpoints (e.g., 8 or 16 weeks). Evidence regarding improvement in functioning from pharmacotherapy studies is less convincing, and the literature on improvements in work functioning specifically following PTSD treatment is scant.

For PD, GAD, and SAD, the time to improvement in symptoms in clinical trials is generally about 3 months. A longer treatment period may be required for partial responders or after relapse. Time to improvement in routine practice is likely considerably longer than in randomized controlled trials because of patient clinical complexity, treatment history, psychosocial factors, and variability in treatment delivery. Notably, the relationship between symptoms and functioning in individuals with anxiety disorders is weak. Even after treatment response or remission from an anxiety disorder, individuals may continue to have significant functional impairments which in turn may predispose them to a relapse of the anxiety disorder.

The committee notes that all of those conditions may be associated with chronic pain, which may contribute to increased risk for mental health disorders, and mental health disorders may result in an increased risk of chronic pain. The types of chronic pain that commonly co-occur with mental health conditions include migraine headaches, neck and back pain, fibromyalgia, and abdominal pain.

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5

Musculoskeletal Disorders

Musculoskeletal disorders comprise diverse conditions affecting bones, joints, muscles, and connective tissues. These disorders may result in pain and loss of function and are among the most disabling and costly conditions in the United States (USBJI, 2014a). The Social Security Administration (SSA) defines disorders of the musculoskeletal system, as conditions that might result from hereditary, congenital, or acquired pathologic processes. Impairments may result from infectious, inflammatory, or degenerative processes: traumatic or developmental events: or neoplastic, vascular, or toxic/metabolic diseases (SSA, 2008).

SSA noted three categories of musculoskeletal disorders—disorders of the back, osteoarthritis, and other arthropathies—as suggestions for conditions that the committee might wish to explore. Based on the committee's clinical expertise and knowledge of the medical and research literature on musculoskeletal disorders, the committee agreed that disorders of the back and osteoarthritis were two of the most disabling musculoskeletal conditions; within the category of "other arthropathies," the committee agreed that inflammatory arthropathies in particular ranked among the most disabling conditions that might improve with treatment. Although rheumatoid arthritis and psoriatic arthritis are classified by SSA as "immune disorders," their most common—and, in many cases, most disabling—manifestation is inflammation of the joints leading to joint destruction and deformity. Thus, the committee believes that those conditions merit consideration as leading causes of musculoskeletal impairment.

The specific conditions being examined in this chapter are listed in Table 5-1. These conditions commonly result in disability; however, they may improve with appropriate treatment and do not necessarily result in permanent disability for most adults.

TABLE 5-1 Selected Musculoskeletal Disorders

Disorder Category	Specific Disorder or Location
Disorders of the bBack	Chronic low back pain
Osteoarthritis	Hip
	Knee
	Wrist and hand
Other arthropathies	Rheumatoid arthritis
	Psoriatic arthritis

As noted, the focus of this chapter is on the musculoskeletal disorders. The chapter begins with a discussion of the epidemiology of those conditions in the general population, which is followed by overall issues that are relevant across the specific musculoskeletal conditions being discussed, such as the types of medical professionals typically involved in care and the settings in which people are diagnosed or receive treatment. The remainder of the chapter presents a detailed discussion of chronic low back pain; osteoarthritis of the hip, knee, and wrist/hand; and inflammatory arthropathies (rheumatoid and psoriatic arthritis) and responds to the remaining issues in the statement of task.

EPIDEMIOLOGY OF MUSCULOSKELETAL DISORDERS IN THE UNITED STATES

Musculoskeletal disorders are prevalent and are among the most disabling and costly conditions in the United States. Chronic pain and a loss of function are the primary mechanisms through which musculoskeletal disorders lead to disability and work loss. The National Health Interview Survey (NHIS[1]) for 2013–2015 estimated that one in two U.S. adults (126.6 million) had a musculoskeletal condition (USBJI, 2014a). The Global Burden of Disease Study, which provides a comprehensive annual assessment of health loss related to specific diseases, injuries, and risk factors, consistently ranks musculoskeletal disorders among the top causes of disability. In 2016 the top causes of years lived with disability in the United States included low back pain (no. 1), other musculoskeletal disorders (no. 4), neck pain (no. 6), osteoarthritis (no. 12), and rheumatoid arthritis (no. 20) (Mokdad et al., 2018).

Musculoskeletal disorders have a considerable economic impact. In 2015 there were 264 million lost work-days due to back and neck pain alone, resulting in $131.8 billion annual earnings lost (USBJI, 2014b). Projections based on NHIS 2010–2012 data estimate that by 2040 one in four adults (78 million) will have doctor-diagnosed arthritis and, of those with arthritis, an estimated 44 percent will report arthritis-attributable activity limitations (CDC, 2019a). In addition, people with osteoarthritis lost $71.3 billion in annual earnings, and those with rheumatoid arthritis lost $7.9 billion. In 2013, there were 62.8 million health care visits for low back pain and 6.4 million hospitalizations for arthritis and other rheumatic conditions (USBJI, 2014a).

CROSS-CUTTING ISSUES FOR MUSCULOSKELETAL DISORDERS

This section discusses issues that are common to each of the musculoskeletal disorders being discussed in this chapter. The issues include the types of medical professionals typically associated with the care of people with musculoskeletal disorders, the settings involved in that care, and, finally, the issue of pain and restricted mobility that may result from these disorders.

[1] The National Health Interview Survey (NHIS) has monitored the health of the nation since 1957. NHIS data on a broad range of health topics are collected through personal household interviews. For more than 50 years the U.S. Census Bureau has been the data collection agent for the NHIS.

Medical Professionals Associated with Care

A wide range of professionals may be associated with the care of people with musculoskeletal disorders. Most musculoskeletal conditions are initially diagnosed and treated in primary care, where family medicine and general internal medicine are the specialties providing most primary care for adults. Additionally, physical medicine and rehabilition physicians also diagnose and treat musculoskeletal disorders. Occupational medicine physicians may be involved in the diagnosis and treatment when a musculoskeletal disorder is associated with work-related injury or impairment. Physical medicine and rehabilitation physicians (i.e., physiatrists), physical therapists, and occupational therapists are often involved in the management of patients with functional limitations due to musculoskeletal conditions.

Patients with potential inflammatory joint or connective tissue diseases or autoimmune disorders are often referred to rheumatologists for diagnosis and, if indicated, treatment with disease-modifying antirheumatic drug therapy. Patients with advanced joint destruction, whether from osteoarthritis, inflammatory disease, or trauma are typically referred to orthopedic surgeons for surgical treatment, including joint replacement. Patients with inflammatory arthropathies complicated by extra-articular disease manifestations may benefit from additional specialist consultation—for example, patients with rheumatoid arthritis (RA)-associated interstitial lung disease benefit from consultation with a pulmonologist.

Patients with disabling chronic pain may receive care from multidisciplinary teams that include physiatrists or pain physicians (who may have a variety of medical specializations) collaborating with psychologists, rehabilitation therapists, and other health professionals. Team-based care may include care managers (often nurses or social workers) or health coaches (who may be health professionals or lay persons).

Treatment Settings

Care for people with musculoskeletal disorders most often occurs in outpatient office-based settings, however, care may be given in ermergency departments and/or urgent care. Exercise therapies are commonly delivered or supervised by physical therapists, but they may be accessed in the community or integrative health settings as well. Studies have shown that initial triaging to physical therapists at primary health care centers has advantages regarding efficiency in the work environment and in the use of health care (Bornhoft et al., 2019). A wide range of exercise approaches have been shown to benefit patients with chronic low back pain, including strength/resistance, coordination/stabilization, aquatics, cycling, and walking (VA/DoD, 2017). Surgical care may occur in hospitals or stand-alone surgical centers. Rehabilitation care may be provided in offices, in the hospital following surgery, in rehabilitation centers, or in skilled nursing facilities.

Research on Musculoskeletal Disorders

Considering the population prevalence and public health burden of musculoskeletal conditions, research on these conditions are funded at a lower rate than for other chronic conditions. Gereau et al. (2014) estimated that in 2012 the National Institutes of Health (NIH) spent $4 per U.S. person affected by chronic pain, compared with $41 for diabetes and $431 for cancer. The gap in research funding is most dramatic for chronic back pain, the most common cause of disability in the United States and wordwide (Mokdad et al., 2018). According to

publicly reported NIH estimates of funding for various disease or condition categories, back pain was not tracked as a condition category until 2016, and annual expenditures for fiscal years 2016–2018 were only $23 million to $30 million, compared with $1.039 billion to $1.108 billion for diabetes and $5.389 billion to $6.335 billion for cancer (NIH, 2019). This dearth of research funding has resulted in important limitations in our understanding of the disease mechanisms, prognosis, and treatments for chronic back pain and for musculoskeletal disorders in general.

Standard Measures of Outcome for Musculoskeletal Pain

Because pain and impaired function are the predominant features of most musculoskeletal disorders, treatment studies typically assess patient-reported measures of pain or function as the primary outcomes. Although pain outcomes and functional outcomes are often correlated, it cannot be assumed that improvements in pain will automatically lead to improvements in function, and vice versa. Measures that focus on or include function are most relevant to this report. Patient-reported pain or condition-specific functional measures that are commonly used in musculoskeletal outcomes research include the Brief Pain Inventory Interference scale, the Roland Morris Disability Questionnaire, and the Oswestry Disability Index.

Treatments for Pain in Musculoskeletal Disorders

Musculoskeletal disorders are the most common causes of chronic pain, and pain accounts for much of the burden of musculoskeletal conditions. According to 2016 NHIS data, the estimated prevalence of chronic pain—defined as pain on most days in the prior 6 months—among U.S. adults was 20.4 percent (50.0 million) (Dahlhamer, 2018). High-impact pain, defined as chronic pain that limited life or work activities on most days or every day during the past 6 months, affected 8.0 percent (19.6 million) (CDC, 2018). Most of that pain is attributable to musculoskeletal disorders.

In the systematic classification of chronic pain developed by the International Association for the Study of Pain (IASP) and adopted by the World Health Organization for the *International Classification of Disease, 11th revision* (ICD-11), chronic musculoskeletal pain is described as persistent or recurrent pain experienced in musculoskeletal structures such as muscles, bones, joints, or tendons (Perrot et al. 2019). The IASP classification distinguishes between (1) chronic pain that cannot be attributed directly to a known disease or damage process and is diagnosed independently of identified biologic or psychologic contributors (chronic *primary* musculoskeletal pain), and (2) chronic pain that arises from an underlying disease (chronic *secondary* musculoskeletal pain). Chronic low back pain is an example of a chronic primary musculoskeletal pain condition, whereas osteoarthritis pain and joint pain associated with inflammatory diseases (rheumatoid arthritis, psoriatic arthritis) are secondary musculoskeletal pain conditions (Nicholas et al., 2019; Perrot et al., 2019).

Numerous medications and nonpharmacologic treatments are available for relieving the pain associated with musculoskeletal disorders. A recent systematic review of evidence on the treatment of musculoskeletal pain found moderate to strong evidence that exercise and psychosocial interventions were effective in relieving pain and improving function across multiple common musculoskeletal pain conditions (Babatunde et al., 2017). Moderate but less consistent evidence suggested that pharmacologic interventions such as oral and topical analgesics and corticosteroid injections (for knee and shoulder pain, but not back or neck pain)

provide short-term pain relief. Limited evidence suggested the potential of manual therapies (e.g., manipulation, massage), acupuncture, and other treatments for the relief of pain.

Guidelines recommend non-drug therapies as first-line treatments for chronic low back pain and osteoarthritis pain (Bannuru et al., 2019; Qaseem et al., 2017). Medications, especially non-steroidal anti-inflammatory drugs (NSAIDs), are typically recommended as second-line or adjunct therapy. Until recently, various bodies recommended opioid analgesics for the treatment of chronic musculoskeletal pain when other treatments were ineffective. That advice was widely disseminated and resulted in widespread long-term opioid use among a large percentage of persons with chronic musculoskeletal conditions; however, the guidance has recently changed based on evidence. Opioids are no longer recommended for chronic musculoskeletal pain conditions because they are not superior to other analgesics (Busse et al., 2018; Krebs et al., 2018) and confer substantially greater risk of serious harm, including addiction, injury, and death (Bannuru et al., 2019; Dowell et al., 2016).

TABLE 5-2 Pharmacologic Treatments Used for Musculoskeletal Pain Conditions

Drug Class	Example Drugs	Notes
Simple analgesics	Acetaminophen	Used for pain relief; available without a prescription; often included in combination with other medications.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Celecoxib, ibuprofen, naproxen, meloxicam, salsalate, topical diclofenac	Diverse class used for relief of pain and reduction of inflammation; some drugs available without a prescription. Available in oral and topical formulations.
Muscle relaxants	Cyclobenzaprine, methocarbamol	Used for chronic back and muscular pain.
Tricyclic antidepressants	Amitriptyline, nortriptyline	Used (usually in low doses) for chronic back pain, widespread pain, fibromyalgia, and insomnia associated with pain.
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine, milnacipran	Used for chronic back pain, widespread pain, fibromyalgia, and depression associated with pain.
Gabapentinoids	Gabapentin, pregabalin	Used for chronic back pain, fibromyalgia, and pain with neuropathic features.
Topical analgesics (non-NSAID)	Capsaicin, lidocaine	Used for joint pain and localized musculoskeletal pain.
Opioids	Hydrocodone, oxycodone, morphine	Used for all types of pain.

SOURCES: Chou et al., 2017a; Curatolo and Bogduk, 2001.

Further discussion of treatments to improve function is presented in relation to each medical condition below.

