# *Autoimmune Diseases*

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- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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***Faculty***

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***Faculty Disclosure***

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

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***Division Planners Disclosure***

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

***Audience***

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.

***Accreditations & Approvals***

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*A complete Works Cited list begins on page 83.*

### Individual State Nursing Approvals

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### Special Approvals

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

### About the Sponsor

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### Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

### Course Objective

The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune disorders according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

### Learning Objectives

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

1. Describe the impact and pathogenesis of autoimmune diseases in the United States.
2. Recognize genetic and environmental risk factors for autoimmune diseases.
3. Evaluate the general characteristics of autoimmune diseases, including the difficulty in reaching a diagnosis.
4. Identify approaches to the management of autoimmune diseases, with special attention to considerations for patients with limited English proficiency and/or health literacy.
5. Analyze the epidemiology, clinical manifestations, and diagnostic criteria of autoimmune thyroiditis.
6. Select the appropriate treatment for Hashimoto's disease and Graves' disease in various patient populations.
7. Appropriately identify and diagnose rheumatoid arthritis according to established diagnostic criteria and clinical manifestations.
8. Outline the recommended treatment of rheumatoid arthritis using pharmacologic and nonpharmacologic interventions.
9. Discuss the importance of follow-up and patient education in the treatment of patients with rheumatoid arthritis.
10. Evaluate the impact and diagnosis of systemic lupus erythematosus (systemic lupus), including indications for appropriate referral.
11. Analyze the available treatments for systemic lupus, including considerations for follow-up and prognosis.
12. Apply the available diagnostic criteria to identify and treat Sjögren syndrome.
13. Outline the diagnostic criteria established for fibromyalgia, and discuss potential difficulties in establishing a diagnosis.
14. Identify appropriate treatment modalities for patients with fibromyalgia and patient education and follow-up needs.
15. Evaluate the clinical manifestations and diagnosis of celiac disease.


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

## INTRODUCTION

Autoimmune disease encompasses an array of 80 to 100 disorders affecting different body systems/organs. It has been difficult to determine the overall burden of autoimmune diseases, primarily because epidemiologic studies have not focused on them as a single entity and also because many of them are rare. However, research on individual autoimmune diseases, along with some studies on the diseases collectively, indicates that the burden is substantial in terms of the number of people affected, morbidity, mortality, and financial cost.

When considered collectively, autoimmune diseases affect approximately 50 million individuals in the United States, a number greater than that for heart disease (26.6 million) and cancer (14.5 million) combined [1; 2; 357]. A 2009 estimate of the overall prevalence of 29 autoimmune diseases is approximately 8.5%, but other studies have suggested that the prevalence is rising [4; 5].

Autoimmune diseases are chronic illnesses, with most having no available cure. As a result, lifelong treatment is needed for diseases that cause substantial morbidity, disability, mortality, and costs. Approximately $100 billion in annual direct healthcare costs are attributed to autoimmune diseases [1].

Many cases of autoimmune diseases remain undiagnosed because of challenges in diagnosis [358]. According to a survey conducted by the American Autoimmune Diseases Association, individuals who had been diagnosed with a serious autoimmune disease had seen an average of five physicians over a period of 4.6 years before a correct diagnosis was made [358]. In addition, more than 45% of individuals with an autoimmune disease reported that they had been labeled as a chronic complainer in the early stages of their disease because no cause for their symptoms could be determined [358].

Evidence-based guidelines for diagnosis, management, and/or follow-up are available for some autoimmune diseases, but diagnosis continues to be a challenge because symptoms are often overlapping and definitive diagnostic testing is lacking for most diseases. Problems exist even when guidelines are available; some guidelines predate the emergence of more effective treatment or lack clinical utility [6; 7; 8; 10; 11]. In addition, guidelines are associated with low rates of familiarity and adherence, especially with respect to recommendations for follow-up. For example, despite guidelines recommending routine monitoring of thyroid-stimulating hormone (TSH) levels for individuals taking medication for Hashimoto's hypothyroidism, studies have shown that up to 40% of these individuals have abnormal TSH levels [12; 13]. In addition, adherence to some recommendations for the treatment of systemic lupus erythematosus (systemic lupus), the monitoring of its comorbidities, and the prevention of glucocorticoid-induced osteoporosis have been found to be suboptimal [11; 14; 15].

This course provides an overview of the current understanding of the pathogenesis of autoimmune diseases and specifically addresses the management of five autoimmune diseases and fibromyalgia in adults: autoimmune thyroiditis, the most prevalent autoimmune disease; rheumatoid arthritis, systemic lupus, and Sjögren syndrome, the leading rheumatic autoimmune diseases; and celiac disease, an autoimmune disease of the gut with an increasing prevalence. Fibromyalgia was once thought to be an autoimmune disease, and while there is some evidence to suggest that it has an autoimmune component, the evidence is weak [16; 17]. Fibromyalgia warrants discussion in this course, however, because it is often found in individuals with an autoimmune disease; it shares similarities in clinical manifestations and can add to the challenge of diagnosing an autoimmune disease; and it is itself similarly difficult to diagnose and treat.

Although type 1 diabetes is a common autoimmune disease, it will not be discussed extensively in this course. Each disease section includes details on epidemiology; potential environmental risk factors; association with other autoimmune diseases; diagnosis, with a focus on established diagnostic criteria and differential diagnosis; treatment options, primarily those based on evidence in guidelines and other systematic reviews and meta-analyses; and recommendations for follow-up. Patient education is highlighted, as self-management is an essential component in the treatment of a chronic disorder [18; 19].

## OVERVIEW OF AUTOIMMUNE DISEASES

Autoimmune disease encompasses a broad array of disorders, and they vary according to the body systems/organs they affect and their associated morbidity. Researchers have identified direct evidence (the ability to transfer autoimmune disease) for 15 autoimmune diseases, and there is indirect evidence (the ability to reproduce the autoimmune disease in animal models) and circumstantial evidence (the association of autoantibodies with disease in appropriate clinical settings) for an autoimmunity component in more than 80 additional diseases [3].

The autoimmune diseases with the highest reported prevalence rates are Graves' disease, rheumatoid arthritis, and Hashimoto's thyroiditis; prevalence rates are lower for such diseases as celiac disease and autoimmune hepatitis [21; 22; 23]. Among the other more commonly occurring autoimmune diseases are systemic lupus, Sjögren syndrome, multiple sclerosis, myasthenia gravis, inflammatory bowel diseases (e.g., ulcerative colitis, Crohn's disease), pernicious anemia, scleroderma, primary biliary cirrhosis, Addison disease, and thrombocytopenic purpura [24]. Estimates of the prevalence of fibromyalgia have been similar to that of common autoimmune diseases [25].

The prevalence of autoimmune diseases differs according to gender, age, and race/ethnicity. Most autoimmune diseases occur far more frequently in female individuals than in male individuals, and although these diseases can occur at any age, many occur during the middle adult years, which represents the childbearing years for women [358]. Some diseases, such as type 1 diabetes, have an onset primarily in childhood and adolescence, and others, such as rheumatoid arthritis, occur primarily among older adults [21]. Differences in the prevalence of autoimmune diseases according to race/ethnicity are only beginning to emerge, and the variations have been studied only within the context of individual diseases [21].

Many autoimmune diseases follow a progressive course, even with appropriate management, and serious or life-threatening complications may develop. Functional limitations, disability, and poor quality of life are substantial concerns. For example, arthritis and rheumatism are one of the leading causes of disability in the United States, affecting as many as 8.6 million people and causing significant declines in ability to perform activities of daily living more than 4 million [26].

Although no autoimmune disease has been listed among the 10 leading causes of death, researchers have evaluated mortality rates for all autoimmune diseases as a category and found that it ranked eighth in the leading causes of death among all female individuals younger than 65 years of age in the United States in 1995 (***Table 1***) [27]. Similarly, researchers found that an autoimmune disease was the sixth or seventh most frequent underlying cause of death among female individuals younger than 75 years of age in England and Wales in 2003 [28]. In both studies, rheumatic fever/heart disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes were among the leading underlying causes of death [27; 28].

| DEATHS FOR WOMEN WITH AN AUTOIMMUNE DISEASE AS AN UNDERLYING CAUSE (UNITED STATES, 1995)[a] | | | | |
|---|---|---|---|---|
| **Autoimmune Disease** | **Death Counts by Age** | | | |
| | **25 to 44 Years** | **45 to 64 Years** | **≥65 Years** | **All Ages** |
| Rheumatic fever/heart disease | 177 | 582 | 2832 | 3613 |
| Rheumatoid arthritis | 14 | 183 | 1244 | 1442 |
| Multiple sclerosis | 254 | 620 | 514 | 1391 |
| Systemic lupus erythematosus | 338 | 353 | 356 | 1118 |
| Systemic sclerosis (scleroderma) | 85 | 318 | 490 | 902 |
| Glomerulonephritis | 44 | 88 | 745 | 893 |
| Type 1 diabetes[b] | 269 | NA | NA | 330 |
| Autoimmune hepatitis | 12 | 51 | 135 | 201 |
| Idiopathic thrombocytic purpura | 21 | 29 | 134 | 188 |
| Myasthenia gravis | 9 | 14 | 150 | 174 |
| Autoimmune hemolytic anemia | 2 | 11 | 77 | 93 |
| Pernicious anemia[c] | 0 | 2 | 68 | 70 |
| Sjögren syndrome[c] | 1 | 16 | 43 | 60 |
| Graves' disease | 4 | 3 | 15 | 24 |
| Thyroiditis | 2 | 2 | 0 | 6 |
| Vitiligo[c] | 0 | 0 | 0 | 0 |

[a]Fibromyalgia was not included in the list of diseases evaluated.
[b]Deaths related to type 1 diabetes were included only for individuals younger than 35 years of age.
[c]Diseases without specific International Classification of Diseases categories.

*Source: [27]* *Table 1*

Much is still unknown about how autoimmune diseases or fibromyalgia develop, but investigators have explored host, genetic, and environmental factors and continue to evaluate potential pathways [29].

## PATHOGENESIS

The immune system is designed to work with a balance of responding to a wide variety of foreign threats, such as harmful bacteria, viruses, or cancer cells, while maintaining self-tolerance (i.e., being nonresponsive to self-antigens). However, in a small proportion of individuals, this balance is disrupted, and there is unregulated activation of the immune system and loss of self-tolerance [30]. The resulting autoimmunity can lead to autoimmune diseases, a heterogeneous group of disorders that involve damage to organs, tissues, or cells [31]. Virtually every body system can be affected, and the target of the immune system can be a specific organ, as in thyroiditis, or multiple organs, as in systemic lupus.

In organ-specific diseases, such as thyroiditis, type 1 diabetes, inflammatory bowel disease, or multiple sclerosis, a normal immune response is misdirected against a self-antigen or organ, and inflammation and production of autoantibodies are usually confined to antigens specific to the target organ [31]. Multiple organs are targets in systemic autoimmune diseases, such as systemic lupus, Sjögren syndrome, or systemic sclerosis. In these types of autoimmune diseases, autoantibodies are directed to different autoantigens, typically resulting in chronic activation of innate and adaptive immune cells and an array of clinical manifestations [31].

Some autoimmune diseases are characterized by an organ-specific immune process but are systemic because they also involve autoantibodies to autoantigens outside of a specific organ. For example, rheumatoid arthritis is primarily a joint-selective disease, but other autoantibodies can cause extra-articular manifestations [31].

Organ-specific autoimmune diseases differ according to whether disease is mediated primarily though autoantibodies, autoreactive T cells, or a combination of the two [31]. Systemic autoimmune diseases can be categorized as being associated with either cell-mediated immunity or autoantibodies, or immune complexes. T-cell or B-cell activation can cause tissue damage directly by binding to cell-surface autoantigens, or indirectly by forming antibody-antigen complexes that become deposited in tissues. The autoimmunity process is cyclic, as tissue damage leads to the release of cytokines, activated T cells, and additional self-antigens, further stimulating the immune response.

The detection of an autoantibody does not necessarily indicate the presence of an autoimmune disease, as some autoantibodies, such as rheumatoid factor and antinuclear antibodies, are found in individuals without evidence of an autoimmune disease. In addition, autoantibodies can be detected years before a related autoimmune disease develops [33]. Some level of autoimmunity is, in fact, present in all individuals, which means that other factors must be involved in the development of an autoimmune disease [34].

## RISK FACTORS

### Genetic Factors

Genetics have been found to play a major role in rendering a person susceptible to an autoimmune disease. In general, autoimmune diseases occur concurrently within affected individuals and their families at higher than expected rates, but there are differences in the diseases that cluster within families [4]. The mode of inheritance of an autoimmune disease is complex, and research indicates that the genes involved in autoimmune disorders are pleiotropic (meaning they affect more than one trait) rather than disease-specific [4]. This research suggests that common alleles may have the potential for alternate clinical phenotypes under different sets of genetic and environmental factors, and data support the premise that clinically distinct autoimmune diseases may have common susceptibility genes [4; 35]. Currently, at least 68 genetic risk variants have been associated with various autoimmune diseases, and several loci have been identified as being associated with more than one autoimmune disease [4; 36].

Studies with monozygotic twins have been done to determine the genetic basis for many autoimmune diseases. Reported concordance rates include 12% to 30% for rheumatoid arthritis, 25% to 57% for systemic lupus, 30% for multiple sclerosis, 30% to 50% for type 1 diabetes, 70% to 75% for celiac disease, and up to 80% for Graves' disease [22; 30; 37; 38]. The concordance rate does not reach 100% for any autoimmune disease, which means that factors other than genetics must have a role in the pathogenesis [31].

### Environmental Factors

The role of environmental factors on the development of autoimmune disease has been studied, but exact triggers and how their interaction with genetic predisposition bears on pathogenesis have not yet been defined [31]. Among the environmental factors that have been found to have influence are infectious agents, stress, sex hormones (estrogens and androgens), and cigarette smoking.

#### *Infectious Agents*

Animal models have provided the best evidence of infectious agents inducing an autoimmune disease by immune-mediated mechanisms. On the basis of studies with these models, researchers have theorized that the immune response is triggered by antigens of a micro-organism that closely resembles self-antigens, a mechanism that has been termed molecular mimicry [3]. Another theory is that autoimmunity is induced by a mechanism known as the bystander effect: the invading micro-organism

directly damages tissue during active infection, thereby exposing self-antigens to the immune system [39; 40].

The diseases most often associated with infection as an etiologic factor are multiple sclerosis, type 1 diabetes, rheumatoid arthritis, systemic lupus, fibromyalgia, myasthenia gravis, and Guillain-Barré syndrome [3; 25; 41; 42; 43; 44]. The micro-organisms most often implicated are viral, including Epstein-Barr virus, hepatitis C virus, parvovirus, and cytomegalovirus [3; 43; 44; 45].

### *Stress*

Several studies in animals and humans have demonstrated that physical and psychologic stress affects the immune system, most probably the result of downstream neuroendocrine alterations that modulate immune function. As a result, researchers have hypothesized that stress may be involved in the development of autoimmune diseases [46; 47; 48]. Inflammatory autoimmune diseases, such as rheumatoid arthritis and systemic lupus, are the most likely diseases to be influenced by stress [48]. Psychologic stress as a trigger for autoimmune diseases and fibromyalgia is further suggested by studies in which as many as 80% of individuals reported emotional stress or major life events before the onset of symptoms, primarily in cases of rheumatoid arthritis, fibromyalgia, and Graves' disease [25; 47; 48; 49; 50]. However, most studies have been retrospective and have lacked the statistical power to determine significance [48].

### *Sex Hormones*

Sex hormones and their metabolites and receptors are involved in immunoregulation and the development of autoreactivity through their roles in lymphocyte maturation, activation, and synthesis of antibodies and cytokines [51]. Studies have shown that sex hormones are a factor in the pathogenesis of autoimmunity and that the expression of sex hormones is altered in individuals with autoimmune diseases [51]. Systemic lupus offers the strongest evidence for sex hormones as a development factor because of its incidence trend (i.e., high after puberty and low after menopause) and the fluctuations in disease severity according to menstrual cycles and pregnancy [51; 52]. More research is needed to better understand the role of sex hormones in autoimmunity and in specific autoimmune diseases.

### *Cigarette Smoking*

Cigarette smoking and exposure to tobacco smoke has also been found to be a potential trigger for autoimmune diseases, most notably rheumatic diseases (rheumatoid arthritis and systemic lupus) and, to a lesser degree, thyroiditis [53; 54]. The exact mechanisms behind the influence of cigarette smoke on the pathogenesis of autoimmune diseases are uncertain [31; 53].

### *Other Factors*

The National Institute of Environmental Health Sciences allocated $2.4 million in grant funding in 2014 to study the role of environmental exposures/toxicants in the development of autoimmunity [362]. In addition to tobacco smoke, factors deemed relevant include exposure to crystalline silica, solvents, and ultraviolet radiation. Research topics include the consequences of environmental exposures on the development of autoimmunity, the consequences of the timing of exposure (e.g., fetal perinatal, prepubertal, pubertal, adult, and aged periods), the interplay between environmental exposures and hormonal factors, and the role of environmental factors in lymphocyte activation [362].

## GENERAL CHARACTERISTICS

Although each autoimmune disease is a distinct entity with its own constellation of signs, symptoms, and clinical manifestations, many autoimmune diseases share some common characteristics, including female preponderance, similar symptom profiles, difficulty in diagnosis, importance of history and physical examination in diagnosis, and similarity in the approach to disease management.

| FEMALE PREDOMINANCE OF AUTOIMMUNE DISEASES AND FIBROMYALGIA | |
|---|---|
| **Disease** | **Approximate Female to Male Ratio** |
| Hashimoto's thyroiditis | 10:1 |
| Sjögren syndrome | 9:1 |
| Systemic lupus erythematosus | 9:1 |
| Antiphospholipid syndrome-secondary | 9:1 |
| Primary biliary cirrhosis | 9:1 |
| Graves' disease | 7:1 |
| Scleroderma | 3:1 |
| Rheumatoid arthritis | 2.5:1 |
| Antiphospholipid syndrome-primary | 2:1 |
| Multiple sclerosis | 2:1 |
| Myasthenia gravis | 2:1 |
| Fibromyalgia | 2:1 |
| *Source: [51; 291; 358]* | *Table 2* |

### Female Preponderance

Autoimmune diseases have a definite gender bias, with women accounting for nearly 80% of cases overall [21; 24; 55; 56]. The female-to-male ratio varies according to disease, from Hashimoto's thyroiditis, which has a female preponderance of 95%, to vitiligo, which has a female preponderance of 52% (***Table 2***) [51; 57; 358]. Fibromyalgia is also twice as prevalent in women [291]. However, a few diseases have been reported to occur more often in men than women, including type 1 diabetes, ulcerative colitis, Guillain-Barré syndrome, and psoriasis [55; 57].

### Similar Symptom Profiles

The symptom profiles associated with autoimmune diseases and fibromyalgia are another shared characteristic. Extreme fatigue is common, and other shared symptoms include low-grade fever, dizziness, and general malaise. In addition, vague, nonspecific symptoms tend to wax and wane over the long-term, causing periods of remission with intermittent disease flare-ups. Clinical presentations with overlapping symptom profiles, along with a high rate of co-occurring autoimmune diseases, make it difficult to confirm the diagnosis of an autoimmune disease or fibromyalgia [4].

### Difficulty in Diagnosis

Evidence of the difficulty in diagnosing autoimmune diseases or fibromyalgia is demonstrated in the results of surveys that have shown that individuals consult an average of four (and as many as 13) healthcare providers, typically over 2 to 5 years, before a diagnosis is made [10; 49; 358]. There are several reasons for the challenge. First, the initial symptoms are often subtle, nonspecific, and intermittent until the disease enters the acute stage. Symptoms can also affect many body organs, making it difficult for specialists in one area to recognize a disease within another specialty area. In addition, because most individual autoimmune diseases are rare, a primary care clinician may be unfamiliar with the clinical manifestations of each disease. Lastly, the diseases lack a single distinguishing feature, creating the need for clinicians to rely on varying combinations of information gathered from the history, physical examination, and laboratory and imaging studies [6; 60; 61; 62; 64]. Diagnostic criteria have been developed to aid in the diagnosis of some autoimmune diseases.

### Importance of History and Physical Examination in Diagnosis

A carefully taken history and comprehensive physical examination are particularly vital for the diagnosis of autoimmune diseases and fibromyalgia. Clinicians should prompt patients about symptoms that the patient may not consider important enough to report. Clinicians should also ask about any family and personal history of autoimmune diseases.

Studies of autoimmune diseases within families have shown significantly higher frequencies of autoimmune disease in general and of specific autoimmune diseases among first-degree relatives compared with controls [4]. Studies have also demonstrated that an individual with a diagnosed autoimmune disease is often at increased risk for

the co-occurrence of another autoimmune disease [4]. These studies have focused primarily on individuals with an index disease of multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis (hypothyroidism), type 1 diabetes, inflammatory bowel disease, and vitiligo. Among the most significant findings are a 90-fold and 68-fold higher prevalence of Hashimoto's thyroiditis and Graves' disease, respectively, among individuals with systemic lupus [65].

Other studies have indicated an increased risk of type 1 diabetes and ulcerative colitis among persons with multiple sclerosis, and an increased risk of rheumatoid arthritis, multiple sclerosis, and a combined category of six other diseases (Addison disease, hemolytic anemia, primary biliary cirrhosis, immune thrombocytopenia purpura, Sjögren syndrome, and systemic sclerosis) among persons with inflammatory bowel disease [66]. In approximately 60% of individuals with Sjögren syndrome, the syndrome is secondary to another autoimmune disease, most commonly rheumatoid arthritis, systemic lupus, or systemic sclerosis [67]. Celiac disease has been associated with the co-occurrence of several autoimmune diseases, most notably Sjögren syndrome and type 1 diabetes [22; 68]. Autoimmune diseases of connective tissue have generally been associated with higher rates of co-occurrence of other autoimmune diseases [69]. Higher-than-expected rates of fibromyalgia have also been found in individuals with autoimmune diseases, most notably systemic lupus, rheumatoid arthritis, thyroiditis, and Sjögren syndrome [17; 25; 70; 71; 72].

Obtaining an accurate history necessitates effective patient-physician communication, which is challenging given the high number of people of various racial/ethnic minorities or with inadequate language proficiency or health literacy [73; 74]. Approaches to overcoming this barrier will be discussed in detail later in this course.

**Approach to Disease Management**

The specific treatment of autoimmune diseases depends on the particular systems or organs affected, but the overall goals of treatment are similar. These goals are primarily to relieve symptoms, preserve organ function, and control the autoimmune process, often with immunomodulatory/immunosuppressant drugs. Challenges in treatment are related to the complexity of symptoms, the need to manage long-term medications for preserving organ function, and the long-term adverse effects of immunosuppressant drugs. As with diagnostic criteria, practice guidelines for the treatment of autoimmune diseases are available but limited. The long-term management of individuals with autoimmune diseases requires a multidisciplinary approach, with potential referral to specialists, such as rheumatologists, endocrinologists, gastroenterologists, neurologists, nutritionists, physical/occupational therapists, and counselors. This multidisciplinary care is best coordinated by the primary care provider, with clear articulation of specific roles. Because of the influence of stress on the immune system—coupled with the stress of a chronic disease—the management of autoimmune diseases should include stress reduction interventions [47; 48].

The management of autoimmune diseases is often complicated by patients' responses to the diagnosis and their coping with the disease. Adherence to the treatment plan is often difficult because of denial about the diagnosis, work and life demands, and frustration with the lack of symptom response to treatment [75]. Unresolved symptoms lead to a high rate of complementary and/or alternative methods used by individuals with autoimmune diseases or fibromyalgia [25; 49; 75; 77; 79]. The chronic nature of the conditions and the need for adherence to long-term management with frequent follow-up visits is essential for optimal outcomes but is also challenging, especially for individuals in racial/ethnic minority populations who may have different perceptions of health and the disease [80]. A strong, supportive patient-clinician relationship is integral to ensuring adherence and effective management.

### *Patient-Clinician Relationship in Disease Management*

To enhance the patient-provider relationship, healthcare professionals are advised to gain an understanding of the patient's perspective of his or her illness or disease and to ensure that the patient's primary concerns have been addressed [81]. Patient trust in healthcare providers has been rated higher for clinicians who seek the patient's perspective of his or her illness [82]. In turn, the healthcare professional's comprehensive knowledge of the patient and higher levels of patient trust have been reported to be substantial influences on adherence to medical advice, patient satisfaction, and improved health status [82; 83].

Effective communication is a cornerstone of the patient-provider relationship. Some communication behaviors that have been found to be positively associated with health outcomes include empathy, reassurance and support, explanations, positive reinforcement, humor, discussion of psychosocial issues, health education and information sharing, courtesy, and summarization and clarification [84]. Other factors essential for effective communication and a successful relationship are knowledge of the patient's language preference; an understanding of and respect for the patient's personal cultural values, beliefs, and practices (referred to as cultural competency); and an awareness of the patient's health literacy level [85; 86; 87].

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2012, more than 62 million Americans (21% of the population) speak a language other than English at home, with more than 25 million (8.5% of the population) reporting that they speak English less than "very well" [88]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [89].

The national standards on Culturally and Linguistically Appropriate Services (CLAS) include four standards related to language access services that are mandated for healthcare organizations [85]. Although these standards are not mandated for individual healthcare providers, the Office of Minority Health encourages clinicians to meet the standards to make their practices more culturally and linguistically accessible [85]. These standards are [85]:

- Offering and providing language assistance services, including bilingual staff and interpreter services, at no cost to each patient/consumer with limited English proficiency at all points of contact in a timely manner during all hours of operation
- Providing patients with both verbal offers and written notices (in their preferred language) that inform them of their right to receive language assistance services
- Ensuring the competence of language assistance provided to patients with limited English proficiency by interpreters and bilingual staff and avoiding the use of the patient's family and friends as interpreters
- Making easily understood patient-related materials available and posting signage in the languages of the commonly encountered groups and/or groups represented in the practice area

Convenience and cost lead many clinicians to use "ad hoc" interpreters (e.g., family members, friends, bilingual staff members) instead of professional interpreters. However, professional interpreters are preferred for several reasons. Several states have laws about who can interpret medical information for a patient, so healthcare professionals should check with their state's health officials about the use of ad hoc interpreters [90]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not

remain objective [90]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [90]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [91].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [92]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [93; 94].