CHRONIC LOW BACK PAIN

Chronic back pain is the leading cause of years lived with disability in the United States and accounts for more than 264 million lost work-days per year. (USBJI, 2014a). In 2013 back pain was the most common reason for health care visits among musculoskeletal disorders, with more than 57 million physician office visits. Office visits for back pain overall have increased over time. The rate of persons visiting a physician because of back pain increased from 11.8 out of every 100 persons in 1998 to 18.1 out of every 100 persons in 2013. Low back pain accounted for most of the increase in visits (USBJI, 2019).

Chronic low back pain is a clinical syndrome defined by the persistence of pain in the lower back for at least 3 months. In some persons, chronic low back pain may progress over time to a complex condition "involving persistent anatomical and functional changes in the central nervous system, in addition to structural changes in the back (e.g., degenerative spinal changes, atrophy, or asymmetry of paraspinal muscles)" (Deyo et al., 2014).

Chronic low back pain is sometimes associated with pain that radiates to the lower extremity in a characteristic distribution (i.e., radicular pain, sometimes called "sciatica") or radiculopathy, meaning objective neurologic abnormalities associated with spinal nerve root involvement. Lumbar spinal stenosis is a clinical syndrome most common in older adults, in which characteristic pain in the buttocks or legs occurs with walking.

The presence of radicular pain or radiculopathy is associated with worse chronic low back pain severity and functional outcomes. Other factors associated with worse functional outcomes in chronic low back pain include co-existing medical and psychiatric conditions and other chronic pain conditions. In addition, the overuse of biomedical approaches to treat chronic low back pain (e.g., opioids and spine surgery) has been identified as a potentially important contributor to disability (Buchbinder et al., 2018).

Professional Accepted Diagnostic Criteria

Chronic low back pain is defined by its location (i.e., between the lower rib margin and the gluteal folds), and by a duration of at least 3 months. It is often described as "nonspecific" because a specific cause is rarely identified (Hartvigsen et al., 2018). The vast majority of chronic low back pain cases, estimated at more than 95 percent in most employed populations, have no definable pathophysiologic abnormality (Hegmann et al., 2019). In the chronic pain classification developed by the IASP and adopted for ICD-11, back pain that persists or recurs for more than 3 months and is associated with significant emotional distress or functional impairment is categorized as a chronic primary pain condition unless the pain is better accounted for by another diagnosis (e.g., axial spondyloarthritis, multiple myeloma) (Nicholas et al., 2019).

Chronic low back pain involves diverse pathophysiologic, cognitive, emotional, and social factors which contribute to its onset, maintenance, and related impairment. Numerous local pain generators are known to be present in the low back. Cognitive and behavioral factors such as catastrophizing and activity avoidance are known to be involved in some individuals. More recently, alterations in the central nervous system structure and function related to the processing of pain and emotion have been identified. Unfortunately, there is little scientific consensus on the relative importance of those factors or the extent to which they are causes rather than consequences of chronic back pain (Vlaeyen et al., 2018). Historical diagnoses such as psychogenic pain disorder, which were previously applied to people who had chronic pain

without obvious local anatomical abnormalities, have been rendered obsolete by advances in scientific knowledge (Katz et al., 2015). Diagnoses such as sacroiliac joint pain and degenerative disc disease have limited value due to the lack of defined diagnostic criteria and inconsistent usage by clinicians and researchers (Battie et al., 2019).

Routine imaging and laboratory testing are not typically indicated in the initial evaluation of chronic low back pain. As noted above, the diagnosis of chronic low back pain is a syndrome defined by subjective pain experience in a defined anatomical region for a duration of time. Imaging and laboratory testing are utilized to exclude high risk sources of back pain in some patients, but specific imaging or laboratory testing for the diagnosis of chronic low back pain are not available. Furthermore, the presence or absence of radiographic abnormalities should not be considered when evaluating the severity or prognosis of chronic low back pain, and repeated imaging is not useful for evaluating the effectiveness of treatment or progress. As noted by authors of the American College of Occupational and Environmental Medicine 2019 low back disorders guidelines, "'abnormal' findings on X-rays, magnetic resonance images, and other diagnostic tests are so common they *are normal by age 40*" (Hegmann et al., 2019). Radiographic evidence of degenerative spine changes such as intervertebral disc and vertebral endplate changes are more common in people with chronic back pain, but they are also frequently present in pain-free persons and are not highly correlated with the severity of pain or degree of functional impairment (Hartvigsen et al., 2018).

Diagnostic testing is not indicated for the vast majority of low back pain patients; however, spine X-rays or magnetic resonance imaging (MRI) may be indicated for back pain that persists despite initial treatment (Hegmann et al., 2019). Targeted imaging or laboratory testing may also be indicated for selected patients with trauma, neurologic deficits, or other "red flag" symptoms or signs as well as for patients being considered for surgery.

Low back pain as a symptom is experienced by most people at some point in their lives. The first episode may occur in the second or third decade of life; approximately 40 percent of children of ages 9–18 report having had back pain (Hartvigsen et al., 2018). The prevalence of back pain may be highest among middle-aged adults, but back pain remains prevalent in old age (Henschke et al., 2015). Back pain has a slight female predominance across all age groups.

Among working adults, the NHIS estimated that the prevalence of any past-year low back pain was 26.4 percent and that the prevalence of frequent and severe low back pain was 8.1 percent. Among workers with frequent and severe low back pain, 19.0 percent reported that the back pain caused them to miss at least one full day of work in the prior 3 months, and 10.7 percent reported they had changed jobs or made a major change in work activities in the past 3 months because of back pain (Luckhaupt, 2019).

Treatments for Chronic Low Back Pain

Numerous treatments have demonstrated effectiveness for improving function in chronic low back pain. These include exercise therapies, behavioral/psychological therapies, and manual therapies. Multidisciplinary approaches, including intensive chronic pain rehabilitation programs and less intensive primary-care-based collaborative care management interventions, also have demonstrated benefits for function.

Exercise therapies are the first-line treatments recommended in guidelines for routine use in chronic low back pain. (Foster et al., 2018; Qaseem et al., 2017; VA/DoD, 2017). These guidelines are supported by a large body of evidence that is somewhat limited by the methodology, size, and heterogeneity of published clinical trials. Studies have evaluated a

wide range of exercise approaches in patients with low back pain, including strength/resistance, motor control/stabilization, and aerobic exercise. In general, the approaches seem to have similar efficacy, and no one approach is effective for the majority of patients.

A comprehensive Agency for Healthcare Research and Quality comparative effectiveness review of pharmacologic and noninvasive nonpharmacologic treatments for low back pain found moderate-strength evidence that exercise therapies improve pain and function in patients with chronic low back pain (Chou et al., 2016). A comparison of trials did not find differences in effectiveness among different exercise techniques (Chou et al., 2016). Although the benefits appear to be similar for different exercise therapy techniques, factors such as the number of sessions and supervision may be associated with greater improvements. A systematic review of exercise therapy for nonacute low back pain focused specifically on work disability as an outcome and found that exercise was associated with a lower likelihood of work disability at an approximately 1-year follow-up (Chou et al., 2017b; Oesch et al., 2010).

Emerging evidence supports movement-based approaches, which are sometimes considered to be complementary or integrative therapies (e.g., yoga, tai chi), as effective treatments for chronic low back pain. A synthesis of five trials of yoga versus education for chronic low back pain found that yoga was superior, with moderate-sized improvements in back-specific function (Chou et al., 2016). Four trials of yoga versus other exercise interventions yielded inconsistent results. One trial found clinically significant functional improvement in 50 percent of patients assigned to 10 weeks of tai chi compared with 24 percent of patients assigned to a wait list control group (Chou et al., 2016)

Psychologic or behavioral therapies are also considered first-line therapies for patients with chronic back pain (Foster et al., 2018; Qaseem et al 2017, VA/DoD, 2017). Cognitive behavioral therapy (CBT) interventions are well-established although the strength of evidence for improvements in pain and function has been rated as low because of limitations in the quantity and quality of published trials (Chou et al., 2016). A systematic review of cognitive behavioral interventions for nonspecific low back pain found greater improvements in pain, function, and quality of life than with a control or other therapies (Richmond et al., 2015). A randomized comparative effectiveness trial found CBT and mindfulness-based stress reduction (MBSR) were each superior to usual care, but not different from each other; the percentage of participants with clinically meaningful functional improvement at 1 year was 60.5 percent for MBSR, 57.7 percent for CBT, and 44.1 percent for usual care (Cherkin et al., 2016). After 2 years, CBT remained significantly better than usual care, and MBSR no longer differed from the other two groups; the rates of meaningful functional improvement were 55.4 percent for MBSR, 62.0 percent for CBT, and 42.0 percent for usual care (Cherkin et al., 2017).

Multidisciplinary rehabilitation, which refers to integrated programs that typically combine exercise, behavioral, and other therapies, often with opioid tapering when applicable, are recommended for patients who do not respond to less intensive interventions, and they may be particularly relevant to the population of patients receiving Social Security Insurance and Social Security Disability Insurance (Foster et al., 2018; VA/DoD, 2017). A systematic review found that multidisciplinary rehabilitation was associated with functional improvement in the short and long term, but not with return to work (Chou et al., 2016). A review of less intensive primary-care-based coordinated care delivery models found evidence that those interventions improve function over 9–12 months (Peterson et al., 2018).

Additional conservative therapies, such as acupuncture, manipulation, and massage, may also be associated with modest long-term improvements (Bronfort et al., 2014; Chou et al., 2016; Qaseem et al., 2017; Rubinstein et al., 2011). To maximize functional outcomes, experts suggest that those therapies should be used together with active approaches, such as exercise (Kligler et al., 2018).

Interventional therapies (e.g., injections, surgery) generally lack evidence of functional benefits in chronic low back pain. The general indications for referring a patient to be considered for low back surgery include progressive neurologic deficit or a new onset of genitourinary or bowel dysfunction that correlates with a anatomic abnormality of the lower back (Abraham et al., 2016).

In general, medications are less beneficial for function than for pain in chronic low back pain, with most of their benefits demonstrated only in short-term. A systematic review conducted for use in developing the American College of Physicians low back pain guideline found evidence that NSAIDs, duloxetine, tramadol, and opioids produced small short-term improvements in functional outcomes (Chou et al., 2017a).

Foster et al. (2018) summarized treatment recommendations from recent evidence-based guidelines for chronic low back pain; these are shown in Table 5-3.

TABLE 5-3 Treatment for Chronic Low Back Pain

Education and Self-Care	
Advice to remain active	First-line treatment, consider for routine use
Education	First-line treatment, consider for routine use
Superficial heat	Insufficient evidence
Non-Pharmacological Therapy	
Exercise therapy	First-line treatment, consider for routine use
Cognitive behavioral therapy	First-line treatment, consider for routine use
Spinal manipulation	Second-line adjunctive treatment option
Massage	Second-line adjunctive treatment option
Acupuncture	Second-line adjunctive treatment option
Yoga	Second-line adjunctive treatment option
Mindfulness-based stress reduction	Second-line adjunctive treatment option
Interdisciplinary rehabilitation	Second-line adjunctive treatment option
Pharmacological Therapy	
Paracetamol	Not recommended
Non-steroidal anti-inflammatory drugs	Second-line adjunctive treatment option
Skeletal muscle relaxants	Insufficient evidence
Selective norepinephrine reuptake inhinbitors	Second-line adjunctive treatment option
Antiseizure medications	Role uncertain
Opioids	Limited use in selected patients, use with caution
Systemic glucocorticoids	Not recommended

Interventional Therapies	
Epidural glucocorticoid injection (for herniated disc with radiculopathy)	Limited use in selected patients
Surgery	
Discectomy (for herniated disc with radiculopathy)	Second-line adjunctive treatment option
Laminectomy (for symptomatic spinal stenosis)	Second-line adjunctive treatment option
Spinal fusion (for non-radicular low back pain with degenerative disc findings)	Role uncertain

SOURCE: Adapted from Foster et al., 2018.

Length of Time to Improvement for Chronis Low Back Pain

The committee did not identify evidence about the likelihood that treatment will reach a point at which low back pain is no longer disabling or how long it would require to reach that point. There is no evidence that the efficacy of chronic back pain treatments differs by age.

OSTEOARTHRITIS

Osteoarthritis (OA) comprises a family of degenerative joint disorders characterized by clinical and radiographic findings. It is the most common form of arthritis, affecting more than 30 million Americans (Arthritis Foundation, 2018). OA has been thought of as being the "wear and tear" form of arthritis, however, it is a complex combination of genetic, metabolic, biomechanical, and biochemical joint changes that can involve the entire joint and surrounding tissues. OA is becoming the most common cause of disability for middle-aged Americans and has become the most common cause of disability for people older than 65 years. In fact, age is one of the strongest risk factors for OA of all joints. Women are more likely than men to have OA, and their OA tends to be more severe (Zhang and Jordan, 2010).

OA is a disease that progressively damages or destroys synovial joint structure and, in particular, the bearing surfaces of the joints, that is, articular cartilage. OA can affect any synovial joint and appears in all populations. There is no known cure or method of reversing the process. For those reasons, therapy for OA is directed at decreasing joint pain and increasing function and includes both pharmacologic and nonpharmacologic interventions. Pharmacologic therapy often begins with analgesic medications or topical analgesics and NSAIDs as needed; such medications might be prescribed by a primary care physician or a physical medicine and rehabilitation physician in a physician's office. Intra-articular injections of corticosteroids[2] can relieve pain, but the effect is of limited duration and should be used infrequently; such injections might be administered in a physician's office. Nonpharmacologic therapy includes patient education, weight loss if clinically indicated, physical therapy directed at maintaining joint

[2] Intraarticular corticosteroid injections can be considered as an adjunct to core treatment for short-term reduction of moderate to severe pain in people with osteoarthritis (Ayhan et al., 2014).

mobility and strengthening muscle groups or an organized low-impact exercise program, and assistive devices as needed; usually those occur within the physical therapy (PT) or occupational therapy setting for osteoarthritis of the hand. Total joint replacement might be prescribed, which would occur in a surgical suite in a hospital (Lane and Thompson, 1997). Thus, health care settings can be located in physicians' offices, PT centers, and hospitals and rehabilitation centers.