Cultural competency is essential for addressing healthcare disparities among minority groups [85]. Among the issues that clinicians should understand are the patients' belief systems regarding health, healing, and wellness; their perceptions on illness, disease, and their causes; their health behaviors and attitudes toward healthcare providers; and the role of the family in decision making [85]. Understanding these aspects is integral to a successful patient-clinician relationship as well as to optimal health outcomes. For example, healthcare professionals should raise the topic of health-related customs, such as the use of complementary and alternative medicines because such use varies substantially among racial/ethnic populations and according to geographic area; may compromise the effect of traditional therapies; and is often not disclosed by the patient [25; 96; 97].

Knowledge of the patient's health literacy is also important, as the patient's understanding of his or her disease and its management is essential to ensuring adherence to the treatment plan and the patient's role in self-management. Yet most individuals lack adequate health literacy. According to the 2003 National Assessment of Health Literacy, 14% of individuals in the United States have "below basic" health literacy, which means they lack the ability to understand health information and make informed health decisions [73; 98]. A systematic review of more than 300 studies showed that an estimated 26% of patients had inadequate literacy and an additional 20% had marginal literacy [99]. Health literacy varies widely according to race/ethnicity, level of education, and gender, and clinicians are often unaware of the literacy level of their patients [87; 100]. Predictors of limited health literacy are poor self-rated reading ability, low level of education, male gender, and nonwhite race [100; 101]. Several instruments are available to test patients' literacy levels, and they vary in the amount of time needed to administer and in their reliability in identifying low literacy [73; 87; 100; 102].

Clinicians should adapt their discussions and educational resources to a patient's identified health literacy level and degree of language proficiency. The use of plain language (free of medical jargon), asking patients to repeat pertinent information, regularly assessing recall and comprehension, providing educational resources in a variety of formats (e.g., print, oral, web-based, video), and using culturally appropriate and translated educational materials can all help ensure that patients better understand their disease and its management, ultimately leading to higher quality care.

## THYROIDITIS

Thyroiditis is the most common autoimmune disease. Autoimmune thyroiditis encompasses both Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, and Graves' disease. Hashimoto's disease and Graves' disease are the leading causes of hypothyroidism and hyperthyroidism, respectively [50; 103]. Hashimoto's disease is more common than Graves' disease [13; 104].

In Hashimoto's disease, antithyroid antibodies destroy thyroid cells, resulting in the decreased production of thyroid hormones. Hashimoto's disease can be associated with either subclinical or overt hypothyroidism, and subclinical disease is the more commonly encountered of the two in the primary care setting [104]. Left untreated, hypothyroidism can cause fatigue, weight gain, mental slowing, heart failure, and elevated lipid levels.

In Graves' disease, circulating thyroid antibodies target the TSH receptor, which stimulates the thyroid gland, causing enlargement of the thyroid gland and increased production of thyroid hormone. As with Hashimoto's disease, thyroid dysfunction with Graves' disease may be subclinical or overt. Mild ophthalmopathy is present in as many as half of individuals with Graves' disease, and severe ophthalmopathy occurs in 3% to 5% [50; 105]. This ophthalmopathy is the result of edema and lymphocytic infiltration of orbital fat, connective tissue, and eye muscles, and exophthalmos is the characteristic sign of Graves' disease [106]. If not treated, overt hyperthyroidism can result in atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric problems.

### EPIDEMIOLOGY

According to the results of the population-based National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 1999–2002, the prevalence of hypothyroidism in the United States is approximately 4% to 5% and the prevalence of hyperthyroidism is approximately 0.5% to 1% [13; 104]. Subclinical hypothyroidism is far more prevalent than overt disease (4.3% compared with 0.3%), whereas the rates of subclinical and overt hyperthyroidism are similar [104].

Hashimoto's disease usually occurs between the ages of 30 and 50 years and is nearly 10 times more common in women than in men [51; 107; 108]. The prevalence of hypothyroidism (subclinical and overt) increases with age; the odds for hypothyroidism are five times greater for individuals 80 years or older than for individuals 12 to 49 years of age [13]. The rate of subclinical hypothyroidism has been reported to be as high as 15% to 20% among women 60 years of age and older [104; 109; 110]. Graves' disease typically occurs between the ages of 40 to 60 years and is about eight to nine times more common in women than men [51].

Data on the prevalence of autoimmune thyroiditis among racial/ethnic populations are limited. The prevalence of antithyroid antibodies has been greater in the white and Mexican American populations than in the black population [104]. Among the Mexican American population, the risk for hypothyroidism has been found to be the same as that for the non-Hispanic white population, but the risk for hyperthyroidism is higher [13]. The risk for hypothyroidism is lower and the risk for hyperthyroidism is higher for the non-Hispanic black population compared with the non-Hispanic white population [13].

### POTENTIAL ENVIRONMENTAL RISK FACTORS

In individuals with genetic susceptibility, iodine deficiency, infection, smoking, and stress have been identified as environmental triggers for both types of autoimmune thyroiditis [54]. Recent childbirth may be an additional trigger for Graves' disease [50].

## ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

A coexisting autoimmune disorder is present in approximately 14% of individuals with Hashimoto's disease and nearly 10% of individuals with Graves' disease [111]. In a British study involving more than 3,000 individuals with autoimmune thyroiditis, rheumatoid arthritis was the most common coexisting autoimmune disorder, appearing in approximately 4% of individuals with Hashimoto's disease and 3% of those with Graves' disease [111]. Among the other autoimmune disorders that have been found to be associated with Hashimoto's thyroiditis are pernicious anemia, systemic lupus, Addison disease, celiac disease, Sjögren syndrome, systemic sclerosis (scleroderma), type 1 diabetes, and vitiligo [111; 112; 113].

Genetic studies have indicated a close relationship between type 1 diabetes and autoimmune thyroid disease, and a fourfold risk of thyroiditis has been found among individuals with type 1 diabetes [4; 38]. In a small study (254 participants), nonthyroid autoimmune diseases were found in approximately 9% of individuals with Graves' disease, and the specific nonthyroid diseases varied according to the presence or absence of ophthalmopathy [112]. Type 1 diabetes was the most prevalent disease among individuals who did not have ophthalmopathy (approximately 7%), and vitiligo was the most prevalent autoimmune disease among those who had ophthalmopathy (4%) [112].

Another small study has suggested that Hashimoto's disease and/or subclinical hypothyroidism may be a predisposition to fibromyalgia; signs and symptoms of fibromyalgia were found in nearly one-third of individuals [72].

## CLINICAL MANIFESTATIONS

Both Hashimoto's disease and Graves' disease may be present with no symptoms or with subtle, nonspecific symptoms, especially with early or subclinical disease. With Hashimoto's disease, approximately 20% of individuals have symptoms at the time of diagnosis, although symptoms may not develop until years after thyroid dysfunction [114]. Symptoms of Graves' disease are usually present for at least 2 to 3 months before diagnosis [50].

The symptoms associated with Hashimoto's disease are the same regardless of whether hypothyroidism is present. In addition to nonspecific symptoms, such as fatigue, weakness, lethargy, and muscle aches, hypothyroidism can also affect a variety of body systems (***Table 3***) [108; 113; 115].

Fatigue and weakness are also among the most common symptoms associated with Graves' disease, and as with Hashimoto's disease, symptoms can be related to many body systems, with the overactivity of the thyroid having the opposite effect [50; 106; 113; 115]. For example, hypothyroidism is typically associated with bradycardia, while hyperthyroidism is usually associated with a rapid, bounding pulse and/or palpitations.

## DIAGNOSTIC EVALUATION

Because of the frequency of nonspecific symptoms and the wide array of other symptoms, healthcare professionals should elicit a detailed history, with emphasis on questions related to [115; 363]:

- Appetite, recent unexplained weight loss, or weight gain
- Tightness, fullness, or pain in the neck
- Eye pain or discomfort, changes in visual acuity
- Nervousness and/or anxiety
- Emotional status
- Abdominal pain
- Constipation or diarrhea
- Exertional dyspnea
- Increased perspiration
- Heat or cold intolerance
- Regularity of menstrual cycles
- Sleep disturbances
- Hair loss

| SIGNS AND SYMPTOMS OF AUTOIMMUNE THYROID DISEASE | | |
|---|---|---|
| **Body System** | **Hashimoto's Disease** | **Graves' Disease** |
| General | Fatigue<br>Weakness<br>Lethargy<br>Hypothyroid speech<br>Forgetfulness<br>Increased sensitivity to medications | Fatigue<br>Weakness<br>Sleep disturbances |
| Psychiatric | Depression | Emotional instability<br>Nervousness, anxiety |
| Metabolic | Weight gain<br>Cold intolerance | Weight loss<br>Heat intolerance |
| Skin | Pale, dry, cold skin (may appear jaundiced)<br>Coarse skin<br>Thick, brittle nails<br>Dry, coarse, brittle hair or hair loss | Warm, moist skin<br>Pretibial myxedema<br>Hair loss |
| Cardiovascular | Slow pulse<br>Bradycardia<br>Diastolic hypertension<br>Peripheral edema | Rapid pulse (≥90 beats/minute)<br>Tachycardia, palpitations, atrial fibrillation<br>Elevated systolic and diastolic blood pressure<br>Edema<br>Dyspnea on exertion |
| Pulmonary | Slow, shallow respirations | Shortness of breath<br>Increased respiratory rate and depth |
| Neurologic | Delayed ankle reflexes | Fine finger/hand tremor |
| Musculoskeletal | Sore muscles<br>Pain and/or stiffness in joints | Proximal muscle weakness or wasting<br>Back pain<br>History of fractures |
| Digestive | Constipation | Increased appetite<br>Diarrhea<br>Vomiting<br>Abdominal pain |
| Hematologic | Easy bruising<br>Macrocytic anemia<br>Normocytic normochromic anemia | Easy bruising |
| Renal | — | Polyuria<br>Polydipsia |
| Reproductive | Menorrhagia<br>Irregular periods<br>Decreased libido<br>Increased rate of miscarriage, still birth, and fetal death | Amenorrhea<br>Irregular periods<br>Decreased fertility<br>Increased risk for miscarriage |
| Ophthalmologic | — | Tearing<br>Gritty sensation<br>Eye discomfort/pain<br>Diplopia<br>Exophthalmos |
| *Source: [50; 106; 108; 113; 115]* | | *Table 3* |

| DIAGNOSTIC ACCURACY OF CLINICAL FINDINGS FOR THYROIDITIS | | |
|---|---|---|
| **Sign/Symptom** | **Sensitivity** | **Specificity** |
| **Hypothyroidism** | | |
| Hypothyroid speech | 37% | 93% |
| Cool and dry skin | 16% | 97% |
| Slow pulse rate | 29% to 43% | 89% to 93% |
| Coarse skin | 29% to 61% | 74% to 95% |
| Delayed ankle reflexes | 48% | 86% |
| **Hyperthyroidism** | | |
| Eyelid retraction | 34% | 99% |
| Eyelid lag | 19% | 99% |
| Fine finger tremor | 69% | 94% |
| Warm and moist skin | 34% | 95% |
| Pulse ≥90 beats/minute | 80% | 82% |
| *Source: [106]* | | *Table 4* |

The comprehensive physical examination should begin with assessment of blood pressure, weight, pulse, and other vital signs. A slow pulse is a clinically significant finding of hypothyroidism, and a rapid pulse (i.e., 90 beats per minute or more) is a clinically significant finding of hyperthyroidism (***Table 4***) [106]. Among individuals with hyperthyroidism, tachycardia occurs less often among older individuals than younger ones [50].

Palpation and auscultation of the thyroid should be done to determine if the gland is enlarged and if nodules are present. In individuals with hypothyroidism, the thyroid gland may not be palpable or a goiter may be present [113]. An enlarged thyroid gland is a significant sign of hyperthyroidism, occurring in 70% to more than 90% of individuals with the disorder [106]. The goiter associated with hyperthyroidism is typically diffuse and symmetric, which distinguishes Graves' disease from toxic nodular goiter, in which nodes are usually felt on palpation of the goiter.

Evaluation of the skin is also important. Skin that is both cool and dry is a clinically significant finding for hypothyroidism; the skin may also feel coarse or appear pale or yellowish [106]. Skin that is both warm and moist is a significant finding for hyperthyroidism. Hair loss is common with both types of thyroiditis.

An eye examination is integral to the diagnosis of Graves' disease, as exophthalmos is a hallmark characteristic and is often the first sign of this disease. Eyelid retraction is the most clinically significant finding of hyperthyroidism, followed by eyelid lag; other ophthalmologic signs of Graves' disease are periorbital edema and limited eye movements [106].

Hypothyroid speech—a low-pitched, hyponasal voice (as if speaking with a cold), spoken at a slow pace—is found in about one-third of individuals with hypothyroidism [106]. This speech is the finding with the most clinical significance for diagnosis of hypothyroidism [106].

A neurologic evaluation is also useful in the diagnosis. Delayed ankle reflexes are a clinically significant finding of hypothyroidism, and fine finger tremor is a clinically significant finding of hyperthyroidism [106]. Tremor is less likely to occur in older than younger individuals with hyperthyroidism [50].

No single clinical finding, when absent, is significant for ruling out hypothyroidism [106]. The lack of thyroid enlargement, a pulse of less than 90 beats per minute, and the absence of finger tremor are findings with the most significance in ruling out hyperthyroidism [106].

Among the differential diagnoses that should be considered when evaluating an individual with suspected Hashimoto's thyroiditis are chronic thyroiditis, thyroid nodules, euthyroid sick syndrome, and lymphoma of the thyroid [106]. The differential diagnosis for Graves' disease includes toxic nodular goiter, subacute thyroiditis, and papillary carcinoma of the thyroid [106].

### Laboratory Testing

Thyroid function tests can confirm a diagnosis of Hashimoto's thyroiditis or Graves' disease. The single best screening test for either disease is the sensitive TSH assay (also known as thyrotropin level), and the free thyroxine (T4) level and the total triiodothyronine (T3) level also help confirm the diagnosis [113; 115; 364]. An elevated TSH level with low levels of T3 and free T4 indicates Hashimoto's hypothyroidism [108; 113]. Subclinical hypothyroidism is indicated by a repeatedly high TSH level with normal free T4 and T3 levels [108; 113]. In contrast, a low TSH level with increased T3 and T4 levels indicates hyperthyroidism [50]. The patient's history is important to remember when interpreting the results of laboratory testing, as a low TSH level can also be caused by glucocorticoids, dopaminergic drugs, severe illness, pregnancy, diurnal variation, or pituitary dysfunction; elevated TSH levels may be caused by adrenal insufficiency [113]. Thyroid autoantibodies (i.e., thyroid peroxidase and thyroglobulin antibodies) may be helpful in the diagnosis [113; 364].

### Other Testing

A radioiodine-uptake scan is not useful in diagnosing hypothyroidism, but it can help distinguish hyperthyroidism from subacute thyroiditis, which is associated with low uptake values, and from multinodular toxic goiter [50]. If a radioiodine-uptake scan is not possible, ultrasonography of the thyroid gland may be done instead, and increased blood flow by Doppler correlates with an increased uptake [50]. Ultrasonography is also useful for detecting nodules and evaluating suspicious structural abnormalities [50; 113]. A fine-needle biopsy should be done to exclude malignancy when a dominant nodule is present [50; 107].

## SCREENING FOR THYROIDITIS

The issue of regular thyroid function screening is controversial. In 1998, the American College of Physicians recommended screening for women older than 50 years of age who have at least one general symptom that could be caused by thyroid disease [116]. Two years later, the American Thyroid Association recommended measuring thyroid function in all adults beginning at age 35 years and every 5 years thereafter and noted that more frequent screening may be appropriate for high-risk or symptomatic individuals [117]. In 2011, the American Academy of Family Physicians found insufficient evidence to recommend for or against routine thyroid screening in asymptomatic adults, and the American College of Obstetricians and Gynecologists recommended that physicians be aware of the symptoms and risk factors for postpartum thyroid dysfunction and evaluate patients when indicated [118; 119]. In 2004, the U.S. Preventive Services Task Force concluded that the evidence was insufficient to recommend for or against routine screening for thyroid disease in adults. The Task Force noted that while there was fair evidence that TSH testing can detect subclinical thyroid disease in asymptomatic individuals, there was poor evidence that treatment improves clinically important outcomes in adults with thyroid disease detected through screening [120].

Despite the potential for serious adverse events associated with either type of autoimmune thyroiditis, the American Association of Clinical Endocrinologists (AACE) recommends "aggressive case finding" (i.e., using symptoms, family history, and personal history of thyroid damage, autoimmune disorders, or abnormal thyroid exam) rather than universal TSH testing for women of childbearing age before or during pregnancy [113]. There is insufficient evidence to support universal screening in this group, mainly because the impact of outcomes has not been demonstrated. Additionally, the AACE warns of the potential for harm with treatment during pregnancy. If testing is performed, the AACE recommends that measurement of total T4 or a free T4 index, in addition to TSH, be done to assess thyroid status [113].

The AACE recommends hypothyroidism screening for individuals older than 60 years of age, especially women [113]. However, hypothyroidism is common in older patients and the evidence supporting benefit or cost effectiveness is insufficient.

## TREATMENT OPTIONS

Both the AACE and the American Thyroid Association have developed guidelines for the treatment of hypothyroidism and hyperthyroidism [113; 115]. Treatment of either thyroid dysfunction must be tailored to the individual patient, and the patient should have a clear understanding of the indications and implications of all forms of therapy, including risks, benefits, and side effects. Clinicians should also encourage the patient to be an active participant in the decision-making process regarding the type of therapy. The goal of treatment for either condition is to achieve a euthyroid state.

### Hashimoto's Disease

The AACE states that most primary care clinicians can diagnose and treat hypothyroidism, but the organization recommends consultation with an endocrinologist for patients with [113]:

- Age 18 years or younger
- Pregnancy (or planned pregnancy)
- Cardiac disease
- Disease that is unresponsive to treatment
- Another endocrine disease
- A goiter, nodule, or other structural change in the thyroid gland
- Unusual causes of hypothyroidism or hypothyroidism caused by medications or medical conditions

Overt hypothyroidism involves lifelong thyroid replacement medication, typically levothyroxine. Various brands of the medication are available, and the AACE recommends using a high-quality brand, with the same brand used throughout treatment in order to maintain consistency [113].

Levothyroxine is prescribed as a daily, oral dose, and treatment begins with a low dose and is gradually titrated up according to the results of TSH testing [113; 115]. An initial daily dose of 25 to 50 mcg has been recommended; lower doses may be more appropriate for older individuals or those with cardiovascular disease [107; 108]. The AACE notes that the mean full replacement dosage is 1.6 mcg/kg per day [113]. Clinical evaluation of the patient and TSH testing should be done every 4 to 8 weeks after a change in dose [113].

When titrating the dose of levothyroxine, healthcare professionals must consider the effects of other drugs the patient takes. Many drugs, including cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide, can interfere with levothyroxine absorption [113]. Also, rifampin and sertraline may accelerate levothyroxine metabolism, calling for a higher replacement dose [113].

It should be noted that a small cohort of patients will retain signs of neurocognitive dysfunction, despite normal serum TSH and free T4, perhaps because more than half of the T3 in the brain is produced locally [365]. Results of a large clinical trial demonstrated that patients carrying a polymorphism in the Dio2 gene are particularly prone to this outcome, and combination treatment with liothyronine is beneficial for patients with persistent neurocognitive symptoms in spite of normal serum concentrations of TSH and free T4 [365].

### *Hashimoto's Disease Without Hypothyroidism*

Recommendations have also been made for individuals who have Hashimoto's disease without hypothyroidism (i.e., who have a goiter but normal TSH levels). Treatment is not required for individuals who are asymptomatic and have a small goiter. However, many endocrinologists prescribe levothyroxine for patients with a goiter, even if the level of TSH is normal, with a goal of decreasing the size of the goiter [107].

### *Subclinical Hypothyroidism*

The appropriate approach to subclinical hypothyroidism has been debated. Proponents of treatment note that although subclinical hypothyroidism is usually asymptomatic, treatment has been shown to offer benefit in reducing the risks of several adverse events, including cardiovascular events, hyperlipidemia, and neuropsychiatric effects [121; 122; 123; 124; 125]. In addition, subclinical hypothyroidism can progress to overt hypothyroidism, with a wide range in risk of progression (3% to 20%) [108; 113].

Despite a recommendation to treat subclinical hypothyroidism, there is no consensus on the TSH level that should prompt treatment [113; 126]. The AACE recommends treatment for individuals with subclinical hypothyroidism and a TSH level greater than 10 IU/mL especially if patients have symptoms of hypothyroidism, positive anti-thyroid peroxidase antibodies (TPOAb), or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases [113]. Treatment should also be considered for individuals who have a strong family history of thyroid disease, who are pregnant, who have a history of heavy tobacco use, and/or who have severe lipidemia [108]. As with the treatment of overt hypothyroidism, the dose should be adjusted according to the TSH level. The TSH target recommend by AACE guidelines for non-pregnant patients should be the normal range of a third generation TSH assay (or between 0.45 and 4.12 mIU/L, when not available), and the level should be determined every 6 to 8 weeks until the target has been reached [113]. More studies are needed before thyroxine replacement therapy can become the standard of care for subclinical hypothyroidism [108; 113].

### *Hypothyroidism During Pregnancy*

Hypothyroidism (even if mild) during pregnancy can have serious adverse effects for both the mother (e.g., hypertension, pre-eclampsia, postpartum hemorrhage) and fetus (e.g., spontaneous abortion, fetal death or stillbirth, low birth weight, abnormal brain development) [113]. The AACE states that pregnant women who have or have had positive levels of serum TPOAb and with a TSH greater than 2.5 mIU/L should be treated with levothyroxine [113]. Additionally, treatment should be considered if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or hypothyroidism [113]. Women with positive levels of serum TPOAb or with a TSH greater than 2.5 mIU/L who are not being treated with levothyroxine should be monitored every 4 weeks in the first 20 weeks of pregnancy for the development of hypothyroidism [113].

Thyroid function should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation to ensure that the requirement for L-thyroxine has not changed; the dose of thyroxine should be adjusted accordingly [113]. Some clinicians may prefer to continue regular monitoring throughout gestation. The upper limit of the normal range should be based on trimester-specific ranges for

that laboratory. If ranges are not available in the laboratory, the following upper normal TSH reference ranges are recommended [113]:

- First trimester: 2.5 mIU/L
- Second trimester: 3.0 mIU/L
- Third trimester: 3.5 mIU/L

**Graves' Disease**

As noted, the goal of treatment of Graves' disease is to make the thyroid function normally or to disable the gland completely and treat the resultant hypothyroidism. The three primary treatment options are radioactive iodine (usually $^{131}$I), antithyroid drugs, or thyroidectomy. In addition, treatment with a beta blocker is recommended to provide relief of symptoms (such as tremor, palpitations, and sweating) until a euthyroid state is reached [115].

***Treatment with Radioactive Iodine***

Treatment with $^{131}$I is considered to be the treatment of choice for most people; however, pregnancy and breastfeeding are absolute contraindications [115]. A pregnancy test should be obtained 48 hours before treatment with $^{131}$I for all women of childbearing age who are sexually active.

The isotope is given orally (as a capsule or in water), and there is no consensus on the optimal dose [127]. The dose is usually determined with a dose-calculation algorithm, and the typical dose range is 5 to 15 mCi of $^{131}$I [115; 127]. Randomized trials have shown no significant differences in outcome between the use of calculated doses and fixed doses, and fixed doses are now used in many institutions [128; 129].

Treatment with antithyroid drugs may be indicated for some individuals, particularly older individuals or those with cardiac disease, before administration of $^{131}$I. Antithyroid drugs should be stopped 1 week before treatment with radioactive iodine is begun and should not resume until approximately 6 weeks after treatment.

The American Thyroid Association and the AACE recommend that individuals be followed up within the first 1 to 2 months after treatment to monitor the transition to a euthyroid and/or hypothyroid state [115]. Hypothyroidism can occur at any time after treatment, but most commonly occurs within 2 to 6 months [50]. Treatment with partial replacement doses of levothyroxine can usually begin 2 months after treatment. The timing of thyroid-replacement treatment depends on the findings of laboratory testing and clinical evaluation [115].

The cure rate for treatment with radioactive iodine is more than 80% [130]. Retrospective studies have shown that factors associated with a lack of response to $^{131}$I are a young age, a large thyroid, severe thyrotoxicosis, previous exposure to antithyroid drugs, and a higher $^{131}$I uptake value [131; 132]. When necessary, a second dose should be given at least 6 to 12 months after the initial treatment, and antithyroid drugs should be stopped before and after a second treatment [127].

Treatment with $^{131}$I is safe, with the primary side effects being acute radiation thyroiditis and hypothyroidism; there is no adverse effect on fertility or on offspring conceived after treatment [50; 115]. Radioactive iodine administration is the recommended modality for women who wish to become pregnant 4 to 6 months after treatment. The findings of some studies have suggested an increased risk for some types of cancer after treatment with $^{131}$I, but the results of other studies have demonstrated conflicting data, with no increases in the incidence of cancer [133; 134].

***Treatment with Antithyroid Drugs***

Antithyroid drugs (thionamides) interfere with thyroid hormone synthesis by preventing iodine from combining with tyrosine residues in thyroglobulin [135]. This approach is usually the treatment of choice for pregnant women, children and adolescents, and individuals who have severe Graves' ophthalmopathy [127; 135]. The goal of treatment is to achieve remission, defined as a biochemical euthyroid state for a minimum of 1 year after discontinuing treatment [115; 135].

The most frequently prescribed antithyroid drugs are methimazole and propylthiouracil [135]. Methimazole has become the preferred drug in the United States, especially after a 2009 U.S. Food and Drug Administration (FDA) Safety Alert noting reports of severe liver injury and acute liver failure (some fatal) in both adults and children treated with propylthiouracil [136]. The FDA recommended that physicians should "carefully consider" the choice of drug for newly diagnosed Graves' disease and that propylthiouracil should not be used in children and adolescents unless the patient is allergic to or intolerant of methimazole and no other treatment options are available [136]. The FDA now requires a boxed warning on the label of propylthiouracil to alert clinicians about the risk of liver damage.