The primary symptom of OA is joint pain that worsens during activity and improves with rest. The main feature of OA is the articular cartilage degeneration in response to stress, injury, mechanical overload, and increasing age (Frontera et al., 2015). The incidence of the disease increases in all synovial joints and all populations with increasing age. Joint injury is a risk factor for OA, but the majority of cases occur without a specific history of injury.

OA typically leads to progressive damage to articular cartilage, which in turn leads to joint pain and impaired joint function. Over time the joint may lose its normal shape. The condition can cause bone spurs to grow on the edges of the joint. Bits of bone or cartilage can break off and float inside the joint space, which causes additional pain and damage. Unlike other forms of inflammatory arthropothies, OA only affects joints and not internal organs. It is most common in older people; before age 45 more men than women have osteoarthritis, while after age 45 it is more common in women (NIAMS, 2016). The prevalence of symptomatic knee OA increases with each decade of life, with the annual incidence being highest between 55 and 64 years old. OA can cause pain, stiffness, and swelling, and in some cases it causes reduced function and disability; some people are no longer able to do daily tasks or work. In some instances, the disease causes progressive joint deformity, joint contractures, and joint swelling.

Primary or idiopathic OA can be localized (affecting a single joint) or generalized (involvement of three or more joints) (Frontera et al., 2019). Although joint injury is a risk factor for OA, the majority of cases occur without a specific history of injury. Obesity is a risk factor for knee OA and, to a lesser extent, for hip and hand OA. Women have a greater risk of knee OA than men. Joint dysplasia and laxity, some neuropathies and metabolic disorders, and genetic predisposition may also increase the risk of OA, as can sustained physically demanding activities.

Specific OA symptoms include pain, stiffness, reduced movement, and swelling of the affected joints. OA is typically exacerbated with activity and relieved with rest (Zhang and Jordan, 2010). Joint tenderness and crepitus on movement may also be present; there are no systemic symptoms (Frontera et al., 2019). In the early stages of the disease pain may be absent, but with advanced disease there may be grinding or locking with joint motion and buckling or instability of joints. Pain is present in patients with advanced disease, and the overuse of muscle groups can lead to the development of pain syndromes in other parts of the musculoskeletal system (Frontera et al., 2019).

The degree of functional limitation depends on the affected joint and the person's social and work activities. Impaired mobility, locomotion, and activities of daily living are found in patients with the disease in hips and knees. Degeneration in the hands limits vocational and recreational activities and self-care. Patients might have trouble with using a computer or lifting boxes, which can progress to difficulties with activities of daily living (Frontera et al., 2019).

Professional Accepted Diagnostic Criteria for Osteoarthritis

No single test can diagnose osteoarthritis. Doctors use several methods to diagnose the disease and rule out other problems (see below). A variety of medical specialties treat OA.

Treatments for osteoarthritis include drugs, nondrug pain relief techniques, surgery, and alternative therapies; these are discussed in detail below.

There are a few tests that a physician can perform to enable a diagnosis of OA. Generally a family physician or an internist will take a medical history to understand the symptoms and to determine if there are other co-occurring disorders. Following a physical exam, the diagnosing physician may then require specific tests for OA, which include

- **Physical exam** to check general health, reflexes, and problem joints.
- **X-rays** to provide information about cartilage loss, bone damage, and bone spurs, although early damage may not show on X-rays.
- **Magnetic resonance imaging (MRI)** to show damage to joint tissues, primarily articular cartilage, menisci, and subchondral bone tissues.
- **Blood tests** may be performed to rule out other causes for symptoms.
- **Joint fluid samples** might be taken to look for other causes of joint pain, such as infection or gout.

Thus, OA can be defined pathologically, radiographically, or clinically. Radiographic OA has long been considered the reference standard (Zhang and Jordan, 2010), although patients may have radiographic OA without evidence of clinical OA.

General Treatments for Osteoarthritis

There are many pharmacologic and non-pharmacologic therapies that can provide *temporary* relief from the pain of OA. The initial treatment should employ both approaches, although there are no pharmacologic interventions that have been shown to cure or alter the disease progress of OA (Frontera et al., 2018). The possible treatments include

- Analgesics ranging in strength from mild to strong. Many can be purchased over the counter, while the stronger medications require a prescription. Oral acetaminophen is recommended by the American College of Rheumatology as a first-line medication for hip and knee OA.
- Topical products such as ointments, gels, sprays, and creams, which can be applied directly to the skin of the affected areas. Topical NSAIDS have been shown to be more effective than placebo in treating OA.
- NSAIDs in ooral or topical form, which provide temporary pain relief. NSAIDs block the action of specific enzymes that are involved in the inflammatory process. There are side effects, particularly stomach pain, nausea, diarrhea, and ulcer formation. NSAIDs may interfere with other medications.
- Anti-neuropathic pain medications, which act on the nervous system to reduce the nerve pain associated with the injury (e.g., gabapentin or serotonin-norepinephrine reuptake inhibitors).
- Corticosteroids, which can rapidly reduce or control inflammation. They may be taken orally or be injected; however, they do have side effects if taken for long periods of time.

The committee chose to focus its discussion on OA affecting two weight-bearing joints (hips and knees) and two non-weight-bearing joints (hands and wrists). Those are the joints most commonly affected with radiographic and symptomatic OA (Helmick, 2014).

The goals of OA treatment are to decrease or relieve pain and to improve or restore function, as there is no pharmacologic cure. Patients vary considerably in their response to treatment, depending on the affected joints and the stage of the disease (mild, moderate, or severe). The rate of progression of OA varies among patients and joints. Although there are numerous treatments available, progressive knee OA may result in reduced mobility and resulting systemic complications of immobility and deconditioning.

Initial treatments that might provide relief from pain include: acetaminophen as a first-line therapy, followed by oral and topical NSAIDs. Orthotics and footwear modifications also might be useful, but their usefulness is patient specific. Exercise programs have been developed for knee OA since maintaining activity is critical to maintaining function. Numerous procedures, such as intra-articular corticosteroid injections may help in reducing local inflammation and improving symptoms (Frontera et al., 2018). A systematic review of intra-articular corticosteroid injections found evidence of pain reduction for up to 6 weeks following injection (da Costa et al., 2016). There is conflicting evidence about the usefulness of acupuncture, but it is recommended for chronic moderate to severe OA when surgery is not possible (Frontera et al., 2018). Platelet-rich plasma, a concentrate of autologous blood growth factors, has been shown in limited studies to provide some symptomatic relief in early knee OA, not only pain relief but functional improvement 1 year post injection (Dai et al., 2017). However, more research is needed to confirm the efficacy and long-term results of this treatment.

A stepped-care approach can be used to optimize the use and timing of the non-surgical treatment options for patients with OA; however, a study from Smink and colleagues (2014) found that there have been no statistically significant differences in changes over a 2-year period in pain and physical function between patients who received a stepped-care approach and those who received regular care. An example of one kind of stepped-care approach can be found in Table 5-4.

Knee and Hip Osteoarthritis

The prevalence of symptomatic knee OA increases with each decade of life, with the annual incidence being highest between 55 and 64 years old. Globally, the age-standardized prevalence of radiographically confirmed symptomatic knee OA is about 3.8 percent, with higher rates in women (4.8 percent) than in men (2.8 percent) (Cross et al., 2014). As noted in Frontera et al. (2018), the knee joint is the most common site for lower extremity OA and can involve all or any of the major knee compartments: medial, patellofemoral, or lateral. OA affects all structures within and around a joint. OA is characterized by a progressive loss or erosion of articular cartilage, subchondral bone sclerosis, and the formation of osteophytes, leading to joint pain and impaired joint function and, in some instances, joint deformity and contracture (AAOS, 2017). Women are more likely to develop knee OA than men, especially after age 50 (CDC, 2019b). Between 2010 and 2011 three in five knee replacements occurred in women, and the mean age for both knee and revision knee replacements was 68 years of age. During that same time period, there were an estimated 465,000 to 512,000 hip replacement procedures, the majority (about 63 percent) of which occurred in women (USBJI, 2014a).

OA of the hip is less common than OA of the knee or hand, but it is the most prevalent pathologic condition at the hip joint. No gender differences have been identified in the rates of

hip OA, but the rates do increase with age. Occupational heavy lifting and frequent stair climbing increase the risk of hip OA (Frontera et al., 2018).

TABLE 5-4 Stepped Care Approach for the Treatment of Osteoarthritis

Severe	Moderate	Mild	Encourage regular exercise Encourage weight loss if necessary Consider physical therapy Patient education concerning activity modification, muscle strengthening, and maintaining joint range of motion Begin with acetaminophen Start NSAID therapy, beginning with ibuprofen or naproxen Switch to different NSAID if initial choice is not effective
			Combination glucosamine and chondroitin for knee OA Discontinue glucosamine and chondroitin if no change after 3 months
			Consider corticosteroid injection for knee OA Consider hyaluronic acid injection for knee OA Total joint replacement for OA of the hip, knee, or shoulder Joint arthroplasty for first carpal metacarpal joint OA Joint fusion or arthroplasty for wrist OA Joint fusion for finger joint OA

SOURCE: Sinusas, 2012.

Professionally Accepted Diagnostic Criteria

The diagnosis of hip and knee OA is typically made based on the patient's history, a physical examination, and plain radiographs. Laboratory tests are typically normal. Joint pain is the primary symptom of hip and knee OA, although many patients also have a decreased range of motion and crepitus, and some patients develop joint deformity (Sinusas, 2012). Knee pain severity is a more important determinant of functional impairment than is the radiographic severity of OA. The primary radiographic evidence of OA is decreased joint space (decreased distance between the bones forming the joint, which is caused by the erosion of articular cartilage). Additional radiographic evidence of OA includes the presences of osteophytes (bone spurs) and changes in subchondral bone, the bone immediately adjacent to the articular cartilage. Subchondral bone changes associated with OA include bone sclerosis, or thickening, and bone cysts.

Groin pain is the classic symptom for hip OA; other presenting symptoms might be buttock pain, hip pain, stiffness, and associated function limitations. Hip OA might have an insidious onset, and it becomes worse with activity (particularly weight-bearing activity). It might be relieved with rest, but advanced hip OA may be painful even at rest (Frontera et al., 2018). Radiography is the primary diagnostic study for hip OA. MRI imaging is typically not necessary, nor is ultrasound, although they might be useful for defining more complex cases. See Table 5-5 for additional clinical diagnostic criteria for OA of the hip, knee, hand, and wrist.

TABLE 5-5 Clinical Diagnostic Criteria for Osteroarthritis of the Hip, Knee, Hand, and Wrist

Hip	Pain on range of motion
	Pain in groin, buttock
	Limitation of range of motion, especially internal rotation
Knee	Pain on range of motion
	Joint contractures
	Joint effusion
	Crepitus on range of motion
	Presence of popliteal cyst
	Lateral instability
	Valgus or varus deformity
	Shortening of the limb
Hand	Pain in range of motion
	Hypertrophic changes at distal and proximal interphalangeal joints
	Tenderness over carpometacarpal join of thumb
Wrist	Pain in range of motion
	Joint stiffness
	Tenderness and swelling

SOURCE: Adapted from Sinusas, 2012.

Treatments Demonstrated to Improve Hip and Knee Function

Exercise has been the mainstay of non-pharmacologic treatment for knee OA. The specific focus is on lower extremity stretching, aerobic conditioning, and balance exercises. Treatments for knee and hip osteoarthritis are similar, with a few differences; in some patients, for example, activity modification is helpful as it can avoid or minimize activities that exacerbate pain. Non-pharmacologic therapy often starts with exercise, and there is strong evidence supporting the use of physical therapy as a treatment to improve function and reduce pain for patients with mild to moderate symptoms of hip OA. Exercise for knee and hip OA has been shown to reduce pain by 6 percent, improve physical function by 5.6 percent, improve self-efficacy by 1.66 percent, and also have small benefits for depression (Hurley et al., 2018). Research involving supervised home-based exercise showed statistically significant improvements in a validated arthritis symptom score at 6, 12, 18, and 24 months (Sinusas, 2012). Research findings recommend that all patients with symptomatic knee or hip osteoarthritis be enrolled in an exercise program commensurate with their ability (Hurley et al., 2018). The decision concerning the type of treatment should be individualized and based on patient preference and ability to perform the exercises (Hochberg et al., 2012). Patients with OA of the first metacarpal joint or the wrist joint may benefit from braces or splints. Moderate-strength evidence indicates that obese patients with symptomatic osteoarthritis of the hip may achieve lower absolute outcome scores after total hip arthroplasty than non-obese patients but still report

a similar level of patient satisfaction and relative improvement in pain and function (AAOS, 2017).