The AACE and the American Thyroid Association recommend the use of methimazole for nearly every patient; however, propylthiouracil should be used during the first trimester of pregnancy, for treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery [115]. Antithyroid drug therapy can be given in two ways: a titration regimen or a block-replace regimen. With a titration regimen, the initial dose is high and the dose is tapered over time. With a block-replace regimen, a high dose of an antithyroid drug is given, followed by levothyroxine once a euthyroid state has been reached. No difference in efficacy has been found between the two methods, according to a systematic review of the literature published in 2010 [138]. The block-replace regimen, however, was associated with a higher rate of adverse effects [138].

The starting dose depends on the severity of the hyperthyroidism, and the typical starting doses have been 10 to 40 mg/day for methimazole and 100 to 600 mg/day (in divided doses) for propylthiouracil [115; 130]. The starting dose is tapered according to the results of thyroid function testing, which should be done once a month until symptoms start to resolve and then every 2 to 3 months [127; 130]. The results of thyroid function testing are also considered when tapering the dose; testing should be done every month. Use of a block-replace regimen requires less frequent testing [130]. Typical maintenance doses are 5 to 20 mg/day of methimazole or 100 to 200 mg/day of propylthiouracil [127; 130].

Two starting doses of methimazole (15 mg/day and 30 mg/day) and propylthiouracil (300 mg/day) were compared in a small randomized study in Japan (240 participants) [137]. Overall, the 30 mg/day dose of methimazole normalized the serum free T4 level in significantly more individuals than the 15 mg/day dose or propylthiouracil at 12 weeks [137]. The higher dose of methimazole was also significantly more effective in the subgroup with severe hyperthyroidism (free T4 level: 7 ng/dL or greater), but there was no difference among the three treatments in the subgroup with mild or moderate disease (free T4 level: less than 7 ng/dL) [137].

With regard to duration of therapy, 1 year of treatment has been reported to offer better rates of remission than 6 months of treatment [50]. However, there has been no significant difference in remission rates at 2 years between individuals treated for longer than 18 months compared with those treated for 18 months [50]. A systematic review indicated that the optimal duration of a titration regimen was 12 to 18 months [138]. The AACE and the American Thyroid Association recommend methimazole be continued for 12 to 18 months, at which point it should be tapered and discontinued if the TSH level is normal [115]. If disease is not in remission after 12 to 18 months, thyroidectomy or $^{131}$I should be considered; low-dose methimazole is recommended if these options are refused or contraindicated.

Hyperthyroidism will recur after antithyroid drug therapy in approximately 30% to 60% of individuals [50; 130]. Studies have suggested that recurrence after antithyroid drug therapy is associated with several factors, including [50; 127; 135]:

- Severe hyperthyroidism
- Long duration of symptoms before initiation of treatment
- Age younger than 40 years
- Male gender
- Family history of autoimmune thyroid disease
- History of cigarette smoking
- Presence of clinical ophthalmopathy
- High serum T3 and T4 concentrations
- Large goiter at diagnosis and/or at end of therapy

However, the association between recurrence and any of these individual factors has not been strong enough to warrant use as a risk stratification factor [127]. Thyroid function tests should continue for 6 to 12 months (at 1- to 3-month intervals) to diagnose relapse early; patients should be vigilant about recognizing the signs of hyperthyroidism [115]. Another course of antithyroid drug therapy, treatment with radioactive iodine, or surgery can be used to treat recurrent hyperthyroidism [130].

Side effects occur in approximately 5% of individuals receiving antithyroid drugs [130]. The most common side effects are rash, arthralgia, gastrointestinal problems, and changes in taste/smell [130]. The most serious side effect, occurring in about 0.1% to 0.3% of individuals, is agranulocytosis [50]. The risk of agranulocytosis increases with higher drug doses and with age and can occur at any time during the course of treatment [50; 137].

### *Thyroidectomy*

Surgery was once frequently used to treat hyperthyroidism, but it is now the least-used treatment option. The AACE and the American Thyroid Association recommend that the specific indications for thyroidectomy are a large goiter, especially with compressive symptoms (which may be resistant to radioactive iodine treatment); severe ophthalmopathy (because of the risks associated with radioactive iodine); or an allergy or intolerance to antithyroid drugs [115]. The primary advantage of thyroidectomy is that it provides definitive treatment of hyperthyroidism with none of the hazards associated with radioactive iodine, the other option with a good cure rate [127; 138]. In addition, surgery offers a rapid normalization of thyroid function [127]. Thyroidectomy usually results in hypothyroidism, occurring in 12% to 80% of individuals during the first year and at a subsequent annual rate of 1% to 3% [127].

Thyroidectomy is associated with a low rate of complications and a mortality rate of nearly zero [50; 115; 127]. This is particularly true if the surgery is performed by a high-volume thyroid surgeon [115]. Total thyroidectomy is recommended over subtotal thyroidectomy because it has been associated with similar complication rates but better cure rates (near 0% recurrence versus 8% recurrence at 5 years, respectively) [115; 139].

### *Treatment of Subclinical Hyperthyroidism*

There is no consensus on whether subclinical hyperthyroidism should be treated. Treatment is generally unnecessary in younger individuals, but the AACE and the American Thyroid Association recommend that individuals 65 years of age or older with a TSH level persistently less than 0.1 mU/L should be strongly considered for treatment or treated using the same principles as outlined for overt hyperthyroidism [115].

### *Treatment During Pregnancy*

As with hypothyroidism, hyperthyroidism can have serious adverse effects during pregnancy, and the goal of treatment is to maintain a euthyroid state with the lowest possible dose of an antithyroid drug. In general, propylthiouracil has been the preferred drug because it crosses the placenta less than methimazole and because methimazole has caused rare cases of embryopathy (including aplasia cutis) [115; 136]. Propylthiouracil is considered more appropriate during the first trimester, even

given the FDA warning regarding liver damage [136]. Methimazole should be used when antithyroid treatment is started after the first trimester [115; 141]. Pregnant women with Graves' disease should be followed up at intervals of 3 to 4 weeks (or more frequently, if necessary); pregnancy has an ameliorative effect on hyperthyroidism, and it may be possible to lower the dose of the antithyroid drug or to discontinue its use in the third trimester [115; 141]. The lowest possible dose should be used to keep total T4 and T3 levels slightly above the normal range [115]. Women treated for hyperthyroidism during pregnancy should be re-evaluated at 6 weeks postpartum, as disease can worsen at that time [115; 141].


The Endocrine Society asserts that subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if 1) a patient has a severe adverse reaction to antithyroid drug therapy, 2) persistently high doses of antithyroid drug are required, or 3) a patient is nonadherent to antithyroid drug therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester.

(http://www.guideline.gov/content.aspx?id=39246. Last accessed July 29, 2014.)

**Strength of Recommendation/Level of Evidence**: C (At least fair evidence that the service can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation)

### *Treatment of Ophthalmopathy*

The primary problems caused by Graves' ophthalmopathy are dryness, redness, and edema. The AACE and the American Thyroid Association recommend that the overall evaluation and management of the condition is best done in a multidisciplinary clinic combining endocrinologists and ophthalmologists with experience treating Graves' ophthalmopathy [115]. Many nonpharmacologic measures for symptoms related to mild Graves' ophthalmopathy, including artificial tears for lubrication, sunglasses to decrease photophobia, eye protectors during sleep, and elevation of the head of the bed to decrease periorbital edema, have been recommended Other interventions include a diuretic at bedtime, application of cool compresses to the eyes, increased fluid intake, and avoidance of secondhand smoke, ceiling fans, and contact lenses. Treatment may include glucocorticoids, retro-orbital radiation, or surgery.

### *Treatment of Thyroid Storm*

A complication of Graves' disease is thyroid storm, a syndrome characterized by exaggerated signs and symptoms of hyperthyroidism accompanied by fever and altered mental status. Thyroid storm is most often precipitated by a concurrent illness or injury and may also occur following discontinuation of treatment with antithyroid drugs or with radioactive iodine [115; 142]. The diagnosis of thyroid storm relies on clinical evaluation, as laboratory testing cannot distinguish thyroid storm from uncomplicated hyperthyroidism [115]. Thyroid storm is a complex, life-threatening syndrome, and an endocrinologist should be involved in the care. Individuals with thyroid storm should be treated in the intensive care unit, with treatment consisting of an antithyroid drug, a drug that inhibits release of thyroid hormone from the thyroid gland, and agents that decrease the peripheral effects of thyroid hormone [115; 142].

## FOLLOW-UP AND PROGNOSIS

The AACE and the American Thyroid Association recommend annual follow-up visits for patients with either Hashimoto's or Graves' disease, after a stable TSH level has been achieved [115]. Both organizations recommend that a TSH level be determined at least annually [115]. This monitoring is important, as studies have shown that as many as 40% of individuals taking thyroid medication do not have a TSH level within the normal range [12; 13]. Clinicians should also ask direct questions about compliance with drug therapy.

| POINTS OF EMPHASIS IN PATIENT EDUCATION FOR AUTOIMMUNE THYROID DISEAES TREATMENTS | |
|---|---|
| **Treatment** | **Education Points** |
| **Hashimoto's Disease** | |
| Levothyroxine | Take drug:<br>• At same time every day<br>• With full glass of water<br>• When stomach is empty<br>Avoid the use of antacids. |
| **Graves' Disease** | |
| Radioactive iodine | Abstain from close personal contact for 1 week after treatment (2 weeks for children and pregnant women).<br>Avoid pregnancy for 4 to 6 months after treatment. |
| Antithyroid drugs | Recognize signs and symptoms of agranulocytosis (fever, sore throat, mouth ulcers), and stop taking drug if they occur. |
| *Source: [50; 108; 113]* | *Table 5* |

Routine follow-up visits provide healthcare professionals with the opportunity to evaluate patients for signs or symptoms of other autoimmune diseases, especially those that have been reported to be associated with thyroiditis, such as rheumatoid arthritis, systemic lupus, pernicious anemia, vitiligo, and fibromyalgia [111; 112]. In addition, because of the strong association between thyroiditis and type 1 diabetes, the patient should be evaluated closely for signs of this disease [4; 38; 112].

For patients with Hashimoto's disease, clinicians should carefully examine the thyroid during follow-up visits, as lymphoma of the thyroid is a serious, yet rare, complication [107]. The FDA recommends that patients taking propylthiouracil for Graves' disease be closely monitored for signs and symptoms of liver injury, especially within the first 6 months after the start of treatment [136]. Individuals with subclinical hypothyroidism should be followed up annually to determine if there are clinical or biochemical signs of loss of thyroid function, indicating progression to overt hypothyroidism [108; 113].

The prognosis for individuals with autoimmune thyroid disease is good, and associated mortality for either autoimmune thyroid disease is low [27]. Remission and mortality vary according to treatment, as discussed.

## PATIENT EDUCATION

A member of the healthcare team should explain the particular type of thyroid disease to the patient, focusing on how the patient can participate in his or her own care. Patient education should emphasize the importance of adhering to drug therapy and the recognition of signs and symptoms of complications (***Table 5***) [108; 113; 138]. For example, women should understand the increased risk of birth-related events associated with autoimmune thyroid disease [113]. In addition, clinicians should highlight the need for patients to report any changes in symptoms or the occurrence of new symptoms, which may indicate the response to therapy or the development of another autoimmune disease. Clinicians should also refer patients to reliable online educational resources (***Table 6***).

| ONLINE PATIENT EDUCATION RESOURCES | |
|---|---|
| **Resource** | **Disease/Condition** |
| American Association of Clinical Endocrinologists (https://www.aace.com) | Hashimoto's disease, Graves' disease |
| American Autoimmune Related Diseases Association, Inc. (http://www.aarda.org) | All autoimmune diseases |
| American College of Rheumatology (http://www.rheumatology.org) | Rheumatoid arthritis, systemic lupus, fibromyalgia |
| American Dietetic Association (http://www.eatright.org) | Celiac disease |
| American Fibromyalgia Syndrome Association, Inc. (http://www.afsafund.org) | Fibromyalgia |
| American Gastroenterological Association (http://www.gastro.org) | Celiac disease |
| American Thyroid Association (http://www.thyroid.org) | Hashimoto's disease, Graves' disease |
| Arthritis Foundation (http://www.arthritis.org) | Rheumatoid arthritis, systemic lupus, Sjögren syndrome, fibromyalgia |
| Celiac Disease Foundation (http://www.celiac.org) | Celiac disease |
| Celiac Sprue Association (http://www.csaceliacs.org) | Celiac disease |
| Fibromyalgia Network (http://www.fmnetnews.com) | Fibromyalgia |
| Graves' Disease Foundation (http://www.ngdf.org) | Graves' disease |
| Know Fibro (http://www.knowfibro.com) | Fibromyalgia |
| Lupus Alliance of America (http://www.lupusalliance.org) | Systemic lupus |
| Lupus Foundation of America, Inc. (http://www.lupus.org) | Systemic lupus |
| Lupus Research Institute (http://www.LupusResearchInstitute.org) | Systemic lupus |
| National Fibromyalgia Association (http://www.fmaware.org) | Fibromyalgia |
| National Fibromyalgia Partnership, Inc. (http://www.fmpartnership.org) | Fibromyalgia |
| National Institute of Arthritis and Musculoskeletal and Skin Diseases (http://www.niams.nih.gov) | Rheumatoid arthritis, systemic lupus, Sjögren syndrome, fibromyalgia |
| National Institute of Diabetes and Digestive and Kidney Diseases (http://www2.niddk.nih.gov) | Celiac disease |
| National Women's Health Information Center (http://www.womenshealth.gov) | Autoimmune diseases, thyroiditis, systemic lupus, fibromyalgia |
| Sjögren's Syndrome Foundation (http://www.sjogrens.org) | Sjögren syndrome |

*Source: Compiled by Author* *Table 6*

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic disease characterized by inflammation of synovial tissue that can lead to long-term damage of the joint, resulting in chronic pain, loss of function, and disability. A cytokine network, which includes tumor-necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, has an integral role in the development of the inflammatory response [48]. The disease is also associated with several extra-articular manifestations and comorbidities [143; 144]. The course and severity of the illness vary considerably, and the disease tends to progress over time, with the occurrence of intermittent disease flares.

Most mortality studies in patients with rheumatoid arthritis have found increased death rates compared with the general population, with research indicating one-third to one-half of the premature deaths in patients with rheumatoid arthritis are due to cardiovascular conditions such as ischemic heart disease and cerebrovascular accidents [149; 367]. It is unclear whether cardiovascular disease results from rheumatoid arthritis or if it precedes the onset [148].

### EPIDEMIOLOGY

An estimated 1.5 million American adults are affected by rheumatoid arthritis [145]. The yearly incidence of rheumatoid arthritis is approximately 53 per 100,000 for women and about half that (27.7 per 100,000) for men [145]. These figures vary significantly based on the age of the cohort. The data show that the incidence of rheumatoid arthritis increases steadily with age in both sexes, until approximately 65 to 74 years of age, when incidence peaks [145]. However, the incidence is much higher for women in all age groups compared with men.

In most cases, updated statistics and costs related to rheumatoid arthritis are included as part of the larger category of related arthritic or rheumatic conditions. There were 21.8 million office visits for primary rheumatic conditions in 2010, totaling nearly 2.2% of all ambulatory care visits that year (2.4% for women, 1.9% for men) [146]. An older report estimated 2.9 million annual ambulatory care visits in the United States attributable to rheumatoid arthritis alone [147]. An estimated 23% (52.5 million) of adults in the United States reported having doctor-diagnosed arthritis between 2010 and 2012, and 50% of adults 65 years of age or older reported an arthritis diagnosis (i.e., some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia) [148]. By 2030, an estimated 67 million Americans 18 years of age or older are projected to have diagnosed arthritis [148].

Overall, rheumatoid arthritis and related arthritic diseases have a significant impact in the United States, causing disability and premature mortality. Although many people with rheumatoid arthritis work full-time, about 10% of those with rheumatoid arthritis become severely disabled and unable to do simple daily living tasks. Many report significant limitations in vital activities such as walking, stooping/bending/kneeling, climbing stairs, and social activities [149]. Rheumatoid arthritis can shorten a patient's life expectancy by an average of 3 to 7 years. However, individuals with severe forms of rheumatoid arthritis may die 10 to 15 years earlier than expected [149]. It has been found that people with rheumatoid arthritis are 2.3 times as likely to die as other people of the same age [148].

There are significant costs associated with rheumatoid arthritis, and these arthritic-related disease costs continue to increase. In 2003 (the year with the most recently available data), the total cost attributed to arthritis and other rheumatic conditions in the United States was $128 billion, up from $86.2 billion in 1997 [147; 150]. Medical expenditures (direct costs) for arthritis and other rheumatic conditions in 2003 were $80.8 billion, up from $51.1 billion in 1997 [150]. Earnings losses (indirect costs) for arthritis and other rheumatic conditions in 2003 were $47 billion, up from $35.1 billion in 1997 [160]. Individuals with rheumatoid arthritis are far more likely to change occupation, reduce work hours, lose their job, retire early, and be unable to find a job compared with people without arthritis [148].

## POTENTIAL ENVIRONMENTAL RISK FACTORS

Environmental factors that have been linked to rheumatoid arthritis include infection, smoking, and stress/depression. Among the infectious microorganisms thought to be associated with rheumatoid arthritis are Epstein-Barr virus, *Mycobacterium tuberculosis*, *Escherichia coli*, *Proteus mirabilis*, retroviruses, parvovirus B19, and hepatitis C virus [3]. Approximately 8% to 15% of individuals have reported the onset of rheumatoid arthritis-related symptoms within a few days after an infectious illness [151].

Smoking has also been identified as a significant risk factor for the development of rheumatoid arthritis, and greater smoking intensity (number of cigarettes per day) and longer smoking history further increase the risk [152]. The risk remains increased for at least 20 years after smoking cessation [152]. Research indicates that the risk of developing rheumatoid arthritis is nearly double for current smokers compared with nonsmokers [368].

Psychologic stress has been thought to play a role in the pathogenesis of rheumatoid arthritis by triggering the inflammatory process and exacerbating disease activity [47; 48]. Rheumatoid arthritis is also strongly associated with major depression (attributable risk of 18.1%), probably through its role in creating functional limitation [366].

In addition, because evidence of rheumatoid arthritis-associated antibodies has often been found many years before the onset of clinical symptoms, early environmental factors have been thought to be a contributor to the disease [153]. High birth weight and early breastfeeding cessation are two such early factors [153].

## ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

As noted, autoimmune diseases of connective tissue are more likely to be associated with other autoimmune diseases [69]. Studies have shown that the coexistence of rheumatoid arthritis, thyroiditis, and type 1 diabetes is high [4; 111]. In addition, features of systemic lupus are common in individuals with rheumatoid arthritis; in one study, four or more lupus features were found in approximately 16% of individuals with rheumatoid arthritis within 25 years after diagnosis [154]. This finding is significant because the co-occurrence of systemic lupus features and rheumatoid arthritis was associated with increased overall mortality [154].

As many as 25% of individuals with rheumatoid arthritis also have Sjögren syndrome, and the risk of rheumatoid arthritis appears to be higher in individuals who have inflammatory bowel disease [4; 67; 144]. An inverse relationship between rheumatoid arthritis and multiple sclerosis has been reported [4]. Fibromyalgia is also commonly found in association with rheumatoid arthritis, with reported rates ranging from 17% to 57% [17; 155].

## CLINICAL MANIFESTATIONS

Pain and stiffness in multiple joints are the primary characteristics of rheumatoid arthritis; approximately one-third of individuals with the disease initially have pain in only one joint [156]. Other common symptoms of rheumatoid arthritis include fatigue, weakness, generalized muscular aches, and anorexia [151]. Approximately 46% of individuals with rheumatoid arthritis have extra-articular manifestations, the most common of which is rheumatoid nodules, followed by pulmonary fibrosis, dry eye syndrome, and anemia of chronic disease [143; 144; 151]. Rheumatoid nodules are soft, poorly delineated subcutaneous nodules, and they also occasionally affect internal organs such as the pleura, sclera, vocal cords, and vertebral bodies [143; 151]. Other frequently occurring extra-articular manifestations include pericarditis, pleuritis, vasculitis, cervical myelopathy, and neuropathy [143]. No reliable predictors of extra-articular manifestations have been identified, but they have been reported to be associated with male gender, smoking, more severe joint disease, worse function, high levels of inflammatory markers, and a positive rheumatoid factor and antinuclear antibody (ANA) titer [144].

## DIAGNOSTIC EVALUATION

When evaluating a patient for suspected rheumatoid arthritis, healthcare professionals should focus both the history and the physical examination on the joints. Questions about symptoms related to the joint should help determine which joints are involved, when joint pain occurs (e.g., during activity, at rest), how long pain and stiffness last, and how pain limits function.

The most commonly involved joints are the wrist joints and the proximal interphalangeal and metacarpophalangeal joints; the distal interphalangeal joints and sacroiliac joints are typically not affected [156]. Affected joints may become warm and tender after long periods of inactivity, and joint symptoms are usually bilateral. Small joints of the hands and feet are not usually painful at rest. Morning joint stiffness associated with rheumatoid arthritis usually lasts more than 1 hour, in contrast to osteoarthritis, in which morning stiffness usually resolves within 30 minutes after waking [157]. For most individuals, symptoms develop over a long period of time (weeks to months); symptoms develop over days to weeks in approximately 15% of patients [156].

The findings on physical examination are usually normal, except for an occasional low-grade fever. The involved joint(s) may feel warm and boggy and may be tender to the touch, but there is usually no accompanying erythema [156]. Affected joints have limitations in the range of motion, and the strength of muscles near affected joints is usually decreased. The patient may keep an affected joint in flexion to avoid pain related to extension. Lymph nodes in the epitrochlear, axillary, and cervical regions may be enlarged. Rheumatoid nodules are often found in pressure areas (e.g., the elbows and finger joints) and the extensor surface of the forearm [151].

### Diagnostic Criteria

In 1988, the American Rheumatism Association (now known as the American College of Rheumatology [ACR]) published its Criteria for the Classification of Rheumatoid Arthritis, and these criteria remained the standard for several years [158]. However, the criteria were criticized for a lack of sensitivity to early disease. In 2010, the ACR and the European League Against Rheumatism (EULAR) collaborated on a new classification system that focuses on features of earlier stages of rheumatoid arthritis that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features [159]. The impetus for this change in focus was the need for earlier diagnosis in order to begin disease-modifying drugs as soon as possible [159].

The new classification criteria apply only to newly presenting individuals, and two requirements must first be met: there must be evidence of currently active clinical synovitis (i.e., swelling) in at least one joint as determined by an expert assessor, and the synovitis must not be better explained by another diagnosis [159]. The ACR/EULAR note that all joints may be assessed, except for the distal interphalangeal joints, the first metatarsophalangeal joint, and the first carpometacarpal joint, as these are most often involved in osteoarthritis [159]. Individuals who are eligible according to the first two criteria are then evaluated by four additional criteria related to joint involvement, serologic testing, acute-phase reactants, and duration of symptoms (***Table 7***) [159]. The classification system includes a scoring system, with a possible total of 10 points; a score of 6 or more indicates "definite" rheumatoid arthritis. Although a person with a score of less than 6 does not have definite rheumatoid arthritis, the score may increase on subsequent testing.

| 2010 ACR/EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS[a] | | |
|---|---|---|
| **Category** | **Criteria** | **Score** |
| Joint involvement | 1 large joint (shoulder, elbow, hip, knee, ankle) | 0 |
| | 2 to 10 large joints | 1 |
| | 1 to 3 small joints (MCP, PIP, second to fifth MTP, thumb IP joints), with or without involvement of large joints | 2 |
| | 4 to 10 small joints, with or without involvement of large joints | 3 |
| | >10 joints (at least 1 small joint and any combination of any other joints) | 5 |
| Serology (at least 1 test result is needed for classification) | Negative RF and ACPA | 0 |
| | Low-positive RF or low-positive ACPA | 2 |
| | High-positive RF or high-positive ACPA | 3 |
| Acute-phase reactants (at least 1 test result is needed for classification) | Normal CRP and normal ESR | 0 |
| | Abnormal CRP or abnormal ESR | 1 |
| Duration of symptoms | <6 weeks | 0 |
| | ≥6 weeks | 1 |

[a]See text for initial criteria and descriptions of criteria.
ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IP = interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor.

*Source: [159] Reprinted with permission, from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580-1588.* *Table 7*

The ACR/EULAR recommended serologic testing involves a rheumatoid factor and an anti-citrullinated protein antibody (ACPA) [159]. A positive rheumatoid factor has long been known as an indicator of rheumatoid arthritis, and studies have shown that this test is positive in approximately 69% to 90% of people with the disease [160; 161]. However, the test may be positive in healthy individuals as well as in individuals with other rheumatic diseases (e.g., Sjögren syndrome, systemic sclerosis, systemic lupus), with chronic infections, or with pulmonary disease [160]. The false-positive rate of rheumatoid factor for rheumatoid arthritis has been reported to be 15% [161]. As a result, the sensitivity and specificity of the test are 69% and 85%, respectively [161]. Testing for ACPA began in the late 1990s, and although the sensitivity of the test (67%) is similar to that of the rheumatoid factor, its false-positive rate is lower, yielding a specificity of 95% [161]. According to the ACR/EULAR classification scoring system, the highest score is given if the results of either the rheumatoid factor or the ACPA test is highly positive, and no points are given if both tests are negative [159]. An ANA titer has a reported sensitivity of about 40% among individuals with rheumatoid arthritis, and false-positive results are common [160]. The ANA titer is not part of either the 1988 or 2010 diagnostic criteria [158; 159].

Other recommended baseline laboratory testing includes a complete blood cell count (CBC) with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) [8; 162]. However, the ESR and CRP results should be interpreted with caution, as the tests are normal in about 40% of people with rheumatoid arthritis [163]. Baseline renal and hepatic functioning should also be determined, not because these tests are sensitive or specific for rheumatoid arthritis but because they are important in guiding the choice of medications [162].

Radiographic evaluation has been recommended as part of the diagnostic work-up for rheumatoid arthritis, but the findings on conventional radiographs of involved joints are often normal, especially in early-stage disease [8]. The findings on imaging studies are not part of the 2010 classification criteria for rheumatoid arthritis [159]. However, imaging studies may be helpful in the differential diagnosis and in establishing baseline images for comparison during follow-up. An analysis of 11 studies of magnetic resonance imaging (MRI) as a diagnostic tool showed a wide range in sensitivity and specificity, with the authors concluding that the data are inadequate to justify widespread use of MRI in the diagnosis of rheumatoid arthritis [164].

### Differential Diagnosis

A wide range of medical conditions should be considered in the differential diagnosis of rheumatoid arthritis, including [151; 156; 165]:

- Connective tissue diseases (e.g., systemic lupus, systemic sclerosis)
- Psoriatic arthritis, gout, and other forms of arthritis
- Fibromyalgia
- Polymyalgia rheumatica
- Thyroid disease
- Sarcoidosis
- Hemochromatosis
- Still's disease
- Viral arthritis
- Paraneoplastic syndrome (when onset is after 55 years of age)

Overlapping signs and symptoms can make it challenging to distinguish rheumatoid arthritis from many of these conditions, especially connective tissue diseases and other forms of arthritis. A positive ANA titer may help distinguish systemic lupus from rheumatoid arthritis, and determination of a TSH level can aid in a diagnosis of hypothyroidism [156; 160]. Early in the course of rheumatoid arthritis, self-limited viral syndromes should be considered, especially hepatitis B and C, parvovirus, rubella (infection or vaccination), and Epstein-Barr virus [3].

## TREATMENT OPTIONS

The primary goal of treatment for rheumatoid arthritis was once to alleviate symptoms using a pyramid approach, but the advent of disease-modifying drugs as a standard of care has shifted the focus to early remission and/or the prevention of further joint damage using a treat-to-target approach [166; 371]. This approach is a tightly controlled, aggressive strategy tailored to each patient, with modifications to the individual medication regimen to achieve a particular target (remission, or alternatively, low disease activity) in a specific period of time (usually 6 months) [166]. Treatment goals are to preserve the structural integrity of the joint, enhance function and quality of life, minimize pain and inflammation, and control systemic complications [9; 156]. These goals are achieved through a combination of disease-modifying drugs, anti-inflammatory agents, and nonpharmacologic measures. Surgery is sometimes needed when medical treatment options fail. In addition, treatment of complications or comorbidities associated with rheumatoid arthritis is often needed.

Several guidelines for the treatment of rheumatoid arthritis exist. In 2016, the ACR published updated guidelines on the use of disease-modifying antirheumatic drugs and biologic agents and emphasizes the use of the treat-to-target approach [9]. The EULAR has developed guidelines for the management of early rheumatoid arthritis and for the use of disease-modifying drugs (updated in 2013) [162; 166].

A 2012 meta-analysis of four studies comparing tight control with usual care found that applying a treat-to-(any)target approach approximately doubled remission rates in patients with early rheumatoid arthritis with high disease activity [371]. One small-scale study comparing early aggressive treatment (i.e., methotrexate) with usual care (i.e., using milder drugs initially, with intensification of treatment as needed) found that there was

approximately 50% remission in each group at the study endpoint (2 years) [374]. However, during the course of the study, 23 of 24 patients in the conventional care group had progressed to aggressive treatment (with methotrexate) and most were given intra-articular corticosteroids much more frequently than those in the tight control group. It is interesting to note that the aggressive treatment (methotrexate) is not considered aggressive by today's standards, as treatment with adalimumab was started only in patients who had poor response 6 months after initiation of treatment. Progression of joint damage (i.e., lack of radiographic remission) occurred among a minority of participants even in the aggressive treatment group who were considered to have clinical remission (based on assessment scores); on average, radiographic and functional scores were similar in both groups at the end of the study [374]. The authors emphasize that their results do not indicate an advantage of one treatment strategy over another; instead factors such as patient preference and risk versus benefit (e.g., weighing the severe side effects of the stronger disease-modifying antirheumatic drugs [DMARDs] against their rapid response) should guide the treatment decision [374]. In addition, the measures of remission are ill defined, and to progress from low disease activity (which may be a satisfactory target) to clinically defined remission may require a medication regimen greater than what is safe or tolerable. Most clinicians in the study were unwilling to push for remission if their patient's disease was reduced to an acceptable level with conservative treatment.

### Disease-Modifying Antirheumatic Drugs

Early treatment is essential to achieving optimal outcomes with disease-modifying drugs, and the EULAR guideline recommends that treatment with disease-modifying drugs begin immediately following the diagnosis [166]. DMARDs are antimetabolite/cytotoxic agents, and several nonbiologic and biologic disease-modifying drugs are now available, allowing clinicians and patients to select a specific drug after considering several factors. In its recommendations for the use of disease-modifying drugs, the ACR discussed the use of 13 drugs (five nonbiologic and eight biologic agents) and noted that other drugs were not included because they were used infrequently, were associated with a high incidence of adverse events, or were not recommended for other reasons (***Table 8***) [9; 167]. For example, anakinra, an IL-1 antagonist, has been found to be less effective than the other biologic agents and so was omitted from the review of the literature informing the guidelines [167; 168]. Since the publication of the guidelines, an additional nonbiologic agent (tofacitinib) has received FDA approval for the treatment of rheumatoid arthritis [356; 369].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In people with newly diagnosed active rheumatoid arthritis, the National Collaborating Centre for Chronic Conditions recommends offering a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.

(http://www.guideline.gov/content.aspx?id=14310. Last accessed July 29, 2014.)

**Level of Evidence**: Expert Opinion/Consensus Statement

Among the recommended nonbiologic agents are methotrexate, generally considered to be the standard first-line treatment; the antimalarial drug hydroxychloroquine; the Janus kinase inhibitor tofacitinib; and sulfasalazine and leflunomide, drugs developed specifically for rheumatoid arthritis [9]. The biologic agents include five anti-TNF-α agents (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and three non-TNF-α agents, including abatacept, a selective costimulation modulator; rituximab, an anti-CD20 monoclonal antibody that depletes B lymphocytes; and tocilizumab, an IL-6 receptor antagonist [9].

**RECOMMENDED DISEASE-MODIFYING ANTIRHEUMATIC DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION FOR THE TREATMENT OF RHEUMATOID ARTHRITIS**

| Agent | Indication[a] | Dose and Administration | Most Common Adverse Effects |
|---|---|---|---|
| **Nonbiologic Agents** | | | |
| Methotrexate | Any disease duration, any degree of disease activity, with or without poor prognosis features | 12–25 mg PO, IM, or SC weekly | Nausea, diarrhea, fatigue, mouth ulcers, rash, alopecia |
| Leflunomide | Any disease duration, any degree of disease activity, with or without poor prognosis features | 100 mg PO daily for 3 days, then 10–20 mg PO daily | Nausea, diarrhea, rash, alopecia; highly teratogenic, even after use is discontinued |
| Hydroxychloroquine | Short or intermediate disease duration, low disease activity, no poor prognosis features | 200–400 mg PO daily | Nausea, headache, possible retinopathy |
| Sulfasalazine | Any disease duration, any degree of disease activity, no poor prognosis features | 2–3 g PO daily (in divided doses) | Nausea, diarrhea, headache, mouth ulcers, rash, alopecia, oligospermia (reversible) |
| Tofacitinib | Moderately to severely active disease despite treatment with methotrexate or intolerance of methotrexate | 5 mg daily | Infections, headache, diarrhea |
| **Biologic Agents** | | | |
| Anti-tumor necrosis factor-α agents (adalimumab, etanercept, infliximab) | In combination with methotrexate: Disease duration of less than 3 months, high disease activity, features of poor prognosis, and no previous treatment with disease-modifying drugs<br>Alone: Inadequate response to methotrexate monotherapy AND disease duration >3 months, moderate disease activity, and poor prognosis features OR disease duration >3 months, high disease activity, with or without poor prognosis features | Adalimumab: 40 mg SC every 2 weeks<br>Etanercept: 25 mg SC twice weekly or 50 mg SC weekly<br>Infliximab: 3 mg/kg IV at weeks 0, 2, and 6, then every 8 weeks | Infusion reactions, increased risk of infection (especially fungal) |
| Golimumab (anti-tumor necrosis factor-α) | In combination with methotrexate: moderate-to-severe disease | 50 mg SC monthly | Serious infections, upper respiratory infection, nasopharyngitis |
| Abatacept | Inadequate response to methotrexate-based combination or sequential administration of other nonbiologic agents, moderate-to-high disease activity, and features of poor prognosis | 500–1,000 mg (depending on body weight) IV at weeks 0, 2, and 4, then every 4 weeks | Headache, nasopharyngitis, dizziness, urinary tract infection, bronchitis |
| Rituximab | In combination with methotrexate: Inadequate response to methotrexate-based combination or sequential administration of other nonbiologic agents, high disease activity, and features of poor prognosis | 1,000 mg IV at week. 0 and 2, then every 24 weeks | Upper respiratory infection, bronchitis, nasopharyngitis, urinary tract infection |
| Tocilizumab | Alone or in combination with methotrexate: Moderate-to-severe disease refractory to 1 or more anti-tumor necrosis factor-α agents | 4–8 mg/kg IV monthly | Serious infection, upper respiratory infection, nasopharyngitis, headache, hypertension |

[a]Disease duration defined as short (less than 6 months), intermediate (6 to 24 months), or long (more than 24 months). Degree of disease activity is defined according to scores on one of several validated disease activity instruments; presence of poor prognosis features is defined as functional limitation, extra-articular disease, positive rheumatoid factor and/or positive anti-citrullinated protein antibody test, and/or osseous erosions on radiograph.

*Source: [9; 20; 356; 369]* *Table 8*

Methotrexate is the most commonly prescribed DMARD and is still considered the so-called anchor drug for the treatment of rheumatoid arthritis [9; 166]. It can be given alone or in combination with one or two other nonbiologic agents. Leflunomide, a competitive inhibitor of an intracellular enzyme needed for de novo pyrimidine synthesis, is a newer DMARD with comparable efficacy that can be substituted for methotrexate and may be particularly useful for patients with intolerance of or contraindications to methotrexate [156; 372; 373]. Patients for whom monotherapy with methotrexate has failed may benefit from the addition of leflunomide, either with methotrexate or other DMARDs [373].

The ACR recommends basing the decision regarding initial treatment with a DMARD on the duration of disease (early or established) and degree of disease activity (low, moderate, or high) [9]. Previous guidelines had also considered prognosis, but this is now considered encompassed by disease activity. Additional factors to consider when choosing a drug are side effect profiles, cost, and access to care.

The treat-to-target approach for patients with early high disease activity typically involves initiation of methotrexate and/or another DMARD(s) immediately upon diagnosis [9; 166; 371]. Initial combination therapies with DMARDs, particularly those including a biologic anti-TNF-α agent, appear to provide earlier clinical improvement and less joint damage progression in patients with early highly active disease. These therapies can be withdrawn successfully, and fewer treatment adjustments are needed than with initial monotherapies [9; 25; 166; 375; 376]. Patients with active disease are monitored closely (every 1 to 3 months), and it is recommended that treatment adjustments be made if there is no improvement at 3 months (or if the 6 month target has not been reached) [9; 166]. For patients with low-to-moderate disease activity or high disease activity without poor prognostic features, DMARD monotherapy is usually given initially.

As discussed, comparative studies of methotrexate, leflunomide, and sulfasalazine have provided no evidence that points to the benefit of one of these drugs over the others; similarly, evidence suggests similar benefit among biologic agents [167; 170; 171; 374]. In addition, a combination of nonbiologic drugs, methotrexate, and a biologic drug have led to better clinical response rates and functional outcomes than either methotrexate or a biologic agent alone, especially in early active disease [170; 172]. However, one systematic review showed no significant advantage of a methotrexate-based combination compared with methotrexate monotherapy among patients receiving initial treatment with a disease-modifying drug [173]. That review did show significant reductions in pain and improvement in physical function for methotrexate-based combinations among patients in whom disease had not responded to methotrexate monotherapy [173].

Several precautions should be taken before beginning treatment with a disease-modifying drug. The ACR recommends determining baseline CBC, liver function studies, and creatinine level before beginning or resuming treatment with any of the drugs; these laboratory tests should also be done after any significant increase in dose [9]. Individuals receiving methotrexate or leflunomide should also be tested for hepatitis B or C infection. If an individual's vaccinations are not current, influenza vaccine should be administered before treatment with a nonbiologic agent is begun, and pneumococcal vaccine should also be given before treatment with DMARDs. Both vaccinations are recommended before treatment with a biologic agent begins [9]. Routine tuberculosis screening should also be done to identify latent tuberculosis infection in individuals who are being considered for therapy with a biologic agent or tofacitinib.

In previous guidelines, acute hepatitis B or C infection was considered a contraindication for most DMARDs and biologic agents. However, in its 2016 update, the ACR recommended that patients with active hepatitis B or C who are receiving effective antiviral treatment may be managed the same as patients without hepatitis [9]. Certain medications may be preferred for other high-risk conditions, including congestive heart failure, treated or untreated malignancy, and serious infection [9].

**Anti-Inflammatory Medications**

Anti-inflammatory medications are used to reduce joint pain and swelling associated with rheumatoid arthritis. Because these drugs do not change the course of disease, they must be used in conjunction with a disease-modifying drug. Treatment typically begins with a nonselective nonsteroidal anti-inflammatory drug (NSAID); a cyclooxygenase-2 (COX-2)-selective inhibitor and/or glucocorticoids may also be used. A gastroprotective agent (proton-pump inhibitor) should be prescribed with an NSAID for individuals at high risk for gastrointestinal complications [176].

There is good evidence that nonselective NSAIDs and COX-2 inhibitors have comparable efficacy and that COX-2 inhibitors are comparable to each other [177]. Although COX-2 inhibitors have better tolerability in general compared with NSAIDs, there is considerable variability across individual drugs in terms of protection against serious gastrointestinal events [177]. A large, double-blind, randomized trial involving nearly 4,500 individuals with rheumatoid arthritis or osteoarthritis demonstrated that the COX-2 inhibitor celecoxib was associated with lower risks of adverse gastrointestinal events than a nonselective NSAID plus a proton-pump inhibitor (diclofenac plus omeprazole) [178].

The adverse event profiles of both nonselective NSAIDs and COX-2 inhibitors should be considered when selecting a specific drug for an individual patient. All individuals treated with NSAIDs should be monitored for long-term complications such as gastrointestinal bleeding, cardiovascular events (e.g., myocardial infarction, stroke), and gastric ulcers and bleeding [176; 177]. The increased risk of cardiovascular events associated with some COX-2 inhibitors has been well publicized, prompting the FDA to re-evaluate the risks and benefits of the COX-2 inhibitors; special care should be taken when prescribing these drugs [177]. Although certain COX-2 inhibitors (such as celecoxib) are still available, they are labeled with strong warnings and a recommendation for prescribing the lowest possible dose for the shortest possible duration [20].

In addition to their anti-inflammatory properties, glucocorticoids may substantially reduce the rate of further joint erosion and should be considered as a temporary adjunct to treatment with disease-modifying drugs [162; 179]. However, because of the substantial risk of adverse effects, glucocorticoids should be given for the shortest time and at the smallest dose possible, and treatment should be discontinued gradually—over at least 1 month-to avoid rebound effects [8]. Administration of a glucocorticoid as an intra-articular injection may reduce swelling and inflammation in a single joint, but the clinical benefit is short term [162].

**Complementary/Alternative Medicine**

Many individuals with rheumatoid arthritis turn to complementary and alternative medicine to alleviate symptoms. The use of complementary and alternative medicine among individuals with rheumatoid arthritis has ranged from 28% to 90%, and the rates of use among all individuals vary across racial/ethnic populations [77; 180; 181].

Most herbal supplements used by individuals with rheumatoid arthritis are safe, but the evidence of their benefit has been weak to moderate [182; 183]. Despite the wide use of complementary and alternative medicine, most individuals (63% to 72%) do not report the use to their healthcare providers [96; 181]. Because of this, clinicians should ask direct questions about the use of complementary and alternative medicine approaches and initiate discussions about their use.

Aside from supplementation with several specific types of oils, the only complementary therapy currently endorsed by the U.S. Department of Health and Human Services for patients with rheumatoid arthritis is to consume a nutritious, balanced diet [377]. Some argue that the typical American diet, which is based on animal proteins (many of which are now devoid of significant levels of nutrients and/or are heavily processed) and typically consisting of high levels of animal fats (e.g., cheese, butter, ice cream) and simple carbohydrates promotes inflammation [382]. However, others argue that restricting the intake of good quality food sources of nutrients, such as fish and real cheese, can lead to dietary deficiencies. A growing body of evidence supports the belief that proper nutrition from food, or more specifically, avoidance or correction of nutritional deficiencies, can prevent the development of inflammatory disorders in genetically predisposed individuals. One group of researchers writes that "diet can affect transgenerational gene expression via 'reversible' heritable epigenetic mechanisms" [378]. It is believed that certain anti-inflammatory bioactive food components (e.g., carotenoids, organosulfurs, polyphenols, phytosterols, tocopherols, tocotrienols) can lessen the rates and negative effects of acetylation, methylation, oxidation, phosphorylation, ribosylation, SUMOylation, and ubiquitination.

One food-sourced supplement, fish oil, is a proven, powerful rheumatoid arthritis therapy and contains several bioactive components, such as the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). A 2010 meta- and mega-analysis of randomized controlled trials confirmed the efficacy of fish oil for the relief of joint pain and found a significantly reduced use of anti-inflammatory drugs in patients with long-standing rheumatoid arthritis [379]. NSAIDs can cause an increased cardiovascular risk, and reduced morbidity and mortality among participants in the research groups was also attributable to fish oil supplementation, as atherosclerosis and NSAID use are both reduced with this therapy. Past research was limited to long-standing cases of rheumatoid arthritis; it is unclear whether fish oil can prevent joint damage in recent-onset rheumatoid arthritis [379]. Though fish oil is most often studied, krill oil (from a small, shrimp-like crustacean) has also shown similarly beneficial results [380]. It should be noted that concerns over bleeding risks (e.g., hemorrhagic stroke) related to a high intake of fish oil have been shown to be unfounded [381]. However, blood thinning is a side effect, and patients should be advised to eat foods rich in vitamin K1 while taking these supplements.

**Nonpharmacologic Therapy**

Physical therapy and/or occupational therapy can help individuals improve their ability to carry out activities of daily living at home, at work, and socially [162]. In addition, physical therapists can provide instruction in a program of range-of-motion and strengthening exercises, in joint protection, and in ways to conserve energy. Evidence of benefit from nonpharmacologic approaches is lacking, however. An overview of systematic reviews found that there was unclear benefit (low quality of evidence) for most nonpharmacologic therapies, including balneotherapy, electrical stimulation, transcutaneous electrical nerve stimulation, assistive devices, and splints [183].

The exceptions were comprehensive occupational therapy and joint protection, which were shown to improve function (with no difference in pain) according to high-quality evidence, and low-level laser therapy, which was shown to reduce pain and improve function according to evidence of moderate quality [183].

Regular participation in activities such as walking or aerobic exercises is recommended, as they can help improve joint mobility, muscle strength, and aerobic fitness; decrease fatigue; and maintain psychologic well-being [8; 184]. Also, because emotional stress can exacerbate disease activity, stress management interventions should be encouraged [47; 48]. Several randomized controlled trials have indicated that significant improvements in pain management and function have resulted from cognitive-behavioral therapy that has focused on therapist-guided training in coping strategies (e.g., relaxation, goal setting, imagery, and cognitive restructuring of negative thoughts related to pain) [48].

### Surgical Procedures

Surgical procedures to treat rheumatoid arthritis are reserved for individuals who have structural joint damage that causes high pain levels, loss of range of motion, or severely limited function (severe disability and/or inability to work) despite pharmacologic and nonpharmacologic therapy [382]. The goals of surgical interventions are to restore function and quality of life, prevent further deterioration of the joint, relieve pain, and correct deformity [185]. The challenge with surgical treatment is that many joints are often involved; priority should be given to the joint that causes the greatest disability and pain [185]. Among the options for surgical treatment are synovectomy, carpal tunnel release, resection of the metatarsal heads, specialized hand surgery, arthrodesis, and joint replacement [185]. The preoperative functional status is an important factor in the postoperative outcome, making early referral for surgery important [382].

### Treatment of Extra-Articular Manifestations

The overall treatment of individuals with rheumatoid arthritis also includes treatment targeted at extra-articular manifestations [144]. Because extra-articular manifestations are associated with poor prognosis, they should be identified and managed promptly. Treatment is primarily limited to glucocorticoids [144].

## FOLLOW-UP AND PROGNOSIS

Close follow-up is needed for individuals with rheumatoid arthritis to evaluate response to treatment, ensure control of symptoms, and monitor for treatment side effects and disease-related comorbidities.

### Response to Treatment

Both the ACR and the EULAR recommend that evidence of disease activity be evaluated, through subjective and objective measures, at each follow-up visit [9; 162]. The follow-up assessment may include:

- Self-reports of degree of joint pain, duration of morning stiffness, limitation of function, and duration of fatigue
- Tender and swollen joints on physical examination
- Evidence of disease progression on physical examination (e.g., loss of motion, instability, malalignment, and/or deformity)
- Elevated ESR or CRP level
- Progression of radiographic damage of involved joints (with use of radiographic assessment scales)
- Global assessment of disease activity (by the physician and the patient)
- Standardized questionnaires to assess functional status and/or quality of life

The recommended follow-up interval is every 1 to 3 months until remission is achieved, and adjustments to the doses and/or choices of monotherapy or combination therapy with disease-modifying drugs should be made if the response is inadequate [9; 162; 166]. Treatment with DMARDs can lead to some level of remission in approximately 30% to 40% of individuals, but sustained remission is less common (17% to 20%), and most individuals will have persistent disease [151; 156; 383]. Again, achieving low disease activity with a conservative medication regimen may be a better course than seeking for clinical remission with aggressive therapy [374].

**Monitoring and Treatment of Drug Side Effects**

A systematic approach to long-term drug monitoring is necessary because of the potential for serious adverse events associated with the long-term use of DMARDs and glucocorticoids [186].

Among the side effects of long-term use of disease-modifying drugs are infection; bone marrow suppression; gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects; pulmonary toxicity; and skin reaction/rash [186]. Infusion site reactions are also commonly associated with anti-TNF-α agents [186]. It is recommended that individuals treated with leflunomide, methotrexate, or sulfasalazine have a CBC, liver function studies, and a serum creatinine at baseline and then every 2 to 4 weeks for the first 3 months after the beginning of treatment; every 8 to 12 weeks during the 3- to 6-month period, and every 12 weeks subsequently [20]. Individuals taking rituximab should have a CBC and platelet count done every 2 to 4 months, and individuals treated with tocilizumab should have neutrophils, platelets, and liver enzymes, as well as CBC, platelet count, and liver function studies, as indicated, assessed every 4 to 8 weeks [20].

Individuals receiving hydroxychloroquine are at risk for severe retinopathy, and ophthalmologic follow-up is important for early detection and minimization of toxicity [187]. The reported incidence of retinopathy associated with hydroxychloroquine is low, especially within the first 5 years of use at a low dose (less than 400 mg/day), but the potential severity calls for ophthalmologic follow-up [187; 188]. The American Academy of Ophthalmology (AAO) recommends a complete ophthalmologic examination within the first year after treatment [187]. If the results are normal, subsequent eye examinations should be performed annually after 5 years of treatment in all patients considered to be at low risk for hydroxychloroquine-related toxicity based on presence of the following factors [187]:

- Duration of use: >5 yrs
- Cumulative dose: >1000 g (total)
- Daily dose: >400 mg/day (>6.5 mg/kg ideal body weight for short individuals)
- Older age
- Kidney or liver dysfunction
- Retinal disease or maculopathy

For people at high risk for toxicity (i.e., those who are treated with higher doses of hydroxychloroquine and/or for longer than 5 years), the AAO recommends an annual eye examination [187]. Age older than 60 years, the presence of renal or hepatic disease, and obesity are also factors that increase the risk for hydroxychloroquine-related retinopathy [187]. The AAO emphasizes that these are minimum recommendations that balance cost with risk, and more frequent screening may be appropriate.

All drugs used to treat rheumatoid arthritis are associated with a high risk of conventional and opportunistic infections, and measures to prevent infection should be taken. The ACR recommends that in addition to receiving an influenza vaccination before beginning treatment with DMARDS, individuals should receive the vaccination annually thereafter [9]. In addition, a pneumococcal

| AMERICAN COLLEGE OF RHEUMATOLOGY RECOMMENDATIONS FOR USE OF BISPHOSPHONATES DURING TREATMENT WITH GLUCOCORTICOIDS FOR MEN AND POSTMENOPAUSAL WOMEN (50 YEARS OF AGE OR OLDER) | | |
|---|---|---|
| **Patient's Risk**[a] | **Dose and Duration of Glucocorticoid** | **Bisphosphonate** |
| Low | ≥7.5 mg/day prednisone for expected duration of at least 3 months | Alendronate, risedronate, or zoledronic acid |
| Medium | Any dose for expected duration of at least 3 months | Alendronate, risedronate |
| | ≥7.5 mg/day prednisone for expected duration of at least 3 months | Zoledronic acid |
| High | Any dose for any expected duration | Alendronate, risedronate, or zoledronic acid |
| | ≥5 mg/day prednisone for expected duration of 1 month or less or any dose for expected duration of more than 1 month | Teriparatide |
| [a]Ten-year risk of a major osteoporotic fracture, as defined with use of the FRAX calculator. Low risk = risk of 10% or less; medium risk = risk of 10% to 20%; high risk = risk greater than 20% or a T score ≤ –2.5 or a history of a fragility fracture. | | |
| *Source: [189]* | | *Table 9* |

vaccination should be given every 5 years [9]. All vaccines should be given based on age and risk. If hepatitis and/or human papillomavirus (HPV) risk factors are present, the hepatitis B and/or HPV vaccine should be administered. Live vaccines (e.g., herpes zoster) should be avoided only in individuals already receiving a biologic disease-modifying drug [9]. Targeted prophylaxis for individuals at high risk for infection may also be appropriate [43; 186].