Knee replacement, which include both total and partial knee replacement, is performed to restore function and relieve pain in patients with severely damaged knees. Although total knee replacement is an effective treatment, postoperative complications include blood clots, wound break down, infection, and loosening or malalignment of the prosthetic component (Scott, 2015). A study by Scott et al. (2017) prospectively assessed 289 patients (≤ 65 years of age) who had total knee replacement. The investigators found that of the 90 percent of patients who were working before total knee replacement, 40 percent returned to work, including 34 percent who returned to the same job. A total of 41 percent retired, and the remaining patients remained on public assistance; patients not working before the surgery did not return to work. Another study by Scott et al. (2018) assessed 55 patients (≤ 65 years of age), 95 percent of whom were working before receiving a revision total hip arthroplasty. The authors found that 1 year after the surgery, 33 percent had returned to work, 48 percent had retired, and 19 percent were receiving public assistance. Age was the most significant predictor of return to work; only 16 percent of patients over 50 years of age returned to work.

A review of hip osteoarthritis and work (Harrris and Coggon, 2015) found several descriptive studies that have documented return to work following hip arthroplasty. The range in time varied from 8 days (with accelerated rehabilitation) to 13.9 weeks; however, the authors noted that published data do not provide guidance on the time to return to work following such surgery.

Joint arthroplasty should be considered for severe cases of OA. In cases of advanced osteoarthritis of the hip, knee, shoulder and wrist, joint replacements may relieve pain and improve function for most patients. However, depending on the patients' preoperative work experience, skills, and education and the physical demands of possible work opportunities, the postoperative work experience will differ; not all patients who have successful joint replacements or fusions can return to gainful employment.

Although there are numerous treatments available, progressive knee OA may result in reduced mobility and the resulting systemic complications of immobility and deconditioning. The risk of falls will likely be increased with decreased mobility of the knee. Complications can result from the use of anti-inflammatory medications, infection can result following joint injections or surgery, and arthroscopy can damage articular surface membranes, which can lead to damage to uninvolved cartilage. Infection, deep vein thrombosis, and intraoperative mortality can result from surgery, thus limiting surgery to a last option (Frontera et al., 2018).

There is some evidence supporting the use of preoperative and postoperative PT to improve early function in patients with symptomatic OA of the hip following total hip arthroplasty. Postoperative PT has been shown to improve early function to a greater extent than no PT management (AAOS, 2017). Furthermore, a review of exercise interventions for knee and hip OA demonstrated that participation in exercise programs may improve physical function and decrease depression and pain (Hurley et al., 2018).

Length of Time to Improvement

The time to improvement varies considerable among patients and depends on such variables as comorbidities (obesity, diabetes, smoking, pain-catastrophizing, and others) and the complexity of the surgery and the pre-surgical condition of the patient. Pre-operative patient

preparation and postoperative therapy can improve results. There is no clear evidence that age has a strong influence on improvement following hip and knee replacement.

Hand and Wrist Osteoarthritis

Osteoarthritis of the hand is the most common form of arthritis and is associated with aging. Estimates of hand OA reach as high as 78 percent in men and 99 percent in women over the age of 65. People may experience pain, stiffness, limitation in function, and reduced grip strength, but since the disease is typically gradual, most people adapt, and complaints of disability are less common than for other types of osteoarthritis (Frontera et al., 2018).

Osteoarthritis of the wrist refers to the painful degeneration of the articular surfaces that make up the wrist joint between the distal radius and the proximal row of carpal bones. Symptoms include pain, swelling, stiffness, and crepitation. Secondary wrist OA is the most common form and most often results from posttraumatic conditions, such as distal radius fractures, carpal fractures, and carpal instability (Frontera, et al., 2018).

Professionally Accepted Diagnostic Criteria

Osteoarthritis of the hand most commonly develops in the first carpal metacarpal joint (the base of the thumb joint), the distal interphalangeal joints of the fingers (the finger joints closest to the tips of the fingers), and the finger interphalangeal joints (the middle joints in the fingers). It is a clinical syndrome characterized by progressive loss or erosion of articular cartilage, subchondral bone sclerosis, and the formation of osteophytes leading to joint pain and impaired joint function and, in some instances, to joint deformity and contracture (AAOS, 2017). The diagnosis of OA is typically made based on the patient's history, a physical examination, and conventional radiographs. Radiographic evidence is highly reliable and is the preferred method of evaluating hand OA. The pain, stiffness, and disability associated with hand OA are weakly to moderately associated with radiographic findings (Frontera et al., 2018).

In the majority of cases, pain is the presenting symptom of wrist OA. The initial physical examination of an arthritic wrist includes an inspection of the entire upper limb; the most obvious finding may be a loss of motion. Other types of imagining modalities are not necessary for the diagnosis. It should be noted that the majority of the limitation in wrist arthritis arises from a lack of motion. The loss of motion mainly affects activities of daily living (Frontera et al., 2018). Wrist OA that progresses to advanced stages results in severely painful limitations of motion, which means that affected people are unable to conduct the activities of daily living (Frontera et al., 2018).

Treatments Demonstrated to Improve Function in Patients with Hand and Wrist OA

There is some evidence that occupational therapy might be beneficial for patients with hand and wrist OA. Oral acetaminophens and NSAIDs may relieve symptoms. Similarly, ice, heat, and topical creams might provide symptomatic relief. Intra-articular injections of corticosteroids or hyaluronate inconsistently provide temporary relief. Common treatments of hand and wrist OA include splinting and joint arthroplasty for the thumb carpometacarpal joint; joint splinting, corticosteroid injections, fusion, and arthroplasty for wrist OA; and joint fusion for finger joint OA. In general, surgery provides fairly predictable pain relief but may reduce function (Frontera et al., 2018). Joint arthroplasty can decrease pain for patients with severe first

carpal metacarpal joint osteoarthritis,[3] and joint fusions can decrease pain and improve function for patients with severe wrist and finger joint osteoarthritis.

Length of Time to Improvement

The length of time to improvement varies with the patients, their preoperative condition, and their postoperative therapy. In general, most patients with a successful surgical intervention achieve near-maximum benefit with 6 months. There is not clear evidence of age as a strong determinant of the outcomes of treating hand and wrist OA. Comorbidities including muscle weakness, neurologic disorders, and diabetes may adversely influence the outcomes of the procedure. Pre-operative preparation and post-operative therapy can improve results but the types of therapy and number of sessions will depend on physician judgement and the condition of the patient.

INFLAMMATORY ARTHROPATHIES

Inflammatory arthropathies are conditions characterized by inflammation of the joints and often other tissues. These include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and systemic lupus erythematosus, among others. Rheumatoid arthritis and psoriatic arthritis are among the most common inflammatory arthropathies and are important causes of disability in adults (Merola et al., 2018; Sangha, 2000), and they are therefore the focus of this section.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes pain, aching, stiffness, and swelling in multiple synovial joints. It typically affects the small joints of the hands and the feet and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and so can affect other organ systems, including the heart, lungs and eyes (NICE, 2018), and it can cause other systemic symptoms, including fatigue, fever, and weight loss (Wasserman, 2011). Because the musculoskeletal impairments associated with RA are typically the most disabling and the major source of functional limitations for individuals with this condition, this section primarily focuses on those impairments, although the committee acknowledges that RA's impacts on other organ systems may also influence global functioning (Filipovic et al., 2011). The common pathophysiology underlying musculoskeletal impairments in RA is inflammation of the synovium (Scott et al., 2010). During disease flares, inflammation results in a short-term worsening of joint pain and swelling; in patients with longstanding and severe disease, persistent inflammation will over time result in the erosion of cartilage and bone,

[3] Osteoarthritis in the hands usually involves the distal interphalangeal joints (Heberden nodes) and proximal interphalangeal joints (Bouchard nodes), and the pain usually resolves in 1 to 2 years. However, first carpometacarpal joint osteoarthritis (CMC1 OA) often remains a chronically painful condition with exacerbations of pain and decreased function over time. Clinical symptoms do not necessarily correlate with commonly observed radiographic changes, and physical examination findings of pain over this joint might be better than a radiograph at predicting a patient's function (Wolf et al., 2014).

leading to joint destruction and deformities that in turn cause chronic pain and functional limitations (Sokka et al., 2001).

Professionally Accepted Diagnostic Criteria for Rheumatoid Arthritis

The diagnosis of RA is based on a patient's clinical history, physical examination, and laboratory findings. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA form the generally accepted diagnostic criteria for the condition, although, notably, these criteria were developed for research studies to allow for the identification of individuals with earlier-stage RA and were not primarily intended for clinical practice. The criteria are outlined in Table 5-6 and are intended to be applied to individuals for whom there is clinical suspicion of RA based on definite synovitis in at least one joint, as determined by physical exam, that is not better explained by a different condition. Patients with a score of at least 6 out of 10 are considered to have "definite RA." The 2010 ACR/EULAR criteria were designed to identify patients with recent-onset and active RA; adults with longstanding or inactive disease may be diagnosed with RA if there is a documented prior history of findings or laboratory testing fulfilling those criteria. Adults with seronegative RA who lack rheumatoid factor and anti-citrullinated protein antibody on laboratory testing might not satisfy the 2010 ACR/EULAR criteria (Humphreys and Symmons, 2013), but may still be diagnosed with RA if their clinical findings are otherwise characteristic of the disease and if alternative diagnoses are excluded. In those cases radiographic findings of bone erosions, which are characteristic of RA, may help support the diagnosis, although radiography is generally not required to establish a diagnosis (Scott et al., 2010).

The lifetime risk of RA is two to three times higher among women than men (Crowson et al., 2011). The onset of RA peaks between the ages of 30 and 50 years, although it may occur at any age (Tehlirian and Bathon, 2008). The risk factors include older age, a family history of RA, and current or prior cigarette smoking (CDC, 2019b; Costenbader et al., 2006).

Standard Measures of Outcomes for Rheumatoid Arthritis

The principal measures used to assess response to treatment and remission for RA are composite, multidimensional outcome measures that incorporate clinical data (i.e., the physical examination, laboratory markers such as erythrocyte sedimentation rate [ESR] and c-reactive protein [CRP], physician's assessment), functional assessment, patient-reported symptoms, and patient-reported global assessment (Felson and LaValley, 2014). For RA, it has long been recognized that because of the heterogeneity of its manifestations,and its impacts on multiple organ systems, improvement cannot be accurately determined based on a single domain (e.g., laboratory markers); accordingly, the use of composite outcome measures reflecting multiple disease domains has become the norm (Aletaha et al., 2008). Notably and of key importance to the current study, the routine assessment of physical functioning is strongly recommended as part of any treatment strategy for RA and is more widespread than for many other disabling medical conditions (Singh et al., 2016). We review the major measures used to assess treatment response below, noting that while these measures are widely used in research and clinical trials, their application in routine clinical practice by U.S. rheumatologists is highly variable (Anderson et al., 2012).

ACR20

For patients with RA, the ACR has developed several definitions of a response to therapy, including the ACR20, the ACR50 and the ACR70, which indicate an improvement of at least 20 percent, 50 percent or 70 percent, respectively, on a set of core outcome measures (Felson and LaValley, 2014). The core measures include the swollen joint count, the tender joint count, and three out of the following five measures: pain visual analog scale (patient-reported pain symptom scale), patient global assessment, physician global assessment, inflammatory marker levels (either ESR or CRP), and a measure of physical functioning (commonly the Health Assessment Questionnaire Disability Index, described below). Of these, the ACR20 is the most widely used, and it has been recommended by the U.S. Food and Drug Administration as a preferred outcome measure in studies of new drugs for RA; accordingly it is commonly used as the primary outcome in clinical trials of RA therapies (Aletaha et al., 2008; Felson and LaValley, 2014). It is not recommended for monitoring treatment response in clinical practice—other disease activity scales, described below, are considered more feasible to implement in clinical settings (Greenberg et al., 2009).

TABLE 5-6 Diagnostic Criteria for Rheumatoid Arthritis

	Score
Target population: Patients with	
(1) have at least one joint with definite clinical synovitis	
(2) with the synovitis not better explained by another disease	
Classification criteria for RA (score ≥6 is needed for classification)	
A. Joint involvement	
1 joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	3
> 10 joints	5
B. Serology (at least one test result is needed)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or highpositive ACPA	3
C. Acute-phase reactants (at least one test result is needed)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

NOTES: ACPA = anti-citrullinated protien antibody; CRP = c- reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.
SOURCE: Aletaha et al., 2010.

Disease activity scales

ACR-endorsed instruments to measure RA disease activity and to define remission include the Patient Activity Scale (PAS), the PASII, the Routine Assessment of Patient Index Data 3, the Clinical Disease Activity Index, the Disease Activity Score (DAS), and the Simplified Disease Activity Index (Anderson et al., 2011, 2012; Fransen et al., 2003; Pincus et al., 2008; Singh et al., 2011; Wolfe et al., 2005). All scales are multidimensional, composite measures drawing on data from several different domains (e.g., physical exam, laboratory markers, functional measures, pain symptoms, physician- and patient-reported global assessments) and are sensitive in discriminating between different levels of disease activity (Anderson et al., 2011). These measures are commonly reported as secondary outcomes in clinical trials of drugs for RA, and they are recommended for routine assessments in clinical practice (Anderson et al., 2012; Greenberg et al., 2009).

Disease activity scores correlate closely with the degree of functional impairment related to RA, and, indeed, several of the aforementioned scores are based in part on functional assessments (Carvalho et al., 2019). However, because RA causes progressive joint damage and deformity, functional impairment is possible among individuals whose disease is quiescent if it was previously active (Ishida et al., 2018; Norton et al., 2014).

Functional assessment

The most widely used measure of functional capacity in RA is the Health Assessment Questionnaire Disability Index (HAQ), which was originally developed in 1978 and assesses a patient's ability to have carried out activities of daily living (dressing/grooming, arising, eating, walking, personal hygiene, reaching, gripping and errands) over the previous week (Maska et al., 2011). The HAQ can be self-administered by patients or administered by a clinician, and it is commonly reported as a secondary outcome in clinical trials of new RA drugs. While it does not explicitly ask patients about work activities, multiple studies have demonstrated that the HAQ is a strong predictor of work disability (de Croon et al., 2004; McWilliams et al., 2014; Wolfe and Hawley, 1998; Young et al., 2000, 2002).