The use of glucocorticoids, especially over the long term, is associated with a wide range of potential adverse events, including osteopenia/osteoporosis, hypertension, cataracts, glaucoma, dyspepsia, weight gain, avascular necrosis of bone, Cushingoid changes, and adverse psychologic effects [186]. The ACR published guidelines in 2010 for the prevention and treatment of glucocorticoid-induced osteoporosis [189]. The ACR recommends daily calcium intake (dietary plus supplement) of 1,200 to 1,500 mg and supplemental vitamin D (400 to 800 IU) to prevent osteoporosis in all individuals taking glucocorticoids [189]. The ACR guidelines also include recommendations for the use of bisphosphonates according to an individual's risk, noting that risk is best assessed with the Fracture Risk Assessment (FRAX) tool, which provides a better overall clinical risk profile than bone mineral density alone (***Table 9***) [189; 190]. In addition, baseline dual x-ray absorptiometry, height, prevalent fragility fractures, and serum 25-hydroxyvitamin D level should be obtained before the start of treatment with glucocorticoids and should be monitored throughout the course of treatment [189]. Better adherence to the ACR guidelines are needed, as one study showed that a baseline bone scan was done in only 39% of patients and appropriate treatment was also prescribed for only 39% [11].

### Prevention of Comorbidities

Other comorbidities are prevalent among people with rheumatoid arthritis, and hypertension, gastrointestinal problems, and psychiatric problems/depression are the most common current and lifetime comorbidities (***Table 10***) [191]. In addition, the association between rheumatoid arthritis and an increased risk for cardiovascular disease and events is well-documented, including its impact on mortality. Follow-up care should include patient assessment and preventive strategies for these comorbidities, as well as treatment as appropriate. Individuals with rheumatoid arthritis should also be monitored for signs and symptoms indicative of autoimmune diseases commonly found in association with rheumatoid arthritis, such as thyroiditis, type 1 diabetes, Sjögren syndrome, and inflammatory bowel disease [4; 111; 144].

| COMORBIDITIES ASSOCIATED WITH RHEUMATOID ARTHRITIS | | |
|---|---|---|
| **Comorbidity** | **Prevalence** | |
| | **Lifetime** | **Current** |
| Any gastrointestinal problem | 50% | 15% |
| Hypertension | 47% | 32% |
| Any psychiatric problem | 36% | 16% |
| Depression | 34% | 15% |
| Any endocrine problem | 30% | 20% |
| Any genitourinary problem | 30% | 4% |
| Cataract | 27% | 10% |
| Any lung problem | 25% | 12% |
| Any cardiovascular problem | 22% | 9% |
| *Source: [191]* | | *Table 10* |

**Prognosis**

Of all the autoimmune diseases, rheumatoid arthritis is a leading cause of mortality, especially among women older than 65 years of age [27; 28]. Studies have consistently shown higher rates of mortality for individuals with rheumatoid arthritis than for the general population [192; 193; 194]. Furthermore, the increasing survival rates documented for the population at large since the 1950s and 1960s have not been found for individuals with rheumatoid arthritis [195]. The increased mortality has been linked to several factors, including extra-articular manifestations, markers of disease severity, and diminished function within the first year [193; 194]. By far, cardiovascular disease has been thought to confer the greatest risk for increased mortality [193; 194].

A meta-analysis of observational studies demonstrated that mortality related to cardiovascular disease is increased by about 50% in individuals who have rheumatoid arthritis (compared with individuals who do not have the disease) [196]. The increased risk cannot be explained by an increased incidence of traditional cardiovascular disease risk factors [197; 198; 199]. The underlying inflammatory mechanism is thought to have a role, and the increased use of disease-modifying drugs is expected to help improve survival in addition to function [194; 200]. To date, only methotrexate has been shown to be associated with a reduced risk of cardiovascular disease among individuals with rheumatoid arthritis [201]. The increased risk of cardiovascular disease highlights the need for clinicians to assess traditional and nontraditional cardiovascular risk factors, such as hypertension, obesity, smoking, hyperlipidemia, inflammation, insulin resistance, and family history of cardiovascular disease, and provide counseling, preventive measures, and treatment as appropriate [202].

## PATIENT EDUCATION

Education and self-management are valuable components of an overall treatment plan for a chronic illness such as rheumatoid arthritis [18; 162]. Studies have demonstrated that patient education improves function, patients' global assessment, adherence to the treatment plan, and psychologic status [48; 183].

| POINTS OF EMPHASIS IN PATIENT EDUCATION REGARDING PREVENTION OF COMORBIDITIES ASSOCIATED WITH RHEUMATIC DISEASES AND THEIR TREATMENT | |
|---|---|
| **Comorbidity/Complication** | **Preventive Measures** |
| Infection | Wash hands frequently.<br>Avoid situations that increase the risk of infection (e.g., crowded areas, public transportation, children and adults who have been recently vaccinated with live vaccines).<br>Take precautions against injuries.<br>Remain up-to-date on influenza vaccination. |
| Osteopenia/osteoporosis | Increase dietary intake of calcium and vitamin D.<br>Take calcium and vitamin D supplements as prescribed.<br>Engage in regular weight-bearing and muscle-strengthening activities.<br>Stop smoking.<br>Avoid excessive use of alcohol. |
| Cardiovascular disease | Maintain proper weight (reduce weight if necessary).<br>Eat a healthy diet, low in fat, salt, and sugars.<br>Engage in regular exercise/activities.<br>Take any medications as prescribed (e.g., for hypertension, hyperlipidemia, or diabetes).<br>Reduce stress.<br>Stop smoking.<br>Avoid excessive use of alcohol. |
| *Source: [3; 189; 269]* | *Table 11* |

Clinicians should emphasize the importance of noting new symptoms that may be related to adverse effects of treatment drugs and the need for strategies to minimize these effects [186]. For example, clinicians should counsel patients treated with glucocorticoids and/or immunosuppressant agents about ways to prevent osteoporosis and reduce the risk of infection and should emphasize to all patients the importance of modifying lifestyle factors that increase the risk for cardiovascular disease (***Table 11***).

Given the high rate of complementary and alternative medicine use, along with a substantial lack of disclosure of such use, clinicians should emphasize the importance of discussing the use of herbal and/or dietary supplements. Education should focus on the risk of disease progression if alternative approaches or supplements are used to replace conventional therapies and the potential for interactions between herbal supplements and treatment drugs.

Patient education should be tailored to address individual needs. Healthcare professionals should emphasize to patients that adhering to the management program will alleviate their symptoms, improve their function, and enhance their quality of life. Clinicians should also refer patients to reliable educational resources.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic inflammatory autoimmune disorder of the connective tissue, primarily affecting the skin, joints, blood, and kidneys; however, other body systems/organs can also be affected. The disease process in systemic lupus is complex, with an often unpredictable course and a prognosis that varies from mild to severe to life-threatening. As with other autoimmune diseases, systemic lupus is characterized by recurring remissions and exacerbations (flares).

Improved treatment options have led to longer survival for people with systemic lupus [75]. Unfortunately, along with longer survival has come an increased risk for chronic diseases, especially cardiovascular disease. In addition, the disability caused by systemic lupus can be substantial. Studies and surveys have shown that the symptoms of fatigue, pain, and neurocognitive dysfunction cause many individuals with systemic lupus to stop working. Approximately 50% of individuals stop working within 13 years after diagnosis [203]. A large telephone survey found that the percentage of individuals with systemic lupus who were working decreased from 74% to 54% between the time of diagnosis and a follow-up interview 1 to 2 years later [204]. The number of people who stop working increases with longer time from diagnosis [204].

## EPIDEMIOLOGY

The prevalence of systemic lupus has ranged from 72.8 to 143.7 per 100,000, with higher rates (127 to 280 per 100,000) among women [32; 59]. The incidence of systemic lupus has nearly tripled since the 1950s [194]. Approximately 161,000 to 322,000 adults in the United States have systemic lupus, according to prevalence and population estimates [56].

The prevalence rates for lupus are 5 to 10 times higher among women than men, reflecting the female preponderance of the disease [32; 59; 63]. Most women affected by the disease are of childbearing age; the average age at the time of diagnosis of adult-onset systemic lupus is 39.3 years [59]. About 3% to 18% of cases have an onset after 50 years of age [207]. The risk of the disease is 20 to 30 times more likely for the sibling of a person who has systemic lupus [42; 394].

Some researchers have evaluated prevalence according to race/ethnicity, and rates of systemic lupus are higher among black, Asian, Hispanic, and Native American populations than among the white population [32; 59; 63; 234; 370]. Studies have shown that the prevalence of systemic lupus is two to three times higher among black women than white women and about twice as common among black men compared with white men [32; 59; 63].

## POTENTIAL ENVIRONMENTAL RISK FACTORS

Several environmental factors have been evaluated as contributors to the development of systemic lupus, and the strongest evidence has been found for infection, cigarette smoking, and hormones. These same factors have been associated not only with a higher incidence of systemic lupus but also with disease of greater severity and/or increased disease activity [31].

A strong association has been identified between systemic lupus and Epstein-Barr infection, with research demonstrating that an immune response to the Epstein-Barr virus plays an important role in the development of systemic lupus in at least some individuals with systemic lupus [3; 41; 42; 43].

As discussed, tobacco smoking has been linked to the inflammatory response in rheumatic diseases. It is thought that smoking can trigger immune responses to anti-double-stranded DNA, antibodies that are relatively specific for systemic lupus [53; 211; 212; 213]. A meta-analysis of nine studies demonstrated a small but statistically significant association between current smoking and development of systemic lupus [214]. No association was identified between past smoking and the development of systemic lupus [214].

The mechanisms of sex hormones as a risk factor in the development of systemic lupus are unclear. A review and meta-analysis found that levels of sex hormones are altered in the presence of systemic lupus, but strong evidence of causal relationships was lacking [215]. Sex hormones and systemic lupus are more closely related among women than among men. Levels of dehydroepiandrosterone/dehydroepiandrosterone-sulfate (DHEA/DHEAS), progesterone, and testosterone are lower and estradiol and prolactin are higher among women with systemic lupus, whereas an increased prolactin level is the only abnormality confirmed among men with systemic lupus [215]. The effect

of exogenous hormones has been debated, with some studies showing slightly increased risk for systemic lupus among women taking oral contraceptives or hormone-replacement therapy [52; 216]. Evaluation of 262 incident cases of systemic lupus in the Nurses' Health Study (total of 238,308 subjects) indicated that early age at menarche, oral contraceptive use, early age at menopause, surgical menopause, and postmenopausal use of hormones were each associated with an increased risk of systemic lupus [52]. However, the development of systemic lupus in children and in women after menopause, as well as the greater severity of disease among men, calls into the question the role of estrogen [216]. Although more research is needed to determine the exact relationships of sex hormones to the development of systemic lupus, it is agreed that the disease involves a complex interaction of multiple sex hormones, including estrogen, prolactin, DHEA, and testosterone [216].

## ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Other autoimmune diseases occur frequently in individuals with systemic lupus. In one study, 41% of subjects with systemic lupus had at least one other autoimmune disease and approximately 5% had two or more autoimmune diseases in addition to systemic lupus [217]. Among the most common autoimmune diseases in individuals with systemic lupus are thyroiditis, rheumatoid arthritis, antiphospholipid antibody syndrome, and Sjögren syndrome; in addition, fibromyalgia often co-occurs with systemic lupus.

With regard to thyroiditis and systemic lupus, the prevalence of the two diseases in a single individual has varied widely [218]. In one study, autoimmune thyroiditis was found in 18% of individuals with systemic lupus [217]. Other researchers found that the prevalence of Hashimoto's thyroiditis was 90-fold higher among individuals with systemic lupus than among the general population; the prevalence of Graves' disease was 68-fold higher [65]. Subclinical thyroid disease has been found more often than overt disease [218].

Researchers believe that there is a common genetic susceptibility to both systemic lupus and rheumatoid arthritis, as genetic studies have shown that several loci are associated with an increased risk for both diseases [154]. Antiphospholipid antibody syndrome and Sjögren syndrome have each been found in about 14% of individuals with systemic lupus [217].

Systemic lupus has also been found to be a significant risk factor for fibromyalgia, with fibromyalgia occurring in 22% to 65% of individuals with systemic lupus [17; 70; 155]. However, race/ethnicity substantially affects the co-occurrence of these two diseases, with significantly positive associations among white populations but negative associations among black and Mexican populations [71; 219].

## CLINICAL MANIFESTATIONS

The clinical manifestations of systemic lupus vary widely, and symptoms may develop abruptly or insidiously. The classic sign of active systemic lupus is a butterfly-shaped rash in the malar area of the face, which is present in up to 90% of cases [7]. Discoid rash may also occur elsewhere on the body, and approximately 40% of individuals have photosensitivity, with a rash resulting from sunlight exposure [220].

Joint pain also occurs in approximately 90% of individuals and is usually symmetrical and typically involves the proximal joints of the fingers [220]. Other common symptoms are general and nonspecific. Nearly all individuals with systemic lupus note fatigue; nearly 80% have a low-grade, unexplained fever; and about 50% have unintentional weight loss or alopecia [220]. Other symptoms vary depending on the body systems affected (***Table 12***) [188; 220].

| MOST COMMON SIGNS AND SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS | |
|---|---|
| **Organ/Body System** | **Symptoms** |
| General | Fatigue<br>Low-grade, unexplained, episodic fever<br>Weight loss<br>Generalized adenopathy |
| Cutaneous | Butterfly-shaped rash on face<br>Photosensitivity<br>Alopecia<br>Oral mucosal sores, ulcers<br>Raynaud phenomenon |
| Musculoskeletal | Arthralgia, arthritis<br>Myalgia, muscle tenderness |
| Cardiovascular | Pericarditis<br>Pericardial effusion<br>Myocarditis |
| Respiratory | Pleuritic pain<br>Pleurisy (with coughing and dyspnea) |
| Renal | Glomerulitis, glomerulonephritis |
| Neurologic | Cognitive dysfunction<br>Headache<br>Seizures<br>Cranial or peripheral neuropathy |
| Gastrointestinal | Abdominal pain<br>Nausea/vomiting |
| Ocular | Dry eye syndrome, uveitis, scleritis |
| *Source: [188; 220]* | *Table 12* |

The clinical manifestations of systemic lupus often differ among older individuals. Malar and discoid rash, photophobia, arthritis, and glomerulonephritis are less common in the older population compared with the younger population, whereas fever, serositis, dry eye syndrome, and lung disease are more common in the older population [207].

## DIAGNOSTIC EVALUATION

The diagnosis of systemic lupus is challenged by the waxing and waning of symptoms over time and variations in the degree of disease severity and in the organ systems involved. Because of the lower prevalence and differences in clinical manifestations among older individuals, diagnosis is especially challenging for that population and is often delayed [207].

The malar rash associated with systemic lupus can be easily misdiagnosed as rosacea or seborrheic dermatitis, but it is usually asymptomatic, lacking symptoms such as burning, itching, and tingling, that accompany other facial rashes [75]. The differential diagnosis of systemic lupus includes several other autoimmune disorders, such as early rheumatoid arthritis, undifferentiated connective tissue disease, fibromyalgia, vasculitis, and idiopathic thrombocytopenia purpura [7].

| CLASSIFICATION CRITERIA OF THE AMERICAN COLLEGE OF RHEUMATOLOGY FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS | |
|---|---|
| **Major Criteria** | **Definition of Criteria** |
| Malar rash | Fixed erythema (flat or raised) over malar eminences, usually sparing the nasolabial folds |
| Discoid rash | Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions |
| Photosensitivity | Skin rash resulting from exposure to sun (by patient history or physician observation) |
| Oral ulcers | Ulceration in mouth or nasopharyngeal passage, usually painless (observed by physician) |
| Nonerosive arthritis | Tenderness, swelling, or effusion in 2 or more peripheral joints |
| Pleuritis or pericarditis | Evidence of pleuritic pain documented by convincing history of pleuritic pain, by pleural friction rub heard by physician, or by demonstration of effusion<br>OR<br>Evidence of pericarditis documented by electrocardiogram, by pericardial friction rub heard by physician, or by demonstration of pericardial effusion |
| Renal disorder | Persistent proteinuria<br>OR<br>Cellular casts (red cell, hemoglobin, granular, tubular, or mixed) |
| Neurologic disorder[a] | Seizures<br>OR<br>Psychosis |
| Hematologic disorder | Hemolytic anemia with reticulocytosis<br>OR<br>Leukopenia (<4,000/mm$^3$ on 2 or more occasions)<br>OR<br>Lymphopenia (<1,500 mm$^3$ on 2 or more occasions)<br>OR<br>Thrombocytopenia (<100,000/mm$^3$) (in the absence of offending drugs) |
| Immunologic disorder | Abnormal anti-DNA titer<br>OR<br>Abnormal anti-Sm titer<br>OR<br>Evidence of antiphospholipid antibodies |
| Positive antinuclear antibody (ANA) titer | By immunofluorescence or an equivalent assay at any point in time and in the absence of drugs |
| [a]In the absence of offending drugs or known metabolic derangements (such as uremia, ketoacidosis, or electrolyte imbalance). | |
| *Source: [221; 222]* | *Table 13* |

### Diagnostic Criteria

Criteria for the classification and diagnosis of systemic lupus have been established by the ACR (***Table 13***) [221; 222]. The criteria include 11 clinical and immunologic manifestations, and at least four of the 11 criteria are needed for a definitive diagnosis of systemic lupus [221; 222]. Because the criteria are based on the presence of signs and symptoms at any time during the course of the illness, an individual with early or atypical disease may not meet the criteria for definitive diagnosis. It is not uncommon for people with systemic lupus to meet only two of the clinical criteria, with the diagnosis subsequently confirmed by laboratory testing [75].

| ANTIBODY TESTING FOR SYSTEMIC LUPUS | | |
|---|---|---|
| **Diagnostic Test** | **Prevalence[a]** | **Comments** |
| Antinuclear antibody titer | 93% to 100% | Positive titer also found in systemic sclerosis (up to 80%) and Sjögren syndrome (up to 70%), as well as many healthy individuals |
| Anti-double-stranded DNA | 70% to 80% | Positive test highly specific for systemic lupus<br>Associated with greater risk of skin disease and lupus nephritis |
| Anti-Ro | 30% to 40% | Also associated with Sjögren syndrome (up to 70%)<br>Associated with greater risk of skin disease, lupus nephritis, and fetal heart problems |
| Antiphospholipid antibodies | 20% to 30% | Associated with greater risk of thrombosis and pregnancy loss |
| Anti-Sm | 10% to 30% | Positive test highly specific for systemic lupus<br>Associated with greater risk of lupus nephritis |
| Anti-La | 15% to 20% | Associated with Sjögren syndrome (up to 50%)<br>Associated with fetal heart problems |
| [a]Among people with systemic lupus. | | |
| *Source: [160; 230; 231; 232; 270]* | | *Table 14* |

Physical examination can identify nearly half of the diagnostic criteria, including malar and discoid rash, oral ulcers, arthritis, and pleuritis or pericarditis. The absence of these signs may not necessarily exclude systemic lupus as a potential diagnosis, however, because of the waxing and waning of symptoms.

Seizures and psychosis are the only two neurologic criteria for the classification of systemic lupus, but many other neuropsychiatric disorders occur in conjunction with the disease [221]. Neuropsychiatric disorders have been reported in up to 80% of adults with systemic lupus and more than 90% of children with the disease [223; 224]. The disorders may be evident before, at the time of, or after the diagnosis of systemic lupus [225]. In various studies of patients with systemic lupus (mainly adults), the most common manifestations of neuropsychiatric lupus were headache (87%), cognitive impairment (66%), and mood disorders (26%) [223; 226].

Laboratory testing can help to identify the remaining clinical criteria: renal, hematologic, and neurologic disorders. The work-up should include a CBC with differential, platelet count, chemistry profile (especially kidney and liver function studies), and urinalysis [220; 227]. Evidence of renal involvement may include proteinuria or red blood cell casts and leukocytes in the urine [220]. Hematologic testing may indicate anemia (in about 40%), thrombocytopenia (in about 25% to 35%), and leukopenia (about 15% to 20%) [227]. Metabolic abnormalities (e.g., uremia, electrolyte imbalance, or ketoacidosis) may be signs of neurologic disorders; seizures or psychosis are other signs [75].

Other recommended laboratory testing includes an ANA titer, as well as anti-double-stranded DNA, antibody to Sm nuclear antigen (anti-Sm), antiphospholipid antibodies, anti-Ro/SSA, and anti-La/SSB antibodies (***Table 14***) [7; 228; 229]. The ANA titer is highly sensitive for systemic lupus, with a positive result in approximately 93% to 100% of individuals with the disease [230; 231]. However, the specificity is low, and a positive titer will also be found in 60% to 80% of people with systemic sclerosis and 40% to 70% of people with Sjögren syndrome, as well as in a substantial number of healthy individuals [230]. Given the low specificity, in combination with the low prevalence of systemic lupus in the primary care setting, the College of American Pathologists recommends an ANA titer when there is a strong clinical suspicion of systemic lupus on the basis of the history, physical examination, and other laboratory tests; however, it should not be used as a test to rule out

rheumatic disease [230]. A negative ANA titer (less than 1:160 on standard substrate) essentially rules out a diagnosis of systemic lupus [75]. The ANA titer is best determined with fluorescent testing because it has better sensitivity and specificity than testing with enzyme-linked immunosorbent assay and can also demonstrate an ANA pattern [75].

Anti-double-stranded DNA and anti-Sm tests can help confirm a diagnosis of systemic lupus, as they have greater specificity than the ANA titer; however, they are not as sensitive as the ANA tier [232]. The prevalence of positive anti-Ro/SSA and anti-LA/SSB titers is also low, and these titers are more often positive among older people [207]. Serum complement levels may also be useful, as decreased levels indicate active or impending exacerbation of disease [7; 75; 228; 229]. The prevalence of positive anti-double-stranded DNA titers and of decreased complement levels is lower among older individuals than among younger ones [207].

A positive finding of antiphospholipid antibodies is the last criterion in the ACR Classification [7]. The presence of antiphospholipid antibodies is determined with testing for anticardiolipin antibodies or for lupus anticoagulant [7; 75]. About 20% to 30% of people with systemic lupus have antiphospholipid antibodies, which increase the risk for thromboembolism and pregnancy loss [232].

## REFERRAL

The ACR recommends that primary care providers refer patients with suspected lupus to a rheumatologist to confirm the diagnosis and to evaluate the activity and severity of disease [7]. The rheumatologist will establish a treatment plan, and when the disease is mild-to-moderate, the primary care provider can monitor the clinical course of the disease and drug-related toxicities. Because of the range in systems/organs that may be affected, a variety of other specialists may be needed during the course of disease. In addition, referral to physical and occupational therapies, social workers, and psychologists may also be appropriate.

## TREATMENT OPTIONS

Data from large, randomized, controlled trials in the treatment of systemic lupus are lacking, creating a weak evidence base for recommendations. The ACR published guidelines for the management of systemic lupus in 1999, before the advent of many of the drugs currently used [7]. The EULAR published guidelines in 2008, acknowledging the lack of strong evidence [233]. Very few drugs have FDA approval for use in systemic lupus, and researchers have been evaluating the efficacy and safety of drugs approved for other conditions, most notably rheumatoid arthritis [235; 236]. Several drugs have been used in clinical practice, with their use depending on the severity of disease (***Table 15***) [7; 75; 186; 225]. First-line treatment has not changed significantly since 1993, with most physicians relying on prednisone and hydroxychloroquine as the initial approach [247].

The goal of treatment of systemic lupus is to adequately control disease and alleviate symptoms while minimizing the risk of treatment side effects. The approach to the treatment of older individuals with newly diagnosed systemic lupus is the same as that for younger individuals, but treatment is complicated in older people because of a greater likelihood of comorbidities and an increased risk of treatment-related toxicity [207].

### Mild Disease (No Organ Involvement)

The cornerstone of treatment of mild systemic lupus without major organ involvement is typically an antimalarial drug and a low-dose glucocorticoid (usually prednisone), two of only three drugs approved by the FDA for use in systemic lupus. Antimalarial agents include chloroquine and hydroxychloroquine, and the latter is preferred because of its better side effect profile [7]. Antimalarial agents offer many benefits. They can alleviate joint-related, cutaneous, constitutional, and serosal manifestations of systemic lupus; they can prevent disease flares; they are well tolerated; they have been associated with a lower risk of infection than other treatment approaches; and they have a protective effect on survival [237; 238].

| TREATMENT OPTIONS FOR SYSTEMIC LUPUS | | | |
|---|---|---|---|
| **Agent** | **Typical Dose[a]** | **Indication** | **Side Effects** |
| Nonsteroidal anti-inflammatory drugs (NSAIDs) | At or near the upper limit of the dose range | Mild-to-moderate arthritis, fever, mild serositis | Gastrointestinal bleeding, renal and hepatic toxicity |
| Immunosuppressants/ cytotoxic agents | Dose varies | Usually used in conjunction with a low-dose glucocorticoid | Infection, leukopenia, anemia, thrombocytopenia, myelosuppression, lymphoma, gastrointestinal effects, alopecia |
| **Antimalarial Agents** | | | |
| Hydroxychloroquine | 200 mg PO twice daily | Preferred first-line treatment; effective for arthritis and rash and for preventing disease flares | Dizziness, nausea and diarrhea (usually resolves over time), macular damage |
| **Glucocorticoids** | | | |
| Prednisone (low dose) | ≤10 mg PO daily | Usually used in conjunction with hydroxychloroquine | Osteopenia/osteoporosis, infection, hypertension, avascular necrosis of bone, weight gain, glaucoma, cataracts, psychologic effects |
| Prednisone (moderate dose) | ≤20 mg PO daily | Moderate disease (without organ involvement) with inadequate response to first-line treatment | |
| Methylprednisolone (high dose) | 40–60 mg PO daily or 1 g IV daily X3 | Lupus nephritis, cerebritis, thrombocytopenia | |
| Topical | Low or intermediate dose | Facial lesions | Skin atrophy, infection, contact dermatitis |
| | Intermediate dose | Lesions on trunk or extremities | |
| | High dose | Lesions on palms or soles | |
| Azathioprine | 25–150 mg PO daily | Nonarthritic disease refractory to antimalarial agent and/or glucocorticoids; maintenance therapy for lupus nephritis, neuropsychiatric lupus | Hepatitis, pancreatitis |
| Methotrexate | 7.5–20 mg PO weekly | Mild-to-moderate disease refractory to first-line treatment; lupus nephritis, neurologic complications | Hepatic fibrosis, cirrhosis, pulmonary infiltrates, stomatitis, mucositis; teratogenic |
| Cyclophosphamide | IV, dose varies | Digital vasculitis; disease with organ involvement (lupus nephritis, cerebritis) | Irreversible ovarian or testicular failure (with long-term use); nausea, alopecia, herpes zoster; teratogenic |
| Mycophenolate mofetil | 1.5–3 g PO daily | Mild-to-moderate lupus nephritis (induction and maintenance therapy); refractory thrombocytopenia; cutaneous manifestations; uncontrolled disease | Diarrhea, nausea; teratogenic |
| Leflunomide | 10–20 mg PO daily | Mild-to-moderate disease refractory to first-line treatment | Diarrhea, alopecia, rash; teratogenic |
| **Topical Calcineurin Inhibitors** | | | |
| Tacrolimus or pimecrolimus | 0.1% | Severe cutaneous lesions resistant to other agents | Peeling and burning sensation |
| **Monoclonal Antibody** | | | |
| Belimumab | 10 mg/kg IV every 2 weeks for 6 weeks, then every 4 weeks | Adjunctive therapy for autoantibody-positive, mild-to-moderate systemic lupus | Nausea, fever, diarrhea, nasopharyngitis, insomnia; possibly teratogenic |
| Rituximab | 375 mg/m$^2$ IV once weekly for 4 doses OR 500–1000 mg on days 1 and 15 | Mild-to-moderate disease refractory to first-line treatment; lupus nephritis | Nausea, fever, fatigue, cytopenias, lymphopenia; possibly teratogenic |
| [a]For most drugs, the typical dose may vary, as no recommended dose has been established because of the lack of FDA approval. | | | |
| *Source: [7; 20; 75; 186; 225; 236]* | | | *Table 15* |

Despite all these advantages, hydroxychloroquine is underutilized in practice [239].