Several other instruments that aim to more specifically measure work-related functioning have been validated for the inflammatory arthropathies, including the Work Productivity and Activity Impairment Questionnaire (Tucker et al., 2019; Zhang et al., 2010), the Work Instability Scale (Revicki et al., 2015), and the Work Productivity Survey (Osterhaus and Purcaru, 2014). At present, such instruments are not widely used in either research or clinical practice, although they may hold promise.

Treatments for Rheumatoid Arthritis

The goals of RA treatment include reducing symptoms of joint pain and swelling, preventing deformity, maintaining quality of life, and limiting extra-articular disease manifestations (Wasserman, 2011). Pharmacologic treatments, specifically disease-modifying antirheumatic drugs (DMARDs), are the mainstay of therapy (Singh et al., 2016): through different mechanisms they limit progressive joint damage and improve function (Scott et al., 2010). DMARDs are typically prescribed under the supervision of a rheumatologist. Care by a rheumatologist is associated with an earlier initiation of DMARD therapy (Rat et al., 2004; Widdifield et al., 2011) and improved treatment response (Criswell et al., 1997), resulting in less joint destruction (van der Linden et al., 2010), lower functional impairment (Ward et al., 1993), and a lower likelihood of requiring orthopedic surgery (Feldman et al., 2013). Traditional (non-

biologic) DMARDs include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine; biologic DMARDs include anti-tumor necrosis factor (TNF) agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), and non-TNF biologics (abatacept, rituximab, tocilizumab). A final class of DMARDs includes JAK-inhibitors, of which tofacitinib is the primary agent used in RA. Traditional DMARDs and tofacitinib are orally administered medications[4] that may be taken at home; anti-TNF biologics are generally available in prefilled syringes that can be injected subcutaneously by patients in their homes (with the exception of infliximab, which must be administered via intravenous infusion in an infusion center); non-TNF biologics are generally administered via intravenous infusion in an infusion center (with the exception of abatacept, which is also available as a prefilled syringe). Medications used for short-term symptom relief include NSAIDs and steroids; the latter may be administered orally, intramuscularly, or intraarticularly. Nonpharmacologic treatments include physical and occupational therapy, exercise, patient education, and psychosocial interventions (Rindfleisch and Muller, 2005). Pain is among the most prominent and distressing symptoms among patients with RA (ten Klooster et al., 2007). It is managed using therapies that target the *underlying disease*, such as DMARDs, as well as through adjunctive therapies targeting *pain symptoms*. The latter are discussed in more detail above in the Musculoskeletal Conditions and Pain section of this chapter. Surgery is indicated for intractable pain, severe loss of motion, or functional impairment that exists despite medical management (Rindfleisch and Muller, 2005).

TABLE 5-7 Medications Used to Treat Rheumatoid Arthritis

Traditional DMARDs	Methotrexate, Leflunomide, Hydroxychloroquine, Sulfasalazine
Biologic DMARDs	
Anti-TNF biologics	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
Non-TNF biologics	Abatacept, rituximab, tocilizumab
JAK-inhibitors	Tofacitinib, baricitinib and upadacitinib
Medications for symptom relief	NSAIDs, glucocorticoids

SOURCE: NICE, 2018.

Evidence-based treatment guidelines for the pharmacologic management of established RA (defined as a disease duration of at least 6 months) include the 2015 ACR guidelines and the EULAR guidelines (Singh et al., 2016); the latter were originally developed in 2010 and most recently updated in 2017 (Smolen et al., 2017a). Both the ACR and EULAR guidelines primarily address the use of DMARDs for RA treatment. Patients who are not in clinical remission and who have any degree of disease activity as measured using validated scales (see Measurement of Outcomes for Rheumatoid Arthritis for more detail) are considered candidates for therapy; indeed, it is recommended that therapy for RA be initiated as soon as possible after the diagnosis

[4] Note that methotrexate may also be administered subcutaneously.

is established, as there is evidence that earlier DMARD therapy is associated with better outcomes. The specific agents recommended are determined by the degree of disease activity, prior treatments used, treatment response and toxicities, and the patients' comorbidities (Anderson et al., 2000; Nell et al., 2004; Smolen et al., 2016). The goal of therapy is sustained clinical remission or low disease activity (Ramiro et al., 2014).

Under the 2015 ACR guidelines, monotherapy with a traditional DMARD is recommended as the first-line initial treatment for RA regardless of the level of disease activity, with methotrexate being the preferred agent. For patients who do not improve sufficiently with traditional DMARD monotherapy (i.e., RA disease activity remains moderate to high), the recommended approach is either a combination of traditional DMARDs, a biologic DMARD (with or without methotrexate), or tofacitinib (with or without methotrexate).[5] For patients on anti-TNF therapy alone who continue to have moderate to high disease activity, the addition of one or two traditional DMARDs is recommended (methotrexate is again the preferred agent) owing to evidence of superior efficacy compared with monotherapy with a biologic. If treatment targets are not achieved with a given biologic DMARD, it is recommended that different biologic DMARDs be tried. Short-term, low-dose glucocorticoid treatment may be added for patients on traditional or biologic DMARDs whose disease activity remains moderate or high, or for RA flares. Once low disease activity is achieved on a specific DMARD regimen, it is recommended that the regimen be continued, given that clinical experience suggests a high risk of relapse and the need for resuming therapy in the absence of DMARD treatment. If remission is achieved, tapering DMARD therapy can be considered, though the guidelines recommend against discontinuing all therapy because of the high risk of relapse.[6]

The 2016 EULAR recommendations for RA treatment are largely similar to the 2015 ACR guidelines: notably, traditional DMARDs (and specifically methotrexate) are recommended as the initial therapy for RA, the addition of biologic DMARDs or tofacitinib is recommended if improvement is not achieved, and if patients do not respond to a biologic DMARD, the guidelines recommend switching to a different biologic DMARD or tofacitinib (Aletaha et al., 2008). There are, however, several distinctions between the ACR and EULAR guidelines worth noting. First, the EULAR guidelines recommend that short-term glucocorticoid therapy be considered when initiating or changing DMARDs, whereas the ACR guidelines reserve glucocorticoid use for patients with moderate or high disease activity despite DMARD therapy. Second, for patients who do not respond to initial monotherapy with a traditional DMARD, the EULAR guidelines recommend that the choice of the subsequent agent be based on prognostic factors. Specifically, for patients with "unfavorable" prognostic indicators (i.e., the presence of autoantibodies especially at high levels, high disease activity, early erosions, or no response to two traditional DMARDs), a biologic DMARD or JAK-inhibitor (tofacitinib or baricitinib) is recommended. For patients in whom such findings are absent, the guidelines recommend adding or changing to a different traditional DMARD. In contrast, the ACR guidelines do not discuss the role of prognostic factors in treatment selection.

[5] The 2015 ACR guideline to escalate therapy in patients not responding to monotherapy with a traditional DMARD is strong but is based primarily on clinical experience and indirect evidence; the ACR notes that the published evidence underlying this recommendation is only of moderate to very low quality.

[6] The 2015 ACR guideline's recommendation to continue DMARD therapy in patients who achieve treatment targets is strong, but it is based primarily on clinical experience; the ACR notes that the published evidence underlying this recommendation is only of variable quality.

The ACR and EULAR guidelines are based on comprehensive and systematic reviews of the evidence on RA treatment, however, they have several limitations in the context of this study. First, the guidelines do not discuss nonpharmacologic treatments for RA or the optimal combination of pharmacologic and nonpharmacologic therapies. RCTs support the use of physical exercise as a strategy to improve muscle strength and quality of life (Baillet et al., 2009; Brodin et al., 2008), whereas complementary therapies such as acupuncture and dietary changes have not been found to provide benefit (Hagen et al., 2009; Kelley, 2009; Smedslund et al., 2010; Wang et al., 2008). Second, since the publication of the guidelines, several additional therapies have been approved for RA or are currently under investigation. Sarilumab is a non-TNF biologic DMARD that was approved for the treatment of moderate-to-severe RA in 2017; it has improved efficacy relative to adalimumab, a commonly used anti-TNF biologic, with a similar safety profile (Burmester et al., 2017). Baricitinib is a JAK-inhibitor[7] which was approved for the treatment of RA in 2018 and is therefore not discussed in the 2015 ACR guidelines; the 2016 EULAR guidelines note that there is some evidence for its superior efficacy relative to adalimumab,[8] but because long-term safety data are limited, as with tofacitinib it is recommended that biologic DMARDs be tried first (FDA, 2018; Taylor et al., 2017). Third, neither guideline explicitly discussed the impact of DMARDs on work-related functional capacity (Nam et al., 2015), which is the outcome of principal interest to the committee as it is especially relevant to the SSA population. Many of the individual studies upon which the guidelines are based do assess the impact of DMARDs on measures of physical functioning, but there are limitations in extrapolating from those scales to estimate impacts on actual work capacity.

Beyond the ACR and EULAR guidelines, an important limitation of the RA treatment literature more broadly is the limited evidence that is available to guide the management of patients with refractory RA (Singh et al., 2016). While there is no universally accepted definition of refractory RA, the term is often used to refer to patients who have not responded to at least two different biologic DMARDs or to two different biologic DMARDs with different mechanisms of action (Buch, 2018; de Hair et al., 2018; Kearsley-Fleet et al., 2018; Roodenrijs et al., 2018). The prevalence of refractory RA is not well-established; the only published national registry study to date is from the United Kingdom, and it estimated that at least 6 percent of patients with RA have been exposed to at least three DMARDs, which is suggestive of a difficult-to-treat disease (Kearsley-Fleet et al., 2018). It is not known what share of SSA beneficiaries with RA satisfy this definition of refractory disease, but because those patients have a lower chance of clinical remission, it is likely that they are disproportionately represented in the SSA population. At present, there is limited evidence to inform the appropriate treatment strategy for patients with refractory RA. Baracitinib was efficacious in a study population in whom the majority of patients had refractory disease (i.e., had previously tried at least two different biologic DMARDs), so it may provide an alternative for those patients (Genovese et al., 2016). Other novel therapies are currently under investigation (Aletaha and Smolen, 2018; Cheung and McInnes, 2017).

[7] Janus kinase (JAK) inhibitors; a class of DMARDs.

[8] The RA-BEAM trial demonstrated superior efficacy of a 4 mg once-daily dose of baricitinib relative to adalimumab; however, FDA approved a 2 mg once-daily dose and declined to approve the 4 mg once-daily dose owing to a less favorable benefit–risk profile.

While pharmacologic treatments for RA can substantially improve symptoms, they also have associated toxicities that are important to consider (Aletaha and Smolen, 2018; Graham, 2006; Harirforoosh et al., 2014; Huscher et al., 2009; Kamata and Tada, 2017; Nash et al., 2013; Rindfleisch et al., 2005; Saag et al., 1994; Sostres et al., 2010). Serious infections are among the most concerning potential adverse effects of biologic DMARDs and glucocorticoids because of their immunosuppressive properties. The toxicities of medications may limit their use in specific patients depending on comorbidities (particularly patients with liver, renal, or cardiovascular disease) and may prompt patients to discontinue or switch medications (Choquette et al., 2019).

Few studies have directly and rigorously assessed the impact of RA treatments on work outcomes. The committee identified a Swedish study comparing traditional DMARDs to combination therapy with infliximab and methotrexate for RA; it found no differences between the treatment arms in the number of work-days lost (Eriksson et al., 2016).

In the absence of direct evidence on the impact of specific RA treatments on work outcomes, the committee reviewed evidence of the impact of RA treatments on measures of physical functioning, specifically the HAQ. HAQ scores are predictive of work disability, and the HAQ is commonly used as a secondary outcome measure in clinical trials testing RA therapies. Among pharmacologic agents, a range of medications including traditional DMARDs (e.g., methotrexate, leflunomide) (Scott et al., 2001) and biologic DMARDs (e.g., golimumab, tocilizumab, baricitinib, certolizumab, filgotinib, sarilumab, tofacitinib, sirukumab, adalimumab, rituximab) have all been demonstrated to improve functional status in RA as measured using the HAQ (Bingham et al., 2014; Burmester et al., 2016; Dougados et al., 2017; Emery et al., 2017; Genovese et al., 2015, 2018; Keystone et al., 2017; Rigby et al., 2011; Strand et al., 2015a,b; Takeuchi et al., 2017; Taylor et al., 2017). Comparative effectiveness analyses and active comparator trials have generally not identified significant differences between biologic DMARDs in their impact on HAQ scores in RA (Jansen et al., 2014; Strand et al., 2016), with the exception of two recent trials that found sarilumab to be superior to adalimumab in its impact on physical functioning as measured using the HAQ (Strand et al., 2018). Among nonpharmacologic treatment strategies, resistance exercises have been found to improve physical functioning as measured using the HAQ (Baillet et al., 2012).

A key limitation of those data is that most studies do not focus specifically on patients with severe or refractory RA, who might be more likely to participate in SSA programs (Kilcher et al., 2018), so it is unclear whether the aforementioned therapies would meaningfully improve work-related functional capacity within the population of interest to SSA. Of the evidence the committee reviewed, the studies that most closely reflected the population of interest (i.e., adults with severe RA resulting in functional limitations that significantly restrict work) were those evaluating the impacts of specific treatments in patients who had not responded to at least one biologic DMARD. In RA, sarilumab (Fleischmann et al., 2017), filgotinib (Genovese et al., 2018), baricitinib (Genovese et al., 2016; Smolen et al., 2017b), and tofacitinib (Strand et al., 2015b) have all been demonstrated to improve HAQ scores in patients with an inadequate response to at least one anti-TNF DMARD. Conversely, secukinumab (Blanco et al., 2017; Dokoupilova et al., 2018) was not found to improve physical functioning as measured using the HAQ in this population.

Length of Time to Improvement for Rheumatoid Arthritis

NSAIDs and low-dose glucocorticoids can provide symptom relief within days. With DMARDs, clinical improvement is typically expected within 3 months of starting therapy,

although a substantial number of patients might not respond until months 3–6 (Kavanaugh et al., 2008, 2010). Accordingly, many clinical trials of RA therapeutics now assess treatment response at both 3 and 6 months, and the EULAR treatment guidelines for RA recommend changing therapy if no improvement is seen after 3–6 months (Ramiro et al., 2014).

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the joints, spine, and entheses. It may affect other tissues as well (e.g., dactylitis, nail involvement) and most commonly occurs in association with psoriasis, an autoimmune skin disease that causes scaly patches over the skin (Coates and Helliwell, 2017). Skin manifestations commonly precede the arthritis; however, in some patients the skin and joint symptoms present simultaneously, and in 10–15 percent of patients the arthritis presents first. PsA is a heterogeneous condition with five recognized subtypes, though it is increasingly recognized that patients may have any combination of these features (Moll and Wright, 1973; Ogdie and Weiss, 2015): (1) mono- or oligo-arthritis (involving ≤4 joints, typically asymmetric); (2) polyarthritis (involving ≥5 joints, typically symmetric); (3) distal-interphalangeal-joint predominant disease; (4) psoriatic spondylitis/sacroiliitis; and (5) arthritis mutilans. Peripheral oligoarticular or polyarticular disease is most common; arthritis mutilans, which is the most severe and deforming disease manifestation, is more rare (Haddad and Chandran, 2013).

Professionally Accepted Diagnostic Criteria for Psoriatic Arthritis

The diagnosis of PsA is based on the clinical history, a physical examination, laboratory findings, and radiography. The most widely used diagnostic and classification criteria for PsA are the Classification of Psoriatic Arthritis criteria (Taylor et al., 2006), which are highly sensitive and specific across varied clinical settings (Chandran et al., 2008; D'Angelo et al., 2009; Leung et al., 2010; van den Berg et al., 2012). The criteria, which are outlined in Table 5-8, are intended to be applied to individuals where there is a clinical suspicion of PsA based on inflammatory disease of the joints, spine, or entheses. Patients with a score of at least 3 points are considered to have PsA. Laboratory markers are less helpful in affirmatively establishing the diagnosis of PsA than they are in excluding other inflammatory arthropathies (Gladman et al., 1987).

TABLE 5-8 Classification Criteria for Psoriatic Arthritis

	Score
Patient must have inflammatory articular disease with ≥3 points from the following 5 categories	
1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis	2
2. Typical psoriatic nail dystrophy including oncycholysis, pitting, and hyperkeratosis observed on current physical examination	1
3. A negative test result for the presence of rheymatoid factory by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range	1

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheymatologist	1
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1

SOURCE: Taylor et al., 2006.

PsA affects men and women equally (Brockbank and Gladman, 2002). The average age at diagnoses is typically between 40 and 50 (Kerschbaumer et al., 2016). Obesity has been identified as a risk factor for the development of PsA (Kerschbaumer et al., 2016; Ogdie and Weiss, 2015).

Standard Measures of Outcomes for Psoriatic Arthritis

As with RA, PsA has heterogeneous clinical manifestations so that improvement cannot be accurately determined by considering only unidimensional measures, such as laboratory markers. The principal measures used to assess response to treatment and remission for PsA are therefore composite, multidimensional outcome measures incorporating clinical data, functional assessment, patient-reported symptoms, and global assessment (Felson and LaValley, 2014). We review the major measures used to assess treatment response below, noting that these measures were primarily developed for research and clinical trials and hence their application in routine clinical practice by U.S. rheumatologists is unclear.

Treatment response criteria for PsA

The ACR20, developed for RA and described above, is also frequently used in clinical trials of medications for PsA. Other treatment response criteria developed specifically for PsA include the Psoriatic Arthritis Response Criteria (PsARC) and the Minimal Disease Activity (MDA) criteria. The PsARC defines treatment response as achieving two of the following: tender/swollen joint count improvement by at least 30 percent (Mease et al., 2005), patient global improvement by one point on a five-point Likert scale, or physician global improvement by the same amount. The MDA criteria are achieved when low scores are obtained in five of the following seven domains: tender joint count, swollen joint count, body surface area affected by psoriasis, pain symptoms, patient-reported global disease activity, Health Assessment Questionnaire Disability Index, and tender entheseal points count (Wong et al., 2012).

Disease activity scales

RA disease activity measures such as the DAS[9] have also been used in PsA clinical trials, though it has been noted that because of differences in the clinical presentation of RA and PsA, some of the RA-specific measures may be less accurate when applied to PsA. The DAS, for example, may not be appropriate for patients who have predominantly lower extremity or distal interphalangeal joint disease as these joints are not included as part of the standard DAS 28-joint count. Measures of disease activity that have been developed and validated specifically for PsA include the Disease Activity Index for Psoriatic Arthritis, the Psoriatic Arthritis Joint Activity

[9] The DAS28, for example, is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for "disease activity score," and the number 28 refers to the 28 joints that are examined in this assessment.

Index, the Composite Psoriatic Disease Activity Index, and the Psoriatic Arthritis Disease Activity Score (Gladman et al., 2010; Mease et al., 2005; Schoels et al., 2016; Wong et al., 2012). All are composite measures based on data drawn from multiple domains (e.g., the physical exam, laboratory markers, pain symptoms, patient or physician-reported global assessments, functional measures and health-related quality of life) (Helliwell and Waxman, 2018; Wong et al., 2012).

As with RA, PsA disease activity scores correlate closely with the degree of functional impairment, and several of these scores are based in part on functional assessments. Functional impairment is still possible, however, among individuals with previously active disease that is now quiescent because PsA can cause progressive joint damage and deformity (Kerschbaumer et al., 2017).

Functional assessment

The HAQ, developed for RA and described above, is also commonly included as an outcome measure in PsA clinical trials (Mease et al., 2005).

Treatments for Psoriatic Arthritis

As in RA, the goals of treatment for PsA include controlling symptoms, preventing structural damage and deformity, and improving physical functioning and quality of life (Gossec et al., 2016). DMARDs are the mainstay of treatment because they are effective in limiting progressive joint damage and are prescribed under the supervision of a rheumatologist. As shown in Table 5-9 there is considerable overlap between the DMARDs recommended for PsA and those recommended for RA, but there are also some notable differences in the specific drug classes used. Among the agents that are specifically used in PsA, the traditional DMARDs are orally administered; the IL–12/23 and IL–17 inhibitors are available in prefilled syringes that can be injected subcutaneously by patients in their home. As in RA, there is a role for NSAIDs and glucocorticoids in short-term symptom relief. Nonpharmacologic treatment options are similar to those for RA (Singh et al., 2019). Patients with PsA commonly experience pain; adjunctive therapies targeting pain symptoms are discussed in detail in the Musculoskeletal Conditions and Pain section of this chapter. Indications for surgical intervention are the same as in RA patients.

TABLE 5-9 Medications Used to Treat Psoriatic Arthritis

Traditional DMARDs	Methotrexate, leflunomide, sulfasalazine, cyclosporine, apremilast
Biologic DMARDs	
Anti-TNF biologics	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
IL12/23 inhibitors	Ustekinumab
IL17 inhibitors	Secukinumab, ixekizumab, brodalumab
CTLA4 immunoglobulin	Abatacept
JAK-inhibitors	Tofacitinib
Medications for symptom relief	NSAIDs, glucocorticoids

SOURCE: Modified from Singh et al., 2019.

Evidence-based treatment guidelines for the pharmacologic management of PsA include the 2018 ACR/National Psoriasis Foundation (NPF) guideline (Singh et al., 2019), the 2015 EULAR recommendations, and the 2015 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations (Coates et al., 2016; Gossec et al., 2016). Under all sets of guidelines, the goal of therapy is clinical remission or minimal to low disease activity (Gossec et al., 2016). The preferred treatment may be influenced by the disease severity, medication toxicities, and comorbidities (e.g., congestive heart failure) and by specific PsA disease manifestations (e.g., severe skin disease, axial disease, enthesitis, uveitis [Singh et al., 2019]). Notably, the evidence base underlying the PsA treatment guidelines is more limited than that underlying the RA treatment guidelines reviewed in the previous section, and there are some notable differences between the major guidelines.

Under the 2018 ACR/NPF guideline (Singh et al., 2019), options for the initial treatment of active PsA in descending order of preference are an anti-TNF biologic DMARD, a traditional DMARD, an IL-17 inhibitor, and an IL-12/23 inhibitor. For treatment-naïve patients with less active disease, NSAIDs may be considered. For patients who have not responded to initial therapy, regardless of the initial treatment strategy used, the subsequent treatment options in descending order of preference are an anti-TNF biologic DMARD, an IL-17 inhibitor, an IL-12/23 inhibitor, and abatacept or tofacitinib. Among patients who have not responded to therapy with an anti-TNF DMARD, switching to a different anti-TNF DMARD is preferred over other biologic DMARDs. For patients who have not responded to a traditional DMARD and are either not candidates for biologic DMARDs or do not wish to take them, the options include adding apremilast to the current traditional DMARD or switching to a new traditional DMARD (except apremilast). Among patients with active PsA and psoriatic spondylitis/axial disease who have not responded to NSAIDs, anti-TNF DMARDs are preferred, followed by IL-17 inhibitors. For patients with active PsA in whom enthesitis is the predominant manifestation, NSAIDs, anti-TNF DMARDs, and tofacitinib are preferred over traditional DMARDs.

The 2015 EULAR recommendations are largely similar to the 2018 ACR/NPF guidelines, although there are several differences worth highlighting (Gossec et al., 2016). First, in the 2015 EULAR recommendations traditional DMARDs are preferred as a first-line therapy over biologic DMARDs. In patients with mild disease, NSAIDs and intra-articular glucocorticoids are considered acceptable initial therapy, but in patients with more severe disease or unfavorable prognostic factors (i.e., many swollen joints, structural damage, high inflammatory markers, and extra-articular manifestations) traditional DMARDs are recommended, and within this class, methotrexate is the preferred agent. Second, whereas IL-17 inhibitors are preferred over IL-12/23 inhibitors in the 2018 ACR/NPF guideline, the EULAR guidelines do not favor one class over the other. Finally, the EULAR guidelines do not address abatacept or tofacitinib, which were approved for the treatment of PsA more recently. The 2015 GRAPPA recommendations are similar to the 2015 EULAR recommendations for the management of peripheral arthritis, axial disease, and enthesitis (Coates et al., 2016).

The ACR/NPF, EULAR and GRAPPA guidelines were all based on systematic reviews of the evidence on PsA treatment together with expert opinion. Similar to the RA treatment guidelines previously reviewed, one limitation of the guidelines—in the context of this study—is that they do not explicitly discuss the impact of pharmacologic treatments on work-related functional capacity, which is the outcome of principal interest to the committee. A challenge in the PsA treatment literature more broadly is the limited evidence available to guide the management of patients with PsA and, in particular, those with arthritis mutilans or other forms

of severe or treatment-resistant disease who may be disproportionately represented in the SSA population (Bakirci Ureyen et al., 2018). Ixekizumab, ustekinumab, and secukinumab were efficacious for patients who had previously been treated with anti-TNF DMARDs with an inadequate response, so they may provide an alternative for these patients (Merola et al., 2017; Nash et al., 2017; Raychaudhuri et al., 2017; Ritchlin et al., 2014). Other novel therapies are currently under investigation (Chiricozzi et al., 2019).

The pharmacologic treatments for PsA overlap substantially with those used for RA, and therefore so do their toxicities. Toxicities of therapies for RA and PsA are summarized in Table 5-10.

TABLE 5-10 Toxicities of Therapies for RA and PsA

NSAIDs	Gastrointestinal ulceration/bleeding Cardiovascular disease Renal dysfunction
Glucocorticoids (oral)	Infections Osteoporosis Gastrointestinal ulceration/bleeding Hypertension Peripheral edema Weight gain Impaired glucose tolerance Mood disturbances
Methotrexate	Nausea Mouth ulcers Rare but serious: bone marrow suppression, pneumonitis, liver disease.
Anti-TNF DMARDs	Infections Reactivation of tuberculosis Activation of demyelinating diseases Drug-induced lupus Nonmelanoma skin cancer
Non-TNF Biologics (abatacept, rituximab, tocilizumab)	Infections Reactivation of tuberculosis (except rituximab) Leukopenia
IL–12/23 Inhibitors	Infections
IL–17 Inhibitors	Infections Oral candidiasis Neutropenia Inflammatory bowel disease Concerns about suicidal ideation (for brodalumab)
Tofacitinib	Infections Reactivation of tuberculosis Reactivation of herpes zoster

Cytopenias

SOURCES: Gossec et al., 2016; Graham, 2006; Mease et al., 2017a,b,c; Singh et al. 2019.

As with RA, few studies have directly and rigorously assessed the impact of PsA treatments on work outcomes. Certolizumab was found to significantly decrease absenteeism and presenteeism relative to placebo in an employed sample (Kavanaugh et al., 2015); infliximab was found to improve patient-reported work productivity, but with no significant impact on employment status (Kavanaugh et al., 2006).