A low-dose oral glucocorticoid is typically used in conjunction with an antimalarial agent to provide further relief of symptoms. For most patients with mild disease (and no major organ involvement), prednisone at a dose of 5 mg per day is effective, although some patients may need 10 mg per day [75]. NSAIDs may also be used to provide symptomatic relief of joint manifestations [7]. The use of both glucocorticoids and NSAIDs should be carefully considered because of their associated toxicity [7]. Glucocorticoids should be given at the lowest possible dose that suppresses manifestations of disease activity and prevents flares [75].

Although antimalarial drugs usually resolve systemic lupus-related rash, the mainstay of treatment for this manifestation is a topical glucocorticoid, available as a cream, liquid, or gel [7]. Intermediate-dose rather than high-dose topical glucocorticoids should be used on areas where atrophy is more likely, such as the face [7]. Novel therapies for cutaneous lesions are calcineurin inhibitors, most notably tacrolimus and pimecrolimus [236]. The use of these immunomodulators has been shown to be effective, but studies have been small [236]. The FDA has approved tacrolimus and pimecrolimus for the treatment of moderate and severe atopic dermatitis in adults and children but has not approved them for use in systemic lupus [236].

If the disease response to antimalarial drugs and tolerable doses of glucocorticoids (i.e., daily dose of prednisone of 10 mg or less) is inadequate, treatment with an immunosuppressant should be started as a glucocorticoid-sparing approach [75]. Methotrexate and leflunomide have been evaluated in mild-to-moderate systemic lupus, and many studies have indicated benefit, especially with regard to joint- and skin-related symptoms, but the data have been conflicting [75; 235]. Azathioprine is often the drug of choice for nonarthritic manifestations that have not responded to antimalarial treatment and low-dose glucocorticoid [75]. Because of the increased risk for infection associated with immunosuppressants, screening for tuberculosis and chronic viral infections should be completed before treatment with an immunosuppressant agent begins [43].

It has been hypothesized that biologics may be the next frontier of lupus treatment. In 2011, the FDA approved belimumab, the first new drug for lupus in more than 50 years [243]. Belimumab, a monoclonal antibody against B-lymphocyte stimulator, has been associated with better clinical response compared with placebo [243; 251]. More research is necessary to determine if the drug is effective in black patients and patients with severe manifestations, especially those with nephritis and neurologic disease [395]. Belimumab is approved to treat patients with active, autoantibody-positive lupus who are receiving standard therapy [243]. It is administered via an intravenous infusion at an initial dose of 10 mg/kg every 2 weeks for 6 weeks; the maintenance dose is 10 mg/kg every 4 weeks [20].

Though not FDA approved for the treatment of systemic lupus erythematosus, rituximab has shown promise in the management of lupus [395; 396]. Like belimumab, rituximab is a monoclonal antibody that selectively depletes B cells. Many open-label studies have shown improvements in lupus symptoms with the use of rituximab, including in patients with severe and/or refractory disease, but two large randomized, double-blind studies failed to show major clinical response compared with placebo [395; 396]. Additional research is ongoing.

Systemic lupus often affects the eyes, with about one-third of patients having dry eye syndrome (keratoconjunctivitis sicca) [188]. Symptoms are usually relatively mild (e.g., irritation and redness), and artificial tear drops can be used to treat milder forms of the condition [188]. Pain in the eye or significant visual impairment at any time during the course of disease warrants immediate referral to an ophthalmologist [188].

Neuropsychiatric disorders have been shown to have a persistent negative effect on quality of life for people with systemic lupus [223; 224]. According to EULAR guidelines, appropriate treatment depends on the cause of the disorder: glucocorticoids and immunosuppressants are recommended for disorders that reflect an immune/inflammatory process, and antiplatelet/anticoagulation therapy is recommended for disorders thought to be related to antiphospholipid antibodies [225]. Prophylaxis with low-dose aspirin may be of benefit for people with positive results on testing for antiphospholipid antibodies, as thromboembolic events occur in approximately 50% of these patients [75].

Systemic lupus is associated with reduced exercise capacity and decreased muscle strength, which are exacerbated by disease-related fatigue and sleep disturbances [240; 241; 242]. To address these issues, routine exercise should be part of the overall treatment plan for people with mild-to-moderate disease [242; 244]. Individuals with systemic lupus who participated in a supervised cardiovascular training program had significant improvements in exercise tolerance, aerobic capacity, quality of life, and depression [245]. Exercise programs should focus on aerobic exercises as well as strength training to improve isometric strength and should begin with a formal, supervised program, as adherence has been better for such programs than for home-based ones [242].

**Uncontrolled or Moderate-to-Severe Disease**

Uncontrolled disease is defined as the persistence of clinical manifestations during treatment. Several manifestations indicate uncontrolled disease, including [7]:

- Pleurisy, pericarditis, and/or arthritis not controlled by NSAIDs
- Rash not controlled by topical therapies
- Vasculitis
- Digital ulcers
- Muscle weakness and/or elevated creatine phosphokinase despite glucocorticoid therapy
- Any central nervous system manifestation
- Continuing evidence of active renal disease, cardiopulmonary disease, or hematologic manifestations despite therapy

The primary care provider should refer patients with uncontrolled disease to a rheumatologist [7]. Moderate doses of a glucocorticoid may be effective for moderately severe disease without major organ involvement (e.g., arthritis, dermatitis, serositis, systemic symptoms) [75]. Glucocorticoids should be tapered as tolerated until a maintenance level can be established [75].

As systemic lupus progresses to moderate-to-severe disease, it can affect any major organ system. However, the kidneys are most commonly involved. Lupus nephritis occurs in 50% to 60% of individuals with systemic lupus within 10 years of diagnosis and leads to end-stage renal disease in 17% to 25% of patients [169]. The prevalence of lupus nephritis is higher in the black, Hispanic, and Asian populations than in the white population and is higher in male patients than female patients [169]. The goal of treating nephritis is to reduce the risk of end-stage renal disease and death, but controlling proteinuria and preventing disease flares are also important aims [169].

Recommended treatment for proliferative lupus nephritis is a glucocorticoid plus another immunosuppressant agent (cyclophosphamide or mycophenolate mofetil) [169; 227]. In 2012, the ACR published a guideline for the treatment and management of lupus nephritis [169]. This guideline outlines an approach to treatment focused on the stage of disease (as determined by renal biopsy) and improvement in symptoms over time. Very early disease (class I or II) generally does not require immunosuppressive therapy [169]. For more advanced disease, the recommended induction therapy is cyclophosphamide or mycophenolate

mofetil with glucocorticosteroids for 3 days, which is replaced by prednisone [169]. After 6 months, response to therapy is assessed and changes in the regimen are made. Mycophenolate mofetil is preferred over cyclophosphamide for black and Hispanic patients. In addition, all patients with systemic lupus erythematosus with nephritis should be treated with a background of hydroxychloroquine, unless contraindicated [169].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Rheumatology Task Force Panel recommend that all patients with clinical evidence of active lupus nephritis, previously untreated, undergo renal biopsy (unless strongly contraindicated) so glomerular disease can be classified.

(http://www.guideline.gov/content.aspx?id=36900. Last accessed July 29, 2014.)

**Level of Evidence**: C (Consensus opinion of experts, case studies, or standard of care)

Biologic agents, including anti-TNF-α factors, IL-6 inhibitors, co-stimulation blockers, and anti-CD20 agents, have also been evaluated for efficacy in systemic lupus but have not been as successful as in rheumatoid arthritis, due to a lack of efficacy and/or high rates of adverse events [251]. Rituximab had preliminary success in treating resistant lupus manifestations, including central nervous system, vasculitic, hematologic, and renal manifestations; however, as noted, the results of two large phase II/III placebo-controlled, randomized controlled trials were negative [235; 251].

Approximately 50% of people with systemic lupus seek symptomatic relief with complementary and alternative methods [252]. However, data and evidence of efficacy are lacking on a variety of these methods, including herbal medicines, dietary supplements, and acupuncture. However, small trials involving vitamin D supplements, tumeric, and omega-3 fatty acids show some promise [252]. In addition, counseling and therapy may improve quality of life and mood [248].

### Treatment During Pregnancy

Pregnancy in women with systemic lupus is associated with risks for both the mother and the fetus, and pregnant women should be managed as high-risk obstetric patients [75]. Pregnancy may cause disease flares, especially in the third trimester and postnatal period, but flares are usually mild and can be controlled without excessive risk to either the mother or the fetus [75; 233]. Many treatment agents may be used during pregnancy, including hydroxychloroquine, prednisone, and azathioprine; evidence suggests that mycophenolate mofetil, cyclophosphamide, and methotrexate should be avoided [233]. Systemic lupus increases the risk for fetal loss, especially in women who have antiphospholipid antibodies [75; 233]. A history of lupus nephritis, antiphospholipid antibodies, and anti-Ro and/or anti-La antibodies are associated with increased risk for pre-eclampsia, miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal congenital heart block [233]. Heparin and aspirin are usually given throughout pregnancy to reduce the risk of miscarriage and thrombotic events.

Pregnant patients with symptomatic lupus nephritis may be treated with hydroxychloroquine (for mild disease) or prednisone plus azathioprine (for clinical active disease) [169]. In cases of severe persistent disease, delivery after 28 weeks may be necessary [169].

## FOLLOW-UP AND PROGNOSIS

Follow-up care is essential for individuals with systemic lupus not only to evaluate the response to treatment but also to monitor for drug-related adverse events and to prevent infection and common comorbidities [7; 169; 227; 233; 253]. The EULAR has established evidence-based guidelines for following up patients with systemic lupus, and an expert panel in the United States proposed several quality indicators for follow-up care (***Table 16***) [227]. Better adherence to the quality indicators is needed, as a survey of 200 patients in a rheumatology clinic showed low rates of adherence, especially for assessment of cardiac risk factors [15]. Having

| QUALITY INDICATORS FOR FOLLOW-UP CARE FOR PATIENTS WITH SYSTEMIC LUPUS | |
|---|---|
| **Patient Population** | **Recommendation** |
| All | Discuss risks and benefits of any newly prescribed medication. Obtain baseline studies before beginning treatment with any new medication and monitoring for drug toxicity, as recommended. Assess cardiovascular risk factors annually. |
| Receiving immunosuppressant treatment | Recommend annual influenza vaccination. |
| Receiving prednisone at a dose of ≥10 mg/day for at least 3 months (or other glucocorticoid equivalent) | Attempt to taper dose, add a steroid-sparing agent, or escalate dose of existing steroid-sparing agent. |
| Proteinuria ≥300 mg/day | Begin treatment with an ACE inhibitor or an ARB. |
| Proteinuria ≥300 mg/day and two or more blood pressure readings (including the most recent reading) with a systolic pressure >130 mm Hg or diastolic pressure >80 mm Hg over 3 months | Begin treatment for hypertension or change current antihypertensive agent (or increase dose). |
| ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker. | |
| *Source: [227]* | *Table 16* |

a primary care physician within the care network increased the likelihood that care met quality indicators [15].

The ACR recommends follow-up visits every 3 to 6 months for individuals with mild disease; the later EULAR guidelines recommend follow-up assessment every 6 to 12 months, although the guidelines note that this frequency is arbitrary [7; 253]. Individuals with more severe disease and/or organ involvement may need follow-up at more frequent intervals.

**Disease Activity/Response to Treatment**

Disease activity should be assessed by a validated instrument, and the most widely used tools are the Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), British Isles Lupus Assessment Group (BILAG) index, and the European Consensus Lupus Activity Measure (ECLAM) [253; 254; 255]. The EULAR also recommends evaluation of quality of life through patient history and/or a patient global assessment at each visit and annual assessment of organ damage [253].

Laboratory testing every 6 to 12 months should include urinalysis, CBC, ESR, CRP, albumin, and creatinine levels [253]. Anti-double-stranded DNA titer and serum complement levels should also be obtained, as an increase in the anti-double-stranded DNA titer and decreases in the serum complement levels often signal a disease flare [75; 253]. As defined by an international panel of experts, a flare is "a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment" [256]. Early treatment with a glucocorticoid may reduce the total dose needed to suppress the flare [75].

Because of the risk for lupus nephritis, patients should be followed up closely for signs of progression of disease to the kidneys. For patients who have persistently abnormal urinalysis results or elevated serum creatinine level, a urine protein/creatinine ratio (or 24-hour urine for protein), urine sediment, and ultrasound of the kidney should be done, and referral for a biopsy should be considered [253]. When evidence of renal disease

is found, CBC, serum creatinine level, urinalysis with microscopic evaluation, and quantitative testing of urinary protein should be done at 3-month intervals [227; 253].

Approximately 50% to 60% of neuropsychiatric manifestations occur within the first year after diagnosis, and patients should be evaluated carefully for relevant signs and symptoms [225]. A focused history can be used to elicit information about such symptoms as seizures, paresthesias, numbness, weakness, headache, epilepsy, and depression [253]. Clinicians should also assess patients for cognitive impairment by asking questions about problems with multitasking, household tasks, or memory [253]. If cognitive impairment is suspected, the patient should be evaluated further [253].

**Monitoring and Treatment of Drug Side Effects**

Infection, osteopenia/osteoporosis, and bone marrow suppression are the major side effects of treatment for systemic lupus; gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects may also occur [186]. Recommended testing for individuals receiving methotrexate, mycophenolate mofetil, or azathioprine is a CBC and platelet count every 3 months [227]. Individuals treated with methotrexate should also have liver function studies done every 3 months [227]. A serum glucose level should be obtained yearly for patients treated with glucocorticoids [227]. Monitoring during treatment with cyclophosphamide should be done monthly, with a CBC, platelet count, and urinalysis [227]. No laboratory testing is recommended to monitor treatment with hydroxychloroquine.

***Prevention of Infection***

Infection has been estimated to be responsible for 30% to 50% of morbidity and mortality among individuals with systemic lupus and is a leading cause of mortality [43; 257]. Approximately 80% of infections are caused by bacterial micro-organisms, with the skin, respiratory tract, and urinary tract accounting for more than two-thirds of affected sites [42].

Viral infections occur less commonly, and parvovirus B19 and cytomegalovirus are the most common viral micro-organisms [42; 258]. Symptoms related to viral infections often mimic disease flares [258]. Women with systemic lupus are at increased risk for infection with the human papillomavirus (HPV)-16 virus and thus are at risk for premalignant cervical lesions [42]. Several factors have been proposed as risk factors for infection, including [42; 43]:

- Active disease
- Neutropenia/lymphopenia
- Low serum complement levels
- Involvement of major organ systems (e.g., kidney, lung, central nervous system)
- Treatment with immunosuppressive agents

Treatment with antimalarial drugs has been shown to have a significant protective effect against infection, further confirming that treatment with antimalarial agents should be the standard of care unless contraindicated [257; 259].

To improve early detection of infection, clinicians should examine the pharynx, eyes, skin, and genitalia and obtain serologic and molecular studies during follow-up visits [258]. Other measures to prevent infection include targeted prophylaxis for individuals at high risk for infection and timely pneumococcal and influenza vaccinations for individuals with stable disease [43; 257].

***Prevention of Osteoporosis***

As noted, long-term use of glucocorticoids is associated with a wide range of potential adverse events, including osteopenia/osteoporosis, hypertension, cataracts, glaucoma, dyspepsia, weight gain, avascular necrosis of bone, Cushingoid changes, and adverse psychologic effects [186; 189]. Of these side effects, osteoporosis is of particular concern, with a prevalence of 4% to 24% among patients with systemic lupus [253]. According to the 2010 ACR guidelines, the following are recommended for the prevention and treatment of glucocorticoid-induced osteoporosis [189; 190]:

| COMORBIDITIES ASSOCIATED WITH SYSTEMIC LUPUS | | |
|---|---|---|
| **Comorbidity** | **Prevalence** | |
| | **Lifetime** | **Current** |
| Any gastrointestinal problem | 61% | 27% |
| Any psychiatric problem | 58% | 34% |
| Depression | 57% | 34% |
| Hypertension | 56% | 37% |
| Any lung problem | 42% | 21% |
| Any endocrine problem | 38% | 25% |
| Any genitourinary problem | 37% | 6% |
| Any cardiovascular problem | 32% | 13% |
| *Source: [191]* | | *Table 17* |

- Daily calcium intake (dietary plus supplement) of 1,200 to 1,500 mg and supplemental vitamin D (400 to 800 IU) to prevent osteoporosis in all individuals taking glucocorticoids
- Use of bisphosphonates according to an individual's risk (noting that risk is best assessed with the FRAX tool, which provides a better overall clinical risk profile than bone mineral density alone)
- Dual x-ray absorptiometry, height, prevalent fragility fractures, and serum 25-hydroxyvitamin D level at baseline (before treatment starts) and at intervals throughout the course of treatment

### *Prevention of Treatment-Related Eye Disease*

As discussed, hydroxychloroquine increases the risk for retinopathy, although this toxicity is rare at doses of less than 6.5 mg/kg/day for fewer than 5 years [187; 188]. Still, ophthalmologic follow-up is important for early detection and minimization of this potentially serious side effect [187]. The AAO recommends a complete ophthalmologic examination within the first year after treatment [187]. Routine examination of the eyes should be done for patients treated with glucocorticoids who are at high risk for cataracts and glaucoma, and studies indicate that adherence to this recommendation is suboptimal [8; 253].

### Prevention of Comorbidities

The EULAR guidelines recommend a high index of suspicion and prompt evaluation for comorbidities commonly associated with systemic lupus, such as atherosclerosis, hypertension, dyslipidemia, and non-Hodgkin lymphoma [233]. Among patients with systemic lupus, the prevalence of hypertension or dyslipidemia has been reported to range from approximately 11% to 75% [191; 253]. Racial disparities exist, with cardiovascular events occurring at a younger age in black women and men [260; 261]. Although the increased risk of cardiovascular disease in the systemic lupus population cannot be fully explained by traditional cardiovascular risk factors, experts agree that such risk factors should be evaluated at least annually and that modifiable risk factors should be treated according to established guidelines [233; 253].

Hypertension and cardiovascular problems are among the most common comorbidities in individuals with systemic lupus (***Table 17***) [191]. Hypertension is the leading current comorbidity, and any gastrointestinal problem is the leading lifetime comorbidity. Psychiatric problems and depression are the second and third leading current and lifetime comorbidities [191]. Follow-up care should include patient assessment and preventive strategies for these comorbidities, as well as treatment as appropriate.

The risk of cancer is slightly increased for individuals with rheumatic diseases in general and for systemic lupus specifically [262; 263]. Although several types of cancer have been reported to occur more frequently, the risk is greater for hematologic cancers, especially non-Hodgkin lymphoma [262; 263; 264]. The underlying link between cancer and systemic lupus is unknown, but both the disease itself and medication exposure are thought to be factors [263]. The risk for HPV infection and cervical dysplasia are increased, making patients with lupus at a greater risk for virus-associated malignancies (e.g., cervical cancer, anal cancer) [249; 265]. Clinicians should assess patients for signs and symptoms of cancer and should ensure that routine cancer screening is carried out [253; 262; 263]. Shorter intervals for gynecologic evaluation are reasonable for women with systemic lupus due to the increased risk for cervical cancers [265].

It is interesting to note that the risk of certain other malignancies, specifically breast, ovarian, endometrial, and prostate cancers, appears to be decreased in patients with systemic lupus erythematosus, likely due to a combination of factors, including long-term use of medications and potential exogenous hormone use [249; 250].

Because of the high percentage of thyroiditis and the potential for polyautoimmunity among people with systemic lupus, clinicians should carefully consider the possibility of these diseases during follow-up, especially among those at highest risk [65; 218]. The highest risk for polyautoimmunity has been associated with female gender, articular involvement, familial autoimmunity, and positive anti-Ro titer [217].

Systemic lupus often has a substantial impact, with disease-related symptoms interfering with quality of life and ability to work [203; 204; 223; 224; 266]. In a survey study, the factors significantly associated with workplace activity limitations were older age, greater disease activity, fatigue, poorer health status, lower job control, greater job strain, and working more than 40 hours per week [266]. Healthcare professionals should ask patients about their ability to cope with the disease and should suggest support groups or counseling as appropriate.

### Prognosis

Systemic lupus is one of the leading causes of death among autoimmune disorders, and its associated mortality is higher than that expected for the general population [27; 209]. Mortality among women is consistent across all age-groups [27]. Survival has improved substantially over the years, from a 4-year survival of 50% in the 1950s to a 5-year survival rate of 95% today [75; 194; 209; 232]. Ten-year and 15-year survival rates have been reported to be approximately 90% and 80%, respectively [209; 267]. Improved survival is thought to be the result of earlier diagnosis, recognition of mild disease, increased use of ANA testing, and better treatment options [194]. Lower survival rates are associated with an older age at the time of diagnosis and male gender, and mortality rates are twofold to threefold higher among the black population than among the white population [209; 260; 261; 267].

## PATIENT EDUCATION

In a study of patients with lupus (predominantly women), the majority of participants indicated that they were very interested in a patient education program. Patients expected a broad range of topics to be covered as part of the program, including pregnancy, possible outcomes of the disease, specific information related to different treatments, and the management of fatigue and pain [246]. In addition, patients should receive clear information regarding management of complications, minimizing sun exposure, and physical activity.


According to the American College of Obstetricians and Gynecologists, combination oral contraceptives are safe for women with mild lupus who do not have antiphospholipid antibodies. (http://www.guideline.gov/content.aspx?id=10924. Last accessed July 29, 2014.)

**Level of Evidence**: A (Recommendation based on good and consistent scientific evidence)

The risk of complications and side effects associated with systemic lupus and its treatment makes it imperative for patients with lupus to understand the measures needed to prevent complications. Education should focus on the importance of the identification and prompt reporting of signs and symptoms related to drug toxicity and to following measures to prevent infection and comorbidities, especially osteoporosis and cardiovascular disease. In addition, clinicians must emphasis the importance of routine cancer screening, especially for cervical cancer, not only because of the increased risk of cancer, but also because the rate of cancer screening has been reported to be lower among individuals with systemic lupus [253; 268]. Patients should also become familiar with the signs and symptoms of disease flares, to aid in early identification and treatment.

Education about avoiding sun exposure is also essential, as ultraviolet rays can induce or exacerbate both cutaneous and systemic flares of systemic lupus [7; 227]. Healthcare professionals must emphasize protective measures such as the use of a sunscreen that shields against both ultraviolet A and B rays, wearing protective clothing, and avoiding exposure to the sun during its hottest periods (typically 10 a.m. to 4 p.m.) [269]. Individuals should also be reminded that fluorescent and halogen lights may emit ultraviolet rays [269]. Education regarding sun avoidance should be documented at least once in the medical record, according to quality indicators established for the treatment of systemic lupus [227].

Healthcare professionals should also counsel patients about the many benefits of regular exercise and the need to avoid exhaustion and to rest when they sense the beginning of a flare [7]. Patient education must emphasize that, although it does not seem intuitive, regular exercise or recreational activities will help alleviate the severe fatigue often associated with systemic lupus as well as enhance overall well-being and reduce the risk of cardiovascular disease [242; 244; 245].

## SJÖGREN SYNDROME

Sjögren syndrome is a systemic chronic inflammatory condition characterized primarily by decreased function of lacrimal and salivary glands, enlargement of the parotid gland, and often, extraglandular manifestations. The syndrome is classified as primary when it develops in a previously healthy individual and as secondary when it is associated with an underlying rheumatic disease.

The pathogenesis of Sjögren syndrome primarily involves organ-specific autoantibodies-antibodies to cellular antigens of salivary ducts, the thyroid gland, the gastric mucosa, erythrocytes, the pancreas, the prostate, and nerve cells. In addition, non-organ-specific autoantibodies are found in approximately 60% of individuals with the disease [67].

### EPIDEMIOLOGY

The prevalence of primary Sjögren syndrome has been estimated to range from 0.05% to 4.8% of the total population [56; 67; 270]. On the basis of prevalence and population estimates, researchers suggest that 0.4 to 3.1 million people in the United States have primary Sjögren syndrome; but experts note that approximately half of all cases are undiagnosed [56; 67; 271].

Sjögren syndrome occurs predominantly in women, at a ratio of more than 9:1, and primarily occurs during the fourth to sixth decades of life [67]. The mean age at the time of symptom occurrence has been reported to be 53 years [272]. Differences in prevalence according to race/ethnicity are unknown.

### POTENTIAL ENVIRONMENTAL RISK FACTORS

Data on potential environmental risk factors for Sjögren syndrome are lacking. Viral triggers, such as Epstein-Barr virus, hepatitis C virus, and human T-cell leukemia virus-1, have been suggested, but their roles have not been definitively determined [45].

## ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Approximately 60% of cases of Sjögren syndrome are secondary to another autoimmune rheumatic disorder, such as systemic lupus, rheumatoid arthritis, or scleroderma [67]. In addition, autoimmune thyroiditis (and/or thyroid dysfunction) was found in 45% of individuals with Sjögren syndrome in one study, and fibromyalgia was found in 22% [67].