Given the limited direct evidence on the impact of specific PsA treatments on work outcomes, the committee reviewed evidence of the impact of PsA treatments on measures of physical functioning, specifically the HAQ, which is predictive of work disability. For PsA, a number of different biologic DMARDs have been found to achieve clinically meaningful improvements in HAQ scores (e.g., apremilast, certolizumab, tofacitinib, golimumab, certolizumab, adalimumab, ixekizumab, ustekinumab) (Edwards et al., 2016; Gladman et al., 2014, 2017; Kavanaugh et al., 2017; Mease et al., 2014, 2017a; Rahman et al., 2016). Abatacept is an exception (Mease et al., 2017b). Evidence of the effect of other DMARDs on physical functioning in PsA as measured with the HAQ is limited. Of note, a clinical trial of methotrexate for PsA found no significant improvement in HAQ scores (Kingsley et al., 2012).

As with RA, a key limitation of the PsA literature is that most studies do not focus specifically on patients with severe or refractory disease who might be more likely to participate in SSA programs, and it is therefore unclear whether the aforementioned therapies would meaningfully improve work-related functional capacity within our population of interest. Of the evidence we reviewed, the studies that most closely reflected our population of interest (i.e., adults with severe PsA resulting in functional limitations that significantly restrict work) were those evaluating the impacts of specific treatments in patients who had not responded to at least one biologic DMARD. In PsA, tofacitinib has been found to improve HAQ scores among adults who have not responded to at least one anti-TNF biologic (Gladman et al., 2017). Ustekinumab has also been evaluated in this population, but it did not achieve a clinically meaningful impact on physical functioning (Rahman et al., 2016).

Length of Time to Improvement for Psoriatic Arthritis

As with RA, NSAIDs and low-dose glucocorticoids can provide symptom relief within days for PsA. With DMARDs, clinical improvement is typically expected within 3 months of starting therapy, though some patients might not respond until months 3–6 (Schoels et al., 2018). Accordingly, as with RA, many clinical trials of PsA therapeutics assess treatment response at both 3 and 6 months, and the EULAR treatment guidelines for PsA recommend changing therapy if no improvement is seen after 3–6 months (Gossec et al., 2016).

NEW AND DEVELOPING TREATMENTS FOR MUSCULOSKELETAL DISORDERS

The use of biologics in orthopedics has become popular as an adjuvant in healing musculoskeletal injuries. Reports of improved outcomes when biologics are combined with standard therapies have led to further clinical interest. For example, biologics have shown some benefit in improving function and pain scores and in reducing time to heal in foot and ankle traumatic injuries (Zhao et al., 2018). The use of Janus kinase (JAK) inhibitors has gained attention because of their potential utility in numerous immune-medicated diseases (Schwartz et

al., 2017), however, there are limitations in their use, such as JAK selectivity, optimal routes, and dosing regimens.

According to Zhang et al. (2019), advanced drug delivery strategies for the treatment of musculoskeletal disorders involve therapeutic drugs (e.g., genes, small molecule therapeutics, and stem cells), novel delivery vehicles (e.g., three-dimensional printing and tissue engineering techniques), and innovative delivery approaches (e.g., multi-drug delivery and smart stimuli-responsive delivery). Those strategies have been developed for various drugs in a variety of vehicle forms and aimed at treating musculoskeletal disorders involving bone, cartilage, tendons, ligaments, and skeletal muscles. The use of bioactive factors in the clinical management of cartilage injury, in particular, has progressed, and innovative biologic and engineering strategies have improved the efficacy and efficiency of those factors (Patel et al., 2019).

Accordingly techniques and methods in material synthesis, polymer modification and functionalization, carrier development, and scaffold fabrications have enabled the delivery of treatments to the joint environment. Similarly, with the application of nanotechnology, new treatments using nanomaterials are creating improvements to the retention profiles of drugs within the joint space related to injected free drugs (Brown at al., 2019). That is important because the joint has poor bioavailability for systemically administered drugs and experiences rapid clearance of therapeutics after intra-articular injection. Martin et al. (2019) describes emerging tissue engineering and regenerative approaches for articular cartilage injuries, noting that cartilage regeneration technology has the potential to repair and prevent the progression of debilitating knee OA.

A review by Gu and colleagues (2018) examines three-dimensional bioprinting techniques which are useful for fabricating scaffolds for biomedical and regenerative medicine and tissue engineering applications. Such techniques permit rapid manufacture with high precision and control over size, porosity, and shape, and they make possible the creation of bones, vascular, skin, cartilage, and neural structures. Additional reviews discuss how the emerging field of regenerative rehabilitation integrates biologic and bioengineering advances—in particular, the use of stem cell therapy to promote tissue repair and regeneration (Loebel and Burdick, 2018) and clinical advances where stem cells and stromal cells have been used to stimulate musculoskeletal tissue, including delivery strategies to improve cell viability and retentions (Rando and Ambrosio, 2018).

SUMMARY AND CONCLUSIONS

Musculoskeletal disorders are a set of diverse conditions affecting bones, joints, muscles, and connective tissues. These disorders may result in pain and loss of function and are among the most disabling and costly conditions in the United States. Chronic pain and loss of function are the primary mechanism through which musculoskeletal disorders lead to disability and work loss.

SSA noted three categories of musculoskeletal disorders in its statement of task to the National Academies: disorders of the back, osteoarthritis, and other arthropathies. Based on the committee's clinical expertise and knowledge of the medical and research literature on musculoskeletal disorders, the committee determined that those disorders encompass the most disabling musculoskeletal conditions and that although rheumatoid arthritis and psoriatic arthritis are classified by SSA as "immune disorders," their most common, and in many cases, most disabling manifestation is inflammation of the joints leading to joint destruction and deformity.

Thus the committee decided that those conditions merited consideration as leading causes of musculoskeletal impairment.

Chronic low back pain is a primary musculoskeletal pain condition defined by pain for more than 3 months. It is highly prevalent in all adult age groups and is the top cause of years lived with disability. Chronic low back pain is sometimes associated with pain that radiates to the lower extremity in a characteristic distribution (i.e., radicular pain, sometimes called "sciatica" or radiculopathy). The presence of radicular pain or radiculopathy is associated with worse chronic low back pain severity and functional outcomes. Other factors associated with worse functional outcomes include co-existing medical and psychiatric conditions and other chronic pain conditions. In addition, the overuse of biomedical approaches to treat chronic low back pain (e.g., opioids and spine surgery) has been identified as a potentially important contributor to disability. On the other hand, numerous treatments have demonstrated effectiveness for improving function in chronic low back pain, including exercise therapies, behavioral/psychologic therapies, and manual therapies. Multidisciplinary approaches, including intensive chronic pain rehabilitation programs and less intensive primary-care-based collaborative care management interventions, also have demonstrated benefits for function. In general, medications are less beneficial for function than for pain in chronic low back pain, with most benefits demonstrated only in the short term. The committee did not identify evidence about the likelihood of treatment leading to a point at which low back pain is no longer disabling or the time it would take to reach that point. There is no evidence that the efficacy of chronic back pain treatments differs by age.

Osteoarthritis is a disease that destroys synovial joints over time. There is no known cure or method of reversing the process. Chronic pain and joint stiffness are hallmarks of this condition. Osteoarthritis can become disabling if it is severe enough to make work and daily tasks difficult. It is most common in older people, and gender differences vary by age. Before age 45 more men than women have osteoarthritis; however, after age 45 it is more common in women. The prevalence of symptomatic knee osteoarthritis increases with each decade of life, with the annual incidence being highest in people between 55 and 64 years old. Although there are numerous treatments available, progressive osteoarthritis may result in reduced mobility and the resultant systemic complications of immobility and deconditioning. There is moderate to strong evidence suggesting that exercise therapy and psychosocial interventions are effective for relieving pain and improving function for many patients with osteoarthritis pain. Complications can result from the use of anti-inflammatory medications. Although joint arthroplasties and fusions can relieve pain and improve function, they can also cause infection and deep vein thrombosis, and sometimes lead to intraoperative mortality. For those reasons, joint replacements and fusions should generally be considered only when non-surgical approaches have not been effective in controlling pain and providing acceptable function.

Inflammatory arthropathies are conditions characterized by inflammation of the joints and often other tissues. These include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and systemic lupus erythematosus, among others. Rheumatoid arthritis and psoriatic arthritis are among the most common inflammatory arthropathies and are important causes of disability in adults.

Rheumatoid arthritis and psoriatic arthritis are systemic inflammatory diseases whose most common and prominent clinical manifestations include inflammation and destruction of the joints. These conditions are an important cause of work-related functional impairment. Effective treatments exist for rheumatoid arthritis and psoriatic arthritis, and the number of treatment

options has expanded significantly in recent years as newer biologic agents have been approved. Because physical functioning is commonly assessed as a secondary outcome in trials of rheumatoid arthritis and psoriatic arthritis therapies, there is more evidence available about the impacts of specific arthritis treatments on functional capacity than for treatments for many other disabling medical conditions.

Many existing pharmacologic treatments for rheumatoid arthritis and psoriatic arthritis have been found to improve physical functioning as measured using the HAQ, including a number of biologic DMARDs, which are indicated for more severe disease. However, the extent to which those therapies can improve work-related functional capacity among individuals with impairments severe enough to qualify for SSA programs remains uncertain for several reasons. First, few clinical trials have tested therapies in individuals with such severe impairments, so treatment outcomes in this population are not well understood. Second, since the likelihood of functional improvement falls as the duration of disease and the number of prior DMARDs trials increases, treatment response is likely to be more modest among those with refractory disease. Third, both rheumatoid arthritis and psoriatic arthritis can result in irreversible joint damage, which may limit how much functional improvement can be achieved through medical management alone in the absence of surgery. Early diagnosis and treatment to prevent joint destruction and deformity is therefore of critical importance for patients with rheumatoid arthritis and psoriatic arthritis. It is unclear how much improvement might be expected in patients who do not receive early DMARD therapy. Finally, evidence linking specific rheumatoid arthritis and psoriatic arthritis therapies directly to work outcomes is extremely limited, though HAQ scores are highly correlated with work disability.

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Appendix A

Mental Health Disorders: Additional Information

GUIDELINES CONSULTED FOR REVIEW OF EFFECTIVE TREATMENTS FOR EACH MENTAL HEALTH DISORDER

The clinical guidelines listed in tables A-1 through A-5 were selected for each of the mental health disorders based on their comprehensiveness and relevance to the questions; their transparency and the clarity about literature search strategies and approaches to evidence-based decisions; recently updated information; and whether the guideline had external peer review.

TABLE A-1 Selected Clinical Guidelines Related to Major Depression Disorder

Resource Title	Organization	Year
Clinical Practice Guideline for the Management of Major Depressive Disorder	Department of Veterans Affairs/Department of Defense	2016
Clinical Guidelines for the Management of Adults with Major Depressive Disorder	Canadian Network for Mood and Anxiety	2016
Practice Guideline for the Treatment of Patients with Major Depressive Disorder (also, "Quick Reference Guide," APA, 2010)	American Psychiatric Association	2010
Depression in Adults: Recognition and Management	National Institute for Health and Care Excellence	2009

TABLE A-2 Selected Clinical Guidelines Related to Bipolar Disorders

Resource Title	Organization	Year
The World Federation of Societies of Biological Psychiatry (WFSBP) for the Biological Treatment of Bipolar Disorders: Acute and Long-term Treatment of Mixed States in Bipolar Disorders	World Federation of Societies of Biological Psychiatry	2018
Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 2018 Guidelines for the Management of Patients with Bipolar Disorders	Canadian Network for Mood and Anxiety International Society for Bipolar Disorders	2018
The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, Grading of the Evidence, and a Precise Algorithm	International College of Neuro-Psychopharmacology	2017
Evidence-Based Guidelines for Treating Bipolar Disorder: Revised Third Edition Recommendations from the British Association for Psychopharmacology	British Association for Psychopharmacology	2016
Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders	Royal Australian and New Zealand College of Psychiatrists	2015
Bipolar Disorder: Assessment and Management Guidelines	National Institute for Health and Care Excellence	2014
Management of Bipolar Disorders in Adults	U.S. Department of Veterans Affairs/U.S. Department of Defense	2010
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2009 on the Treatment of Acute Mania	World Federation of Societies of Biological Psychiatry	2009
Practice Guideline for the Treatment of Patients with Bipolar Disorder	American Psychiatric Association	2002

TABLE A-3 Selected Clinical Guidelines Related to Posttrautatic Stress Disorder

Resource Title	Organization	Year
Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder	American Psychological Association	2017
VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder	U.S. Department of Veterans Affairs/U.S. Department of Defense	2017
ISTSS PTSD Prevention and Treatment Guidelines Methodology and Recommendations	International Society for Traumatic Stress Studies	2019
Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder: A Systematic Review Update	Agency for Healthcare Research Quality	2018

TABLE A-4 Selected Clinical Guidelines Related to Obsessive Compulsive Disorder

Title	Organization	Year
Practice Parameter for the Assessment and Treatment of Children and Adolescents with Obsessive Compulsive Disorder	American Academy of Child and Adolescent Psychiatry	2012
Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder	American Psychiatric Association	2007
Obsessive-Compulsive Disorder and Body Dysmorphic Disorder: Treatment	National Institute for Health and Care Excellence	2005
Obsessive-Compulsive Disorder Evidence Update September 2013	National Institute for Health and Care Excellence	2013
Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines from the British Association for Psychopharmacology	British Association for Psychopharmacology/ Baldwin	2014
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders	Anxiety Disorders Association of Canada	2014
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive Compulsive and Post-Traumatic Stress Disorders—First Revision	World Federation of Societies of Biological Psychiatry	2008

TABLE A-5 Selected Clinical Guidelines Related to Anxiety Disorders

Generalized Anxiety Disorder		
Guide Title	Organization	Year
Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines from the British Association for Psychopharmacology	British Association for Psychopharmacology	2014
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders	Anxiety Disorders Association of Canada	2014
Guidelines for the Pharmacological Treatment of Anxiety Disorders, Obsessive–Compulsive Disorder and Posttraumatic Stress Disorder in Primary Ccare	World Federation of Biological Psychiatry	2012
Generalized Anxiety Disorder and Panic Disorder in Adults: Management	National Institute for Health and Care Excellence	2011
Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for the Treatment of Panic Disorder, Social Anxiety Disorder and Generalized Anxiety Disorders	Royal Australian and New Zealand College of Psychiatrists	2018
Panic Disorder		
Guide Title	Organization	Year
Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines from the British Association for Psychopharmacology	British Association for Psychopharmacology	2014
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders	Anxiety Disorders Association of Canada	2014
Guidelines for the Pharmacological Treatment of Anxiety Disorders, Obsessive–Compulsive Disorder and Posttraumatic Stress Disorder in Primary Care	World Federation of Biological Psychiatry	2012
Generalized Anxiety Disorder and Panic Disorder in Adults: Management	National Institute for Health and Care Excellence	2011
Australian and New Zealand Clinical Practice Guidelines for the Treatment of Panic Disorder and Agoraphobia	Royal Australian and New Zealand College of Psychiatrists	2003

Social Anxiety Disorder		
Guide Title	Organization	Year
Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines from the British Association for Psychopharmacology	British Association for Psychopharmacology	2014
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress and Obsessive-Compulsive Disorders	Anxiety Disorders Association of Canada	2014
Social Anxiety Disorder: Recognition, Assessment, and Treatment	National Institute for Health and Care Excellence	2013
Guidelines for the Pharmacological Treatment of Anxiety Disorders, Obsessive–Compulsive Disorder and Posttraumatic Stress Disorder in Primary Care	World Federation of Biological Psychiatry	2012

DECIDING ON A MANAGEMENT APPROACH

Once a full assessment has been conducted to identify the severity of the disorder (e.g., risk of suicide), clinicians are guided by decisions-making algorithms, depending on the patients' status. Presented below are the algorithms for major depressive disorder (See Figure A-1) and for a mania/hypomania episode in bipolar disorder (See Figure A-2) from the U.S. Department of Veterans Affairs/U.S. Department of Defense (VA/DoD) guidelines as examples of how to decide on a management approach.

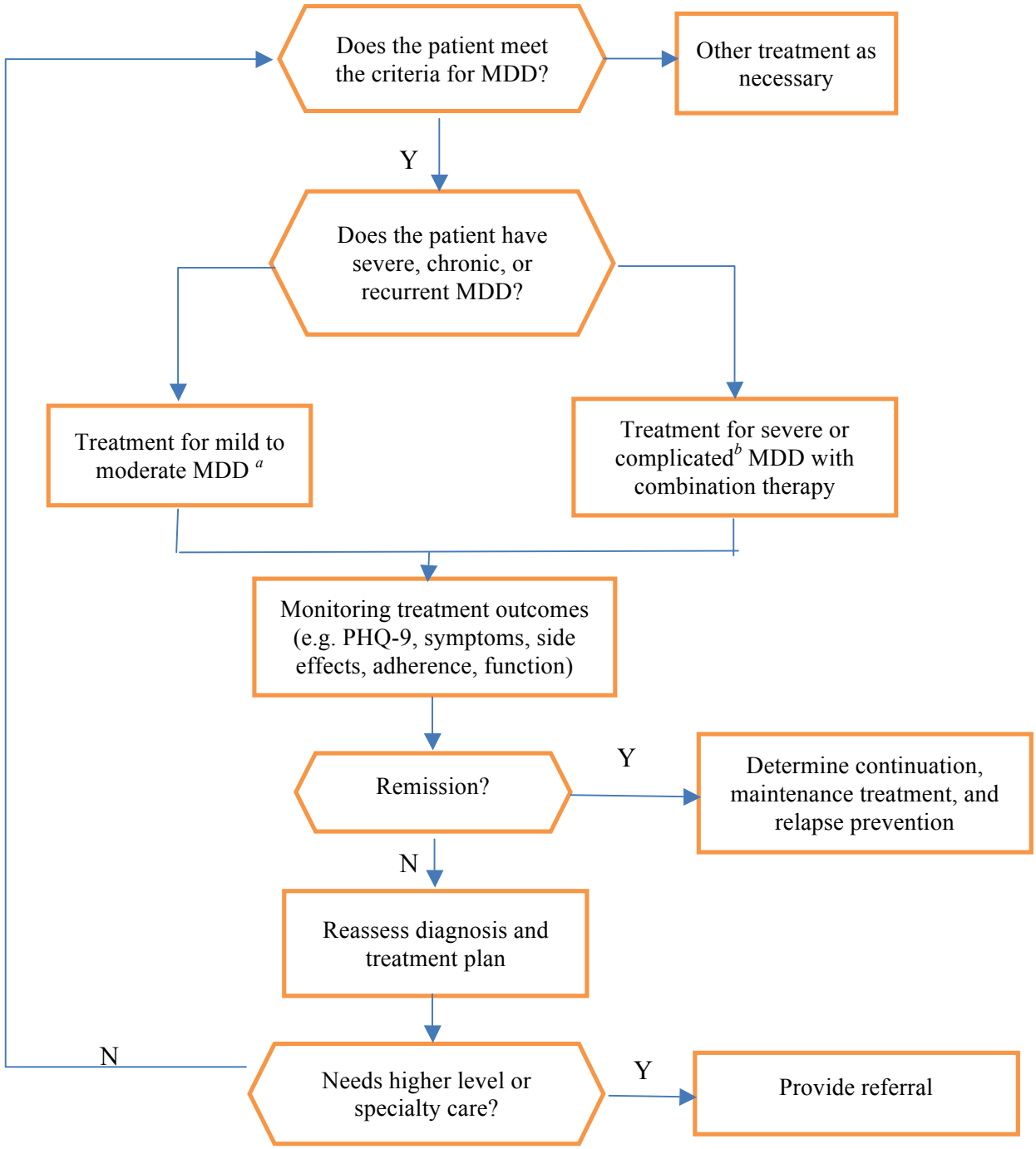

FIGURE A-1 Approach to management of depressive disorder. Adapted from the VA/DoD guidelines.
[a] For mild to moderate major depressive disorder (MDD), monotherapy with psychotherapy or pharmacotherapy is recommended.
[b] For severe or complicated MDD, a combination of a psychotherapy modality and pharmacotherapy is recommended. The DoD/VA guidelines define complicated major depression disorder when mania, depression with psychosis, or coexisting cognitive impairment co-exist.

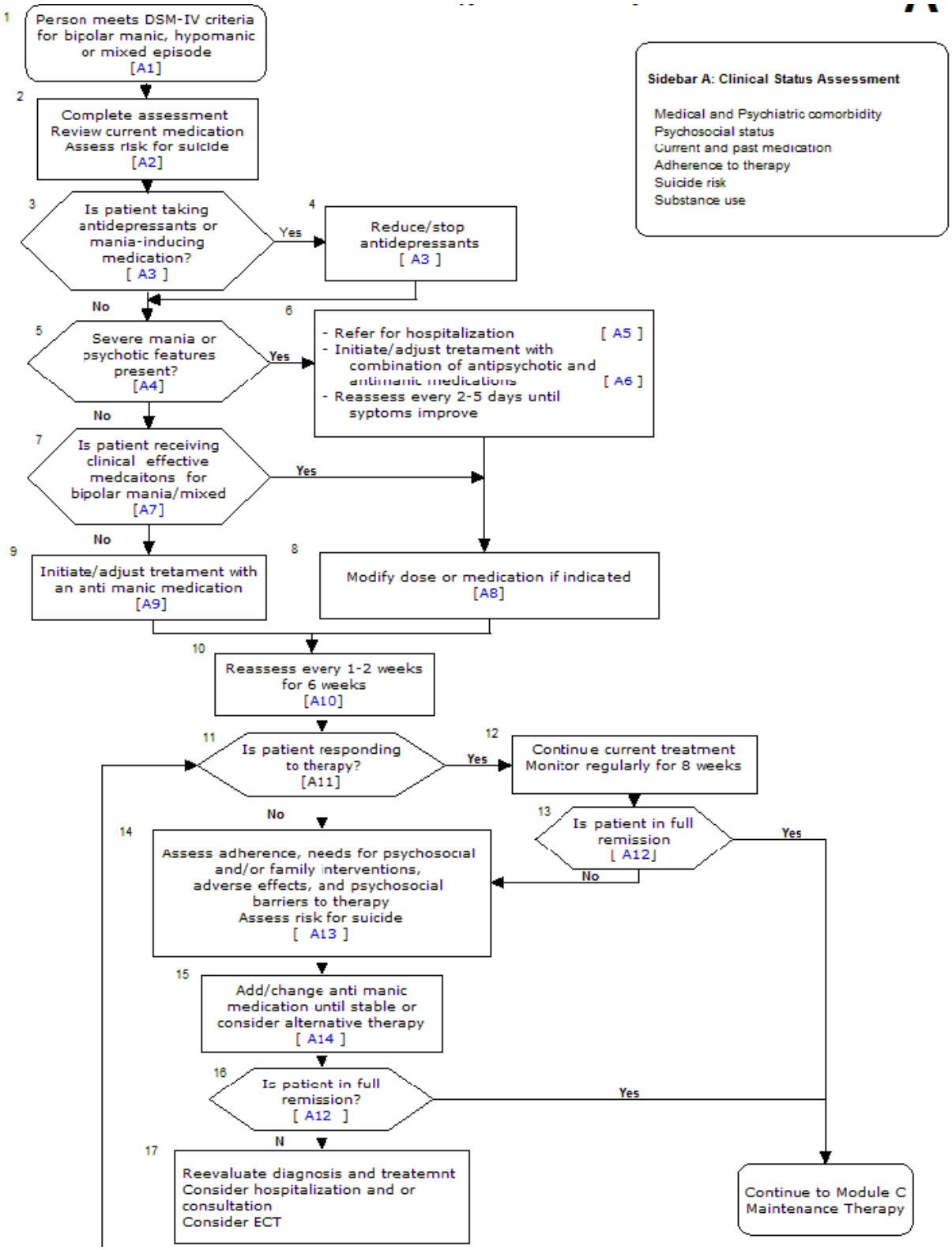

FIGURE A-2 Approach to management of mania, hypomania, or mixed episode.

SOURCE: Adapted from the VA/DoD guidelines.

OBSESSIVE COMPULSIVE DISORDER DIAGNOSTIC CRITERIA COMPARISON

The committee notes that the diagnostic criteria for obsessive compulsive disorder changed to some extent between the *Diagnostic and Statistical Manual for Mental Disorders, 4th Edition* (DSM-IV) which was used before 2013, and the *Diagnostic and Statistical Manual for Mental Disorders, 5th Edition* (DSM-5). Table 6 shows the differences between DSM-IV and DSM-5. In DSM-IV, obsessive compulsive disorder was considered in the class of Anxiety Disorders. This changed to a new class in DSM-5, Obsessive-Compulsive and Related Disorders. The changes allow the individual to have a diagnosis of obsessive compulsive disorder without any insight into the fact that the thoughts/behaviors are a product of the individuals mind or reach the threshold of delusion. DSM-5 also allows specification of the presence of a current or past tic disorder. The fact that obsessive compulsive disorder in DSM-IV allows for a psychosis suggests that a diagnosis of obsessive compulsive disorder could be even more severe than under DSM-IV.

TABLE A-6 DSM-IV to DSM-5 Obsessive Compulsive Disorder Comparison

DSM-IV	DSM-5
Disorder class: Anxiety Disorders	Disorder class: Obsessive-Compulsive and Related Disorders
Presence of either obsessions or compulsions:	Presence of obsessions, compulsions, or both:
Obsessions as defined by (1),(2), (3) and (4):	*Obsessions are defined by (1) and (2):*
1. Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.	1. Recurrent and persistent thoughts, urges or images that are experienced, at some time during the disturbance, as intrusive, unwanted, and that in most individuals cause marked anxiety or distress.
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.	DROPPED
3. The person attempts to ignore or suppress such thoughts, impulses, or images or to neutralize them with some other thought or action.	2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some thought or action (i.e., by performing a compulsion).
4. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as with thought insertion).	DROPPED
Compulsions as defined by (1) and (2):	*Compulsions are defined by (1) and (2):*

1. Repetitive behaviors (e.g., hand washing, ordering checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to the rules that must be applied rigidly.	1. Repetitive behaviors (e.g., hand washing, ordering checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to the rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation. However, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.	2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation. However, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.
At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.	DROPPED
The obsessions and compulsions cause marked distress, are time consuming (take more than 1 hour per day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.	The obsessions or compulsions are time consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder, hair pulling in the presence of trichotillomania; concern with appearance in the presence of body dysmorphic disorder: preoccupation with drugs in the presence of a substance use disorder: preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia: or guilty ruminations in the presence or major depressive disorder).	The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possession, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder); stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).
The disturbance is not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical	The disturbance is not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical

condition.	condition.
Specify if: With poor insight: If, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable.	*Specify* if: With good or fair insight: The individual recognizes that obsessive-compulsive beliefs are definitely or probably not true or that they may or may not be true. With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true. With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true. *Specify* if: Tic related: The individual has a current or past history of a tic disorder.

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