## CLINICAL MANIFESTATIONS

The typical clinical features of Sjögren syndrome are dry eyes (xerophthalmia or keratoconjunctivitis sicca) and dry mouth (xerostomia), which have been reported to occur in 93% and 98% of cases, respectively [272]. In addition to dryness, symptoms related to xerophthalmia include grittiness, itchiness, and sensation of a foreign body in the eye. Symptoms related to xerostomia include difficulty eating, swallowing, and speaking and the premature and accelerated loss of teeth. As with other autoimmune diseases, nearly half of individuals report debilitating fatigue [67].

Individuals with Sjögren syndrome may also have extraglandular involvement; among the most common manifestations are joint pain and/or swelling (37% to 75%), gastrointestinal symptoms (54%), pulmonary disease (e.g., chronic cough, recurrent bronchitis, fibrosis) (29%), and Raynaud phenomenon (16% to 28%) [272; 273]. Occurring less frequently are cutaneous vasculitis, lymphadenopathy, and renal involvement (e.g., proteinuria, interstitial nephritis, glomerulonephritis) [272; 273]. Peripheral neuropathies are often associated with Sjögren syndrome, and the reported prevalence of this complication has ranged widely, from 10% to more than 60% [226; 274]. Cognitive dysfunction has been reported in about half of individuals [226].

## DIAGNOSTIC EVALUATION

Diagnosing primary Sjögren syndrome is challenged by its slow, insidious onset, its variable course, its wide range of clinical features, and its symptoms, which are nonspecific and not always concurrent [67; 271]. These factors have led to delays in diagnosis, often over several years [67]. Early diagnosis is essential, however, to prevent complications and to allow for surveillance to detect serious systemic manifestations.

There is no single diagnostic characteristic of Sjögren syndrome. Although xerophthalmia and xerostomia are found in nearly all individuals with the syndrome, they may be symptoms of other conditions. As a result, the diagnosis should be based on a combination of characteristic symptoms, the history and physical examination, diagnostic testing, and the distinguishing of Sjögren syndrome from other conditions with similar signs and symptoms. Differentiating Sjögren syndrome from other autoimmune diseases with similar clinical features, such as systemic lupus, rheumatoid arthritis, and scleroderma, is important to ensure appropriate treatment [67]. Healthcare professionals should remember that if another rheumatic condition is diagnosed, Sjögren syndrome may still be present, given the high rate of secondary disease [67].

In 2012, the American College of Rheumatology published classification criteria for Sjögren syndrome as part of a collaborative expert consensus (***Table 18***) [275]. According to these criteria, a diagnosis of Sjögren syndrome is made when two of three objective features are present. Subjective measures used in older criteria, including daily dry eyes or dry mouth, have been eliminated in the ACR classification because they were shown to have poor specificity for Sjögren syndrome [275]. The objective measures chosen by the panel were strongly associated with the disorder.

**ACR CLASSIFICATION CRITERIA FOR SJÖGREN SYNDROME**

The classification of Sjögren syndrome, which applies to individuals with signs/symptoms that may be suggestive of the disease, will be met in patients who have at least two of the following three objective features:

- Positive serum anti-SSA (Ro) and/or anti-SSB (La) OR positive rheumatoid factor and ANA ≥1:320
- Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm
- Keratoconjunctivitis sicca with ocular staining score ≥3 (assuming that individual is not currently using daily eye drops for glaucoma, and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)
- Prior diagnosis of any of the following conditions would exclude participation in Sjögren syndrome studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:
- History of head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome (AIDS)
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

*Source: [275]* *Table 18*

The physical examination should focus on evaluation of the eye, mouth, and parotid glands. In examining the eye, the clinician should look for signs of corneal ulceration and superficial erosions of the corneal epithelium, conjunctival injection, and clouding or irregularity of the cornea [67; 276]. The mucous membranes of the mouth may appear dry, with a decreased salivary pool. In more severe cases, there may be erythema, fissuring, and ulceration of the mucous membranes [277]. There may also be evidence of dental caries as a result of reduced salivary flow. The parotid glands may be swollen or tender. Objective tests to assess oral and ocular symptoms are included in the 2012 criteria, and most of these tests are performed by specialists rather than primary care providers.

The non-organ-specific autoantibodies commonly found in serologic testing include ANA, rheumatoid factor, or antibodies to the anti-SSA (Ro) and anti-SSB (La) antigens [67]. Testing for ANA has been reported to be positive in 55% to 97% and rheumatoid factor is positive in 32% to 95% [67; 160]. Anti-SSA and anti-SSB antigens have been found in 16% to 70% and 7% to 50%, respectively [270; 271; 272; 277]. The presence of anti-SSA and anti-SSB antibodies is usually associated with extraglandular manifestations [160]. The ACR classification panel strongly agreed that positive anti-SSA/B is the most specific serologic marker for Sjögren syndrome, but that a positive rheumatoid factor and an ANA titer of 1:320 or greater is also a strong indicator in instances when anti-SSA/B serology is negative [275].

Tests to obtain the Sjögren's International Collaborative Clinical Alliance ocular staining score (OSS) use two different vital dyes to grade different areas of the ocular surface: fluorescein to grade the cornea and lissamine green to grade the bulbar conjunctiva [275; 385]. In the Corneal Fluorescein Staining Pattern test, fluorescein is instilled into the cornea, and 4 to 8 minutes after, punctate epithelial erosions that stain with fluorescein are counted and scored using a slit lamp. Additional points are added if one or more patches of confluent staining, including linear stains, are found anywhere on the cornea, punctate epithelial erosions occur in the central 4-mm diameter portion of the cornea, or one or more filaments is seen anywhere on the cornea [385]. The punctate epithelial erosions are graded according to the form, and any additional points are added to the grade for a total of 6 points for each cornea. In the Conjunctival Lissamine Green Staining Pattern test, stained dots on the conjunctivae are counted and scored with

the slit lamp at 10 times magnification immediately after lissamine green dye is applied to the eyes [385]. Temporal and nasal areas of the conjunctiva are counted separately, with a maximum grade of 3 for each area or a total maximum grade of 6 for each eye. The fluorescein score for the cornea and the lissamine green scores for the conjunctiva (nasal and temporal) are added to give the total OSS for each eye. The maximum possible score for each eye is 12. Unlike previously recommended dyes used for other ocular tests, these dyes are nontoxic and nonirritating [385]. The OSS provides a simplified, non-irritating, quantitative grading system that is easily applicable to clinical practice without the need for specialized equipment other than a slit lamp.

After the Corneal Fluorescein Staining Pattern test and before the Conjunctival Lissamine Green Staining Pattern test, an external eye exam should be performed using the slit lamp, noting the presence or absence of [385]:

- Abnormalities of the conjunctiva, cornea, and lids
- Specific diseases that might affect the OSS, such as entropion, lagophthalmos, pinguecula, and pterygium
- Clinical signs of blepharitis (e.g., ulceration around the base of the lashes, collarettes, misdirected lashes, absent lashes, poliosis, tylosis)
- Evidence of meibomitis (e.g., expression of thick material from the glands, inflammation of the meibomian glands, plugging of the orifices with inspissated secretions, lid telangiectasia)
- Signs of rosacea

Labial salivary gland (LSG) biopsy and histopathology is the third component of diagnosing Sjögren syndrome in the ACR classification [275; 384]. LSG biopsy has demonstrated much more specificity for Sjögren syndrome than testing unstimulated salivary flow rate and/or self-reported dry mouth (or dry eyes). A biopsy sample of 4 $mm^2$ (preferably 10–20 $mm^2$) is required for histopathologic exam [384]. Samples are stained with hematoxylin and eosin, and lymphocytic aggregate and infiltrate foci are counted. A score of 12 foci/4 $mm^2$ is typically the highest that can be counted; above that number of foci, infiltrates appear confluent [384]. Distinguishing focal lymphocytic sialadenitis from non-specific or sclerosing chronic sialadenitis is important for accurate diagnosis. Focal lymphocytic sialadenitis with a score of 1 focus/4 $mm^2$ or more is strongly associated with ocular and serologic indications of Sjögren syndrome [384].

## TREATMENT OPTIONS

No evidence-based guidelines are available for the treatment of Sjögren syndrome. Treatment focuses on alleviating symptoms and preventing complications, as no cure is available.

Treatment of dry eye involves artificial tears to replace moisture, and a topical anti-inflammatory agent should be used for moderate-to-severe symptoms. Preservative-free artificial tears have been better tolerated than tear solutions with preservatives because of the irritation that can be caused by frequent use of the latter type [67]. Randomized controlled trials have shown that topical ocular cyclosporine (0.05%) significantly improves objective measures of dry eye, blurred vision, and use of artificial tears in patients with moderate or severe dry eye [278]. In its guidelines for dry eye, the AAO includes topical cyclosporine as a level IA recommendation for moderate dry eye [279].

If symptoms are not relieved by artificial tears or anti-inflammatory agents, a muscarinic agonist can increase tear production by stimulating muscarinic receptors. These receptors are a type of cholinergic receptor and are present on exocrine glands as well as on heart muscle and smooth muscle [276]. The two muscarinic agonists shown to be effective for dry eye are pilocarpine (a nonselective agonist) and cevimeline (a selective muscarinic agonist). According to a review of the literature, placebo-controlled trials have provided evidence of improvement with these agents. In three trials, pilocarpine was associated with subjective and objective improvement of dry eye in 42% to 53%

of patients (compared with 26% for the control), and in two trials, cevimeline was associated with improvement in 39% to 72% (compared with 24% to 30% for the control) [278]. Systemic cholinergic agents, such as pilocarpine and cevimeline, are a level IA recommendation for severe dry eye in the AAO guidelines [279].

Treatment of dry mouth involves stimulating production of saliva and using saliva substitutes; muscarinic agonists can be used for severe dry mouth. Saliva production can be stimulated with the use of sugar-free chewing gum and sour lozenges [276]. Saliva substitutes are available as over-the-counter and prescription products and are manufactured as lozenges, rinses, sprays, and swabs [67]. As with dry eye, muscarinic agonists can improve subjective symptoms of dry mouth. Three placebo-controlled trials showed improvement with pilocarpine in 61% to 70% of patients (compared with 24% to 31% in the placebo group), and two placebo-controlled trials showed improvement with cevimeline in 66% to 76% (compared with 35% to 37% in the placebo group) [278].

A systematic review published in 2010 demonstrated a low level of evidence for most of the systemic drugs that are used to treat Sjögren syndrome [278]. Systemic immunomodulatory agents, such as glucocorticoids and hydroxychloroquine, have not offered significant benefit in terms of improvement in sicca symptoms, parotid enlargement, or fatigue, myalgia, and arthralgia [278]. Similarly, immunosuppressant therapy with azathioprine or oral cyclosporine has not provided significantly improved outcomes, and methotrexate, leflunomide, and mycophenolic mofetil have led to limited improvements in sicca symptoms only [278]. Furthermore, these systemic agents have all been associated with a high rate of adverse events [278]. The off-label use of biologic agents, such as infliximab and etanercept, has also not improved outcome [278]. Rituximab has been found to have limited benefit in improving some extraglandular features (i.e., vasculitis, neuropathy, glomerulonephritis, and arthritis), but the trials have been small and primarily uncontrolled [278]. On the basis of these findings, glucocorticoid, immunosuppressive, and biologic agents are not recommended for the treatment of Sjögren syndrome. Rituximab may be considered as a rescue therapy for individuals who have not had a response to standard treatment [278].

## FOLLOW-UP AND PROGNOSIS

In general, the prognosis for patients with established Sjögren syndrome is good, and studies have shown no increase in the rate of all-cause mortality [264; 280; 281]. However, close follow-up is needed for the prevention and/or early recognition of complications [276]. Among the complications reported to be associated with Sjögren syndrome are oral infections, infection or a tumor of the parotid gland, and lymphoproliferative diseases [67].

Lymphoma, primarily non-Hodgkin lymphoma, is the most serious complication of Sjögren syndrome, with a risk that has been reported to be 40 times greater than that for the general population [276]. Among the possible indicators of lymphoma are low levels of complement protein C3 or C4 at the time that Sjögren syndrome is diagnosed, persistently enlarged parotid glands, lymphadenopathy (regional or general), splenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinemia [67; 276]. The average time from the diagnosis of Sjögren syndrome to the development of non-Hodgkin lymphoma has been 6 to 7 years [276].

## PATIENT EDUCATION

Patient education should focus on the importance of careful eye and oral care. Oral care should include frequent dental examinations, use of fluoride, and daily rinsing with an antimicrobial solution [67; 282]. Healthcare professionals should emphasize the importance of maintaining general health, reporting any changes in symptoms, following the prescribed use of medications, and keeping appointments for follow-up visits.

## FIBROMYALGIA

Fibromyalgia is a complex rheumatic disorder characterized by chronic widespread pain, with consistent focal areas of tenderness (tender points) [6]. The definition of the syndrome has been expanded to include the presence of fatigue, stiffness, and nonrestorative sleep; however, individuals with fibromyalgia usually have a broad range of additional symptoms and comorbidities [6; 62; 283]. The onset of fibromyalgia is insidious, symptoms wax and wane in intensity, and the course is variable [283; 284].

Acceptance of fibromyalgia as a discrete clinical entity (not associated with an apparent organic disease) has been slow [10; 44; 283; 285; 286]. In fact, at one time, there was a 40% bias of a person with fibromyalgia being labeled "neurotic" [283]. Despite increasing support for the validity of the syndrome, consensus is lacking about its cause, diagnosis, and optimal treatment [25; 44; 286].

Fibromyalgia has a substantial negative effect on physical, psychologic, and social well-being, and the syndrome is associated with a significant burden in terms of both disability and healthcare costs. Fibromyalgia has been found to have a greater negative impact on quality of life than many other diseases, including osteoarthritis, chronic obstructive pulmonary disease, and permanent ostomies [25]. Activities of daily living and work within the home are often substantially limited. In a large survey of women 31 to 78 years of age, more than 25% had difficulty taking care of personal needs and bathing and more than 60% had difficulty doing light housework, going up/down one flight of stairs, walking one-half mile, or lifting/carrying 10 pounds [287]. The average survey respondent was assessed as having less functional ability than a typical woman in her 80s [287]. Approximately 20% to 50% of individuals with fibromyalgia are able to work few or no days; 36% are absent from work 2 or more days each month; 31% have lost employment; and 26% to 55% receive disability or Social Security payments [10].

The economic burden is also high. According to studies of large U.S. claims databases, the healthcare costs of fibromyalgia are two to three times higher (compared with controls) as a result of more visits to the physician's office or emergency department and a higher number of prescription medications [288; 289]. Healthcare utilization and costs are high in the year preceding as well as following the initial diagnosis of fibromyalgia [289].

### EPIDEMIOLOGY

According to prevalence and population estimates, fibromyalgia affects approximately 5 million people in the United States [58]. Determining the true prevalence is difficult because of the problems associated with defining its diagnosis according to the available criteria [10; 58]. The prevalence is estimated to be 2% to 8% of the population, with significant variation based on differences in diagnostic criteria [290; 291].

As with autoimmune diseases, the prevalence of fibromyalgia is higher among women than men, although data are conflicting. A female-to-male ratio of 6:1 to 9:1 has been reported in some studies [10; 289; 293]. However, estimates that use newer, symptom-based diagnostic criteria show a female-to-male ratio of 2:1 [290; 291].

The prevalence of fibromyalgia is 5% to 6% among patients seen in family or general medicine practice settings and among 15% to 20% of patients seen by rheumatologists [286]. As such, the syndrome is among the 100 most common diagnoses made in the family medicine setting, as well as one of the most common diagnoses in office-based rheumatology practice [286; 295]. Fibromyalgia is usually diagnosed between the ages of 20 and 55 years, but the prevalence increases with age, peaking at 70 to 79 years of age (at approximately 7% for women and 1% for men) [10].

The prevalence of fibromyalgia according to race/ethnicity in older studies has been inconclusive, as studies have either included a predominantly white population or have not specified the race/ethnicity of the subjects [58]. In general, the prevalence is similar among racial and ethnic groups [292]. There is no evidence of a higher prevalence of fibromyalgia in industrialized countries and cultures. Among a cohort of 266 individuals with systemic lupus, black race had a negative association with fibromyalgia, and the prevalence has been low among Hispanic and Mexican individuals as well [71; 219].

## PATHOGENESIS

Several etiologies for fibromyalgia have been postulated and explored; the syndrome has been thought to be an inflammatory condition, an autoimmune disease, an unexplained medical syndrome, or a psychiatric condition [16; 283; 285; 286; 296]. However, research has provided little or no evidence to support these bases, and the pathogenesis of the syndrome continues to be poorly understood [17; 25; 286].

Pioneering sleep studies in the 1970s demonstrated that people with fibromyalgia had abnormal sleep physiology, suggesting a central pathology [297]. Since then, substantial evidence has supported a mechanism of central sensitization, or the amplification of pain in the spinal cord through spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses [10; 25; 44; 284]. Studies have also shown that, compared with healthy individuals, people with fibromyalgia experience pain differently and have physiologically lower pain thresholds [44]. Research has also indicated significant dysregulation of the hypothalamic-pituitary-adrenal axis is found in fibromyalgia [25]. In addition, there may be abnormalities of descending inhibitory pathways, neurotransmitters, or neurohumoral responses; low levels of serotonin and norepinephrine metabolites have been found in the cerebrospinal fluid of individuals with fibromyalgia [10; 25; 44].

Genetics is thought to be a factor in the susceptibility of fibromyalgia. Family clustering has been reported, and the risk for fibromyalgia is eight times higher for first-degree relatives of individuals with the syndrome [298]. Abnormalities in the serotonin transporter gene and the catecholamine-O-methyltransferase gene have been identified [10; 25; 299]. These abnormalities affect the metabolism or transport of serotonin and norepinephrine, which decrease the sensitivity of pain-processing systems through the descending central nervous system pain pathways [10].

## POTENTIAL ENVIRONMENTAL RISK FACTORS

As with autoimmune diseases, several environmental risk factors have been thought to act as triggers for the development of fibromyalgia. Because research on the etiology of fibromyalgia is lacking, individuals' perceptions of triggers have been the source of some of the available information [49]. Perhaps as a result, data on the frequency of environmental triggers are conflicting, with some studies showing that half of all cases have a distinct physical or emotional trigger and other studies indicating that three-quarters of cases or more had no triggering event [19; 25; 49].

Psychiatric conditions have long been associated with fibromyalgia, and research suggests that such conditions may precede fibromyalgia and act as a trigger for the disease [44; 286]. In one study, when individuals were asked what they perceived to be a trigger for fibromyalgia, 73% attributed the development of the disease to emotional trauma or chronic stress; 24% noted emotional/physical abuse as an adult or child as a perceived trigger [49].

Injury/trauma and physical illness may also be triggers. Approximately one-third of individuals who attributed fibromyalgia to an environmental trigger noted physical injury (including those from a motor vehicle accident) as the perceived trigger [49]. Acute illness was perceived as a trigger in 27% of individuals in the same survey [49]. Viral infections have been associated with the development

of fibromyalgia, and hepatitis C, Epstein-Barr virus, HIV, parvovirus, and Lyme disease are thought to be viral triggers, but no causality has been established [19; 25; 44]. Other pain conditions, hyperprolactinemia, and autoimmune diseases have also been reported to be factors [19; 25].

## ASSOCIATION WITH AUTOIMMUNE DISEASES

Several autoimmune diseases have been found in conjunction with fibromyalgia. In a retrospective study of 2,595 cases of fibromyalgia in a nationwide claims database, the likelihood of systemic lupus or rheumatoid arthritis was two to seven times greater than that for controls [294]. Other studies have confirmed an association between fibromyalgia and systemic lupus and rheumatoid arthritis, with reported rates of up to 65% and 57%, respectively [17]. High rates of Sjögren syndrome (up to 50%), and thyroiditis (up to 31%) have also been reported among individuals with fibromyalgia [25; 72; 283].

## CLINICAL MANIFESTATIONS

Chronic widespread pain (for at least 3 months) is the characteristic feature of fibromyalgia, occurring in nearly all individuals with the syndrome [6]. This pain is often associated with a tenderness to touch [283; 300]. In addition, a constellation of other symptoms are common and vary across patients. Stiffness (especially in the morning), fatigue, and sleep abnormalities are the most common symptoms [6; 49; 62; 283; 300; 301; 302; 303].

The likelihood of depression is high among individuals with fibromyalgia [303]. Major depression has been identified in 20% to 62% of individuals with the syndrome [19; 49; 300; 303; 304]. Factors associated with major depression have included younger age, female gender, being unmarried, number of chronic conditions, and limitations in activities [303].

Cognitive dysfunction (often referred to as "fibrofog") is another common symptom in fibromyalgia, affecting approximately 40% of individuals [10]. The primary effect is on memory (working, episodic, and semantic), especially when tasks are complex and the individual's attention is divided [305]. Although memory impairment is not as common as many other symptoms, patients have considered them to be among the most troublesome, which is not surprising given that the impairment is equivalent to about 20 years of aging [49; 301; 305]. Attentional control/function is also commonly impaired in individuals with fibromyalgia [305; 306; 307]. Studies have indicated that cognitive dysfunction cannot be attributed solely to symptoms such as depression, anxiety, and sleep problems, but it does seem to be related to the level of pain [305; 306; 307].

## DIAGNOSTIC EVALUATION

Fibromyalgia cannot be diagnosed on the basis of laboratory tests, imaging studies, or pathologic results. As a result, the diagnosis relies on a carefully taken history and comprehensive physical examination. The American Pain Society guideline recommends that the physical examination include a complete joint examination, manual muscle strength testing, and a neurologic examination [284]. The ACR established diagnostic criteria for fibromyalgia in 1990, but the classification system, designed for use in clinical research rather than clinical practice, has many limitations [6; 62; 283; 308].

The lack of objective testing has led to substantial delays in the diagnosis of fibromyalgia, with a diagnosis confirmed only after many visits to healthcare professionals, referrals, diagnostic tests, and several possible diagnoses [10]. Nearly half of individuals with the disease consulted three to six healthcare providers before the diagnosis was made, and 25% saw more than six providers before diagnosis [49]. Physicians also acknowledge diagnostic delay, noting that an accurate diagnosis of a chronic pain disorder (including fibromyalgia) often is not made until after 2 to 3 years and consultations with eight to 13 healthcare professionals [10].

A self-administered questionnaire developed in 2010 may aid in detecting fibromyalgia. The tool, Fibromyalgia Rapid Screening Tool (FiRST), was developed by a group of rheumatologists and pain experts and consists of six questions that can be answered with a yes/no response [309]. A score of five "yes" responses gave the highest rate of correct identification of fibromyalgia patients (87.9%), with a sensitivity of 90.5% and a specificity of 85.7% [309]. FiRST is meant to be used as an initial screening tool, with established diagnostic criteria used to subsequently confirm the diagnosis [309].

The current challenge in diagnosing fibromyalgia stems from many factors, including a wide range and variation in symptoms, a complex differential diagnosis, and difficulty with the established diagnostic criteria.

### Range and Variation in Symptoms

There is a wide range of symptoms and comorbidities associated with fibromyalgia, and they occur in a variety of combinations and differ in terms of severity. After the three primary manifestations (fatigue, stiffness, and sleep disorders), the most common symptoms are headaches (usually migraine), dry mouth, low back pain, and paresthesias (***Table 19***) [6; 49; 283; 300; 301; 302; 303]. In an online survey conducted by the National Fibromyalgia Association (NFA), 19 symptoms, affecting virtually all body systems, were noted by at least 25% of the respondents [49]. Nearly all individuals with fibromyalgia are polysymptomatic [49].

Most individuals with fibromyalgia describe pain as arising from muscles and joints and also have tender skin [283]. Pain is typically axial in distribution, and pain/stiffness usually occurs in the morning and evening [283]. Patients may note a feeling of swelling in the soft tissues, primarily around the joints, but there is no objective evidence of swelling [19; 283]. The American Pain Society recommends using self-reports as the primary source for pain assessment, focusing on such details as [284]:

**COMMON SYMPTOMS OF FIBROMYALGIA**

| Symptom | Reported Prevalence |
|---|---|
| Stiffness | 76% to 91% |
| Fatigue | 24% to 90% |
| Sleep abnormalities | 76% |
| Headaches | 47% to 75% |
| Dry mouth | 18% to 71% |
| Low back pain | 67% |
| Paresthesias | 44% to 67% |
| Restless legs syndrome | 32% to 64% |
| Depression | 20% to 62% |
| Irritable bowel syndrome | 36% to 60% |
| Anxiety | 30% to 56% |
| Raynaud phenomenon | 9% to 53% |
| Muscle spasms | 46% |
| Balance problems | 45% |
| Cognitive dysfunction (impaired memory and/or concentration) | 40% |
| Bloating | 40% |
| Sinus problems | 37% |
| Tooth disorders | 32% |
| Jaw pain | 29% |
| Bladder problems | 26% |

*Source: [6; 10; 19; 49; 283; 296; 300; 301; 302; 303; 304]* *Table 19*

- Type and quality of pain
- Source
- Location
- Duration
- Time course
- Pain affect
- Effects on quality of life

Several pain assessment tools may be useful in the setting of fibromyalgia (***Table 20***) [25; 296; 310].

| INSTRUMENTS FOR ASSESSMENT OF FIBROMYALGIA-RELATED SYMPTOMS | |
|---|---|
| **Symptom** | **Assessment Tool** |
| Pain | Visual analog scale<br>Brief Pain Inventory<br>Short Form-McGill Pain Questionnaire<br>Daily pain diary |
| Fatigue | Visual analog scale<br>Multidimensional Assessment of Fatigue Instrument<br>Multidimensional Fatigue Inventory<br>Fatigue Severity Scale |
| Sleep | Visual analog scale<br>Medical Outcomes Study Sleep Scale<br>Pittsburgh Sleep Quality Index<br>Sleep Assessment Questionnaire |
| Depression/anxiety | Beck Depression Inventory<br>Patient Health Questionnaire<br>Beck Anxiety Inventory<br>Hospital Anxiety and Depression Scale |
| Quality of life/functional assessment | Fibromyalgia Impact Questionnaire<br>Short Form-36 Health Survey |
| *Source: [25; 296; 310]* | *Table 20* |

Healthcare professionals should also ask about factors that may exacerbate musculoskeletal symptoms, as these symptoms are modulated in approximately 60% to 79% of individuals [6]. Emotional distress has been the most commonly reported exacerbating factor (83%), followed by changes in the weather (80%), sleeping problems (79%), and strenuous activity (70%) [49]. Many other factors are perceived to worsen symptoms, including fatigue, physical inactivity, mental stress, soft-tissue injuries, travel in a car or plane, and work-related conflict [49; 283].

Patient assessment must include evaluation of the severity of symptoms most often associated with fibromyalgia, as well as overall quality of life and functional assessment [25; 284; 296]. Most assessment tools used have been validated in other settings and are not fibromyalgia-specific. Healthcare professionals should ask patients about how their symptoms affect their ability to work, as physical limitations and cognitive dysfunction may result in an inability to maintain normal employment [283; 284]. A daily pain diary may also be useful in documenting how pain influences activities of daily living and quality of life [25].

In relating their history, individuals will often focus on the symptoms that are of most concern or that are most troublesome. According to the NFA survey, the most troublesome symptoms were (in descending order): morning stiffness, fatigue, nonrestorative sleep, pain, forgetfulness, poor concentration, difficulty falling asleep, muscle spasms, anxiety, and depression [49]. In another study, 100 individuals with fibromyalgia ranked symptoms slightly differently, but the top five symptoms were similar: pain or physical discomfort, joint pain/aching, fatigue or lack of energy, poor sleep, and cognitive dysfunction [301].

Because of the predominance of fibromyalgia among women, there are few data on the clinical profile for men with the syndrome. The available research points to differences in the clinical presentation according to gender. Women tend to report more symptoms, to describe more symptoms as major problems, and to report greater life

| COMORBIDITIES ASSOCIATED WITH FIBROMYALGIA | | |
|---|---|---|
| **Comorbidity** | **Prevalence** | |
| | **Lifetime** | **Current** |
| Any gastrointestinal problem | 72% | 34% |
| Any psychiatric problem | 68% | 39% |
| Depression | 68% | 39% |
| Hypertension | 49% | 35% |
| Any genitourinary problem | 48% | 5% |
| Severe allergies | 41% | 21% |
| Any endocrine problem | 40% | 28% |
| Any lung problem | 37% | 19% |
| *Source: [191]* | | *Table 21* |

interference from pain [286; 292; 311]. Men have noted significantly lower health perceptions and more physical limitations [311]. With regard to specific symptoms, fatigue and sleep disorders are more common among women, with some studies showing a threefold higher rate [286]. "Pain all over" is also more frequently reported by women than men [286]. The most powerful discriminator between women and men with fibromyalgia is the number of tender points [286].

### *Comorbidities*

Given the broad range of symptoms and conditions found in association with fibromyalgia, it is difficult to differentiate true comorbidities from manifestations of the syndrome itself [191]. For example, irritable bowel syndrome and restless legs syndrome are traditionally thought of as comorbidities but may be part of the overall clinical syndrome [6; 191; 286]. This is true for many autoimmune diseases but particularly for fibromyalgia, which has been described as overlapping with virtually every other unexplained syndrome [285]. In a study in which current and lifetime comorbidities associated with fibromyalgia, rheumatoid arthritis, and systemic lupus were evaluated, fibromyalgia was associated with significantly higher rates of depression and psychiatric conditions, gastrointestinal problems, and severe allergies (***Table 21***) [191].

### Complex Differential Diagnosis

The multitude of symptoms and comorbidities associated with fibromyalgia add to the complexity of making a differential diagnosis. Many other conditions can mimic widespread pain, and these conditions must be considered in the differential diagnosis (***Table 22***). Although objective testing cannot confirm a diagnosis of fibromyalgia, it can play an important role in ruling out other possible diagnoses. A CBC, ESR, muscle enzymes, liver function studies, and thyroid function tests can help identify other conditions [284]. However, given the high rate of conditions that occur concurrently with fibromyalgia, clinicians must remember that finding another diagnosis does not automatically rule out a diagnosis of fibromyalgia [283]. Differentiating fibromyalgia from other rheumatic diseases and conditions involving widespread pain is especially difficult. Individuals who have widespread pain and fibromyalgia are typically more symptomatic, dysfunctional, and depressed than people who have widespread pain without fibromyalgia [283].

| DIFFERENTIAL DIAGNOSIS OF FIBROMYALGIA | | |
|---|---|---|
| **Diagnoses to Consider** | **Shared Manifestations** | **Distinguishing Features** |
| Myofascial pain syndrome | Painful, tender areas in the muscles, commonly affecting the axial muscles | Pain arising from trigger points in individual muscles during examination |
| Chronic fatigue syndrome | Chronic pain and fatigue | Low-grade fever, enlargement of lymph glands, continuous subclinical inflammatory process, and acute onset of illness |
| Rheumatoid arthritis | Joint pain/stiffness | Involvement of hands and feet, positive rheumatoid factor (in 80% to 90% of cases), radiographic evidence of joint erosion |
| Systemic lupus erythematosus | Involvement of multiple systems, joint pain | Malar rash, positive antinuclear antibody test |
| Hypothyroidism | Profound fatigue, muscle weakness, mental slowing | Weight gain, hair loss, increased TSH level |
| Polymyalgia rheumatica | Pain/stiffness in sacrohumeral and pelvic girdle | Increased ESR (in 80% to 90% of cases), age older than 65 years, treatment with glucocorticoids resolves symptoms |
| Spondyloarthropathy | Pain in neck, mid-thoracic, anterior chest wall, or lumbar regions | Pain localized to specific spinal areas, radiographic evidence of sacroiliitis, or radiographic changes in vertebral bodies |
| Polyarticular osteoarthritis | Pain in multiple joints | Radiographic evidence of joint degeneration |
| Polymyositis or other myopathies | Muscle weakness | Proximal, symmetrical muscles affected, increased serum levels of muscle enzymes, abnormal findings on EMG testing and on evaluation of biopsy samples |
| Neuropathic pain syndromes | Tingling, numbness | Burning, shooting pain |
| EMG = electromyography; ESR = erythrocyte sedimentation rate; TSH = thyroid-stimulating hormone. | | |
| *Source: [19; 205; 283; 286]* | | *Table 22* |

### Difficulty with Diagnostic Criteria

The ACR designed the classification criteria for fibromyalgia for epidemiologic classification but noted that the criteria would also be useful for diagnosis [6]. However, the criteria are used by only about half of rheumatologists in routine practice and are seldom used in the primary care setting [283]. The classification system consists of two criteria: a history of widespread pain and pain in 11 of 18 tender point sites on digital palpation [6]. It has a sensitivity of 88%, a specificity of 81%, and an accuracy of 85%, but several important problems have been identified.

A primary problem with the criteria is the focus on the tender point evaluation, which has been difficult for clinicians, especially primary care providers, to perform correctly [62; 283]. Perhaps equally as problematic is that widespread pain as the only criterion for diagnosis does not seem sufficient, given the broad range of symptoms associated with the syndrome [283]. A third major problem is the lack of a severity scale, which means that an individual with fibromyalgia may not satisfy the diagnostic criteria for the syndrome if symptoms or pain at tender points improve [283]. As a result of these drawbacks, the diagnosis of fibromyalgia often has been symptom-based, and researchers have sought ways to modify the criteria or use alternative approaches [62; 283; 308].

**REVISED AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA FOR FIBROMYALGIA**

**Criteria**

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

- Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.
- Symptoms have been present at a similar level for at least 3 months.
- The patient does not have a disorder that would otherwise explain the pain.

**Ascertainment**

| | |
|---|---|
| WPI | Note the number areas in which the patient has had pain over the last week. In how many of the following areas has the patient had pain? Score will be between 0 and 19.<br>• Shoulder girdle, left<br>• Shoulder girdle, right<br>• Upper arm, left<br>• Upper arm, right<br>• Lower arm, left<br>• Lower arm, right<br>• Hip (buttock, trochanter), left<br>• Hip (buttock, trochanter), right<br>• Upper leg, left<br>• Upper leg, right<br>• Lower leg, left<br>• Lower leg, right<br>• Jaw, left<br>• Jaw, right<br>• Chest<br>• Abdomen<br>• Upper back<br>• Lower back<br>• Neck |
| SS scale score | For the symptoms of fatigue, waking unrefreshed, and cognitive symptoms, indicate the level of severity over the past week using the following scale:<br>0 = No problem<br>1 = Slight or mild problems, generally mild or intermittent<br>2 = Moderate, considerable problems, often present and/or at a moderate level<br>3 = Severe: pervasive, continuous, life-disturbing problems<br>Considering somatic symptoms[a] in general, indicate whether the patient has:<br>0 = No symptoms<br>1 = Few symptoms<br>2 = A moderate number of symptoms<br>3 = A great deal of symptoms<br>The final score will be between 0 and 12. |

[a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

*Source: [62] Reprinted with permission from Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Rheum. 2010;62(5):600-610.* *Table 23*

In one study to assess alternative approaches, survey criteria consisting of a Regional Pain Scale score of at least 8 and a fatigue score of at least 6 was found to be concordant with the ACR criteria in 72% of cases [308]. Clinical diagnosis (the clinician's impression irrespective of the ACR criteria) was concordant with the ACR criteria in 75% of cases. The authors concluded that all diagnostic methods have utility [308]. In another study, an effort to modify the criteria to include the three most common symptoms—morning stiffness, sleep disturbances, and fatigue—yielded a sensitivity of 81%, a specificity of 61%, and an accuracy of 72% [283].

To address the problems inherent in its classification system, the ACR published new preliminary diagnostic criteria in 2010 [62]. The ACR used a symptom severity scale and the Regional Pain Scale (renamed the Widespread Pain Index) to construct a new case definition of fibromyalgia: a Widespread Pain Index score of 7 or greater and a symptom severity score of 5 or more [62]. The Widespread Pain Index has been found to correlate well with findings of the tender point examination, eliminating the need for that examination [62]. The symptoms evaluated by the symptom severity scale are fatigue, cognitive dysfunction, and waking unrefreshed (***Table 23***) [62]. The new diagnostic criteria correctly classify 88% of cases classified by the original ACR criteria [62]. In addition, the new criteria eliminate the potential contradiction of having a diagnosis of fibromyalgia but without fulfilling the criteria (if pain at tender points improves) [62]. Another advantage is that the criteria can demonstrate change in the individual's health status and allows for fibromyalgia to be seen as part of a continuum [62].

## TREATMENT OPTIONS

As with all chronic illnesses, the goal of treatment in fibromyalgia is to reduce symptoms, improve function, and engage the patient's involvement in self-care [296]. Studies have shown that treatment is most effective when it includes a combination of pharmacotherapy and nonpharmacotherapy approaches that involve at least one educational or other psychologic therapy with at least one exercise therapy [284; 286; 312; 313; 314; 315].

Treatment guidelines for fibromyalgia have been established by the American Pain Society and EULAR, and subsequent systematic reviews and meta-analyses have provided further findings to support both pharmacologic and nonpharmacologic treatment [284; 313]. Familiarity of guidelines and recommended treatments, especially among primary care providers, is low, and adherence is suboptimal [10; 79]. For example, a substantial number of people with fibromyalgia take pain medications that lack evidence for effectiveness or that are less effective than alternative options [49; 79].

In addition, the practice guidelines for fibromyalgia have many limitations, the most important of which is that their evidence base predates the FDA approval of three drugs for the treatment of the condition. The treatment guidelines may also lack clinical utility because of the crucial need to customize treatment of fibromyalgia according to the unique combination of symptoms in an individual patient. A pooled analysis showed that pain reduction alone does not make people with fibromyalgia feel better; instead, improvements in fatigue, physical functioning, mood, and impact on daily living are important factors in feeling better [316]. These factors must therefore be considered when developing a treatment plan, and optimum treatment will depend on the level of various symptom involvement for the patient [10; 310]. Effective treatment of fibromyalgia may also necessitate guideline-based treatment for comorbidities (e.g., irritable bowel syndrome and restless legs syndrome) [310].

| PHARMACOLOGIC TREATMENTS USED IN FIBROMYALGIA | | | |
|---|---|---|---|
| **Drug** | **Dose** | **Common Adverse Events** | **Comments** |
| **Antidepressants** | | | |
| Amitriptyline | 25–50 mg PO at bedtime | Nausea, vomiting, dry mouth, dizziness, drowsiness, headache | Recommended by American Pain Society and EULAR |
| Duloxetine | 60 mg PO daily | Nausea, dry mouth, constipation, drowsiness, decreased appetite | Approved by FDA for fibromyalgia in 2008 |
| Milnacipran | 50–100 mg PO twice daily | Nausea, headache, constipation, dizziness, hot flush, dry mouth | Approved by FDA for fibromyalgia in 2009 |
| **Anticonvulsants** | | | |
| Pregabalin | 300–450 mg PO daily | Diarrhea, dizziness, blurred vision, dry mouth, vomiting | Approved by FDA for fibromyalgia in 2010 |
| Gabapentin | 1,200–2,400 mg PO daily | Viral infections (in children), dizziness, somnolence, ataxia | Limited data on effectiveness |
| **Analgesics/Muscle Relaxants** | | | |
| Cyclobenzaprine | 10–30 mg PO at bedtime | Drowsiness, xerostomia, dizziness | Recommended by American Pain Society |
| NSAIDs | — | — | No evidence to support use, but may be of benefit in treating comorbidities |
| Glucocorticoids | — | — | No evidence to support use, but may be of benefit in treating comorbidities |
| **Opioids** | | | |
| Low-dose (tramadol) | 200–300 mg PO daily | Hot flush, dizziness, headache, constipation, nausea | Recommended by American Pain Society and EULAR |
| Potent | — | — | Not recommended; should be used only if all other approaches have been exhausted |
| **Sedative Hypnotics** | | | |
| Zolpidem | 5–10 mg PO at bedtime | Headache, somnolence, dizziness | Improves sleep; no effect on pain |
| Benzodiazepines and sedatives | — | — | Evidence of effectiveness is lacking |
| *Source: [10; 19; 20; 299; 310; 317; 318; 326; 386; 387]* | | | *Table 24* |

### Pharmacologic Treatment

No single drug has been found to manage all fibromyalgia symptoms, and a combination approach is often used [49; 310]. Antidepressants were the first medications used to treat fibromyalgia; drugs in this class include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [299; 310]. In general, antidepressants reduce pain through a direct effect rather than an indirect effect mediated by an effect on depression [310]. Other drugs that have been shown to be effective include anticonvulsant drugs, some analgesics/muscle relaxants, and nonbenzodiazepines (***Table 24***) [10; 19; 299; 310; 317; 318].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, the pharmacologic therapies with U.S. Food and Drug Administration approval for fibromyalgia include pregabalin, duloxetine, and milnacipran. Other agents that have been shown to be effective in controlled trials include gabapentin, cyclobenzaprine, tramadol, and tricyclic antidepressants.

(http://www.guideline.gov/content.aspx?id=47646. Last accessed July 29, 2014.)

**Level of Evidence**: Low-quality evidence

### *Antidepressants*

Both the American Pain Society and EULAR found strong evidence (level I) for the use of a tricyclic antidepressant (amitriptyline) for the treatment of fibromyalgia [284; 313]. The American Pain Society recommends using amitriptyline for the initial treatment of fibromyalgia, whereas EULAR notes that any of a number of antidepressants should be "considered" [284; 313]. According to a 2009 meta-analysis, there is strong evidence for an association between treatment with antidepressant medications and reductions in pain, depression, fatigue, sleep disturbances, depressed mood, and a better health-related quality of life for people with fibromyalgia [319]. Treatment with an antidepressant does not completely eliminate pain, but tricyclic antidepressants have been found to be more effective for pain relief than either SSRIs or SNRIs [284; 319]. Amitriptyline was the fifth leading "ever used" drug in the NFA survey (reported by 55% of respondents), with 42% of those using the drug saying it was helpful [49]. In addition, use of prescription antidepressants was the third-highest ranked intervention overall in the survey [49].

Two of the three drugs approved by the FDA are SNRIs: duloxetine and milnacipran [10]. Duloxetine was approved on the basis of two trials. In the first study, duloxetine led to a clinically significant treatment response (at least a 30% reduction in pain severity on the Brief Pain Inventory) in more than half of the study participants [320]. Two doses were evaluated: 60 mg once daily and 60 mg twice daily; both doses were associated with significantly higher response rates than that for the placebo group [320]. Duloxetine also significantly improved function and quality of life. Similar results were achieved with the same doses of the drug in the other study [321]. Neither study showed improvement in sleep; however, duloxetine did not interfere with sleep [310; 320; 321]. The drug was also well tolerated, and nausea was the most common side effect. Given the similarity in response with the two doses of duloxetine, the approval is based on the once-daily dose. A 2014 Cochrane review indicated that there is a lack of efficacy data, but that 60–120 mg daily doses were associated with a greater improvement in mental symptoms than in somatic physical pain [388].

Two studies of milnacipran demonstrated the effectiveness of the drug in achieving a composite endpoint of improvement in scores for pain (30% improvement on a visual analog scale), patient global assessment ("very much" or "much" improved), and physical component of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (six points) [322; 323]. The studies also evaluated the effect of the drug on pain only (improvement in pain and patient global assessment but not SF-36). Two doses were used: 50 mg twice daily and 100 mg twice daily. In both studies, milnacipran was associated with significant improvements in pain, fatigue, patient global assessment, and physical function [322; 323]. Further follow-up has shown the efficacy to be maintained for 12 months [310]. The drug was well tolerated; the most common side effects were mild-to-moderate nausea and headache, both of which resolved with continued use of the medication [322; 323]. The FDA approved milnacipran at both doses.

A systematic review to compare the effectiveness of the three antidepressants demonstrated several differences [324]:

- Amitriptyline was superior to both duloxetine and milnacipran in reducing pain, sleep disturbances, fatigue, and limitations of health-related quality of life.

- Duloxetine was superior to milnacipran in reducing pain, sleep disturbances, and limitations of health-related quality of life.
- Milnacipran was superior to duloxetine in reducing fatigue.
- No differences in tolerability were found among the three drugs.

### *Anticonvulsants*

The third FDA-approved drug for the treatment of fibromyalgia is pregabalin, an anticonvulsant agent. Several studies have shown pregabalin to significantly improve pain, patient global assessment, fatigue, and health-related quality of life, as well as sleep disturbances [310; 325; 326]. The effect of the drug has lasted for as long as 6 months [310]. The drug was well tolerated, with the common side effects being dizziness and sedation, which tended to resolve with time of treatment [310].

Anticonvulsants have been evaluated in several trials, and the American Pain Society found level II evidence for this class of drug, whereas the later EULAR guidelines note level I evidence for pregabalin specifically [284; 313]. Another anticonvulsant drug, gabapentin, has also demonstrated efficacy with respect to pain, patient global assessment, function, and sleep [310; 317; 326]. Gabapentin has not been approved by the FDA to treat fibromyalgia, and the drug is not specifically noted in treatment guidelines [284; 313]. Approximately one-third of the respondents in the NFA survey said they had "ever used" gabapentin, and 46% who had used it considered the drug helpful [49]. The side effect profile of gabapentin is similar to that of pregabalin, but the pharmacokinetic and pharmacodynamic profile is not as favorable [310]. An overview of systematic reviews of anticonvulsants showed that both drugs had a modest effect on pain reduction, and it was not possible to conclude if one drug was better than the other [326]. The long-term safety and efficacy of both drugs is also unknown, and many patients are expected to discontinue therapy due to a high incidence of adverse effects. The overview found no evidence of clinical benefit with any other anticonvulsant, including carbamazepine [326].

### *Analgesics*

With a primary symptom of pain, fibromyalgia has often been treated with analgesics. According to the NFA survey, acetaminophen, ibuprofen, and naproxen were the top three ever-used medications (94%, 87%, and 66%, respectively) [49]. Slightly more than one-third to about one-half of the survey respondents said that these medications were helpful [49]. In another study, nearly 30% of 434 women with fibromyalgia reported taking NSAIDs [79]. However, with no inflammatory mechanism, fibromyalgia is not expected to respond to NSAIDs, and there is no evidence to support the use of NSAIDs or glucocorticoids as a treatment modality [284; 313]. NSAIDs may be of benefit in relieving pain associated with comorbidities, such as osteoarthritis, rheumatoid arthritis, or systemic lupus, which may account for their high rate of use in the NFA survey [49; 310].

Strong evidence has also been documented for cyclobenzaprine, which has both muscle relaxant and tricyclic antidepressant properties [299; 318; 327]. A systematic review of five randomized controlled trials showed that individuals treated with cyclobenzaprine for fibromyalgia were three times as likely to report overall improvement and to note reductions in symptoms, especially sleep disturbances, than controls [327]. Among the NFA survey respondents, 64% had ever used cyclobenzaprine and 58% of these patients considered the drug to be helpful [49].

Neither the American Pain Society nor EULAR recommend the use of potent opioids for the treatment of fibromyalgia, noting that they should be used only if all other pharmacologic and nonpharmacologic options have been exhausted [284; 313]. The American Pain Society found moderate evidence (level II, III) and EULAR documented level I evidence for tramadol, a mild opioid [284; 313]. The drug is recommended in both guidelines

and may be used alone or as an adjunctive measure [310; 313; 318]. The dose of tramadol should be increased slowly over time and should be tapered gradually when discontinued [284]. Caution should be used when prescribing tramadol because of the risk of dependence and abuse [313].

### *Sedative Hypnotics*

Benzodiazepines and sedatives are not recommended for the treatment of fibromyalgia symptoms [19]. Zolpidem, a short-acting nonbenzodiazepine sedative, has been used to improve sleep in people with fibromyalgia, but because zolpidem does not relieve pain, it is useful only as an adjunct medication, and it has not been included in treatment guidelines for fibromyalgia [284; 310; 313]. Approximately 41% of the NFA survey respondents said they had ever used the drug, and 64% of these individuals considered it helpful [49]. In general, prescription sleep medication was the intervention that respondents considered the most effective of all interventions [49].

## Nonpharmacologic Treatment

Nonpharmacologic measures are important components of an effective fibromyalgia treatment plan. Strong evidence has been documented for exercise (aerobic and/or muscle-strength training), cognitive-behavioral therapy, and patient education, and the combination of the three components is the recommended approach [19; 312; 313; 315].

### *Exercise*

Exercise not only helps to alleviate many fibromyalgia symptoms but also helps to reverse the effects of deconditioning and improve physical fitness [286; 314; 328; 329; 330; 331]. In a study of 207 women who were actively treated with medication for confirmed fibromyalgia, progressive walking, simple strength-training exercises, and stretching activities led to several improvements, including higher scores for functional status, reduced fatigue, better mental health, reduced depression, and greater self-efficacy [328]. The benefits of exercise are enhanced when combined with targeted self-management education [19; 328].

A meta-analysis published in 2007 showed that supervised aerobic exercise training has beneficial effects on physical capacity and symptoms related to fibromyalgia and that strength training may also have benefits on some fibromyalgia symptoms [329]. Another meta-analysis published in 2010 showed that aerobic exercise has a significant positive effect on a variety of disease-related symptoms, with reductions in pain, fatigue, depressed mood, and limitations of health-related quality of life, as well as improved physical fitness [331]. A 2013 Cochrane review found low-quality evidence that resistance training (moderate-to-high intensity) improves functioning, muscle strength, pain, and tenderness in women with fibromyalgia [389]. Other low-quality evidence suggests that aerobic exercise is superior to resistance training for improving pain, but resistance training is superior to flexibility exercise training in women with fibromyalgia for improvements in pain and multidimensional function. Moderate-to-high resistance training is safe for women with fibromyalgia [389].

Both the American Pain Society and EULAR recommend exercise programs as part of treatment for fibromyalgia [313; 318]. The American Pain Society recommends beginning with low levels of exercise and working gradually to a goal of moderately intense aerobic exercise at least two to three times per week [318]. However, fewer than one-third of NFA survey respondents said they engaged in aerobic exercise; more respondents said they participated in "gentle walking" (64%) and stretching (62%), and fewer noted use of physical therapy (24%) or strength training (18%) [49]. Aquatic physical therapy has also been recommended for relief of fibromyalgia-related stiffness [390].

EULAR notes that exercises should be tailored to the individual patient, and modifications should be made according to the severity of symptoms [313]. For example, a sedentary individual with moderate-to-severe fibromyalgia should begin with breathing, posture, and relaxation training, move to flexibility exercises, then to strength and balance exercise, and finally, to aerobic exercise [330].

### *Cognitive-Behavioral Therapy*

The goal of cognitive-behavioral therapy is to move patients toward more adaptive beliefs about their ability to cope with symptoms, which in turn increases self-management [314]. Cognitive-behavioral therapy is designed to help individuals improve the way they think about fibromyalgia and cope with the overall effects of its symptoms [286]. It is most effective when it focuses on a specific outcome, especially one that is the subject of the patient's maladaptive thoughts and expectations [286; 314].

A systematic review of 23 studies showed that of 30 psychologic treatments for fibromyalgia, cognitive-behavioral therapy was associated with the greatest effect sizes, especially for short-term reduction in pain [332]. In addition to short-term and long-term reductions in pain, cognitive-behavioral therapy has been associated with reductions in sleep disturbances and depression and improvements in functional status [286; 313; 314; 318; 332]. Benefit is typically achieved in 10 to 20 sessions [19]. Despite recommendations for cognitive-behavioral therapy, it may be underutilized. According to the NFA survey, only 8% of respondents had used this strategy [49].

Cognitive-behavioral therapy has been significantly beneficial in many individuals with psychiatric illnesses, such as depression and anxiety disorders, and so may be most useful for individuals with fibromyalgia who have these symptoms [314]. The individuals most likely to respond are probably those who have greater emotional distress, fewer coping skills, or less social support [19; 314].

### *Other Approaches*

Relaxation techniques are often part of cognitive-behavioral therapy for fibromyalgia, and their effectiveness is generally accepted, even though direct evidence is lacking [314]. Relaxation/meditation was practiced by 47% of the NFA survey respondents [49]. Mindfulness-based stress reduction therapy has also been evaluated; however, only weak evidence exists for benefit in fibromyalgia [392].

The EULAR guidelines include a recommendation (level IIb) for heated pool treatment, with or without exercise, on the basis of studies showing improvement in pain and function [313]. A subsequent meta-analysis of 10 randomized controlled trials demonstrated moderate evidence that hydrotherapy has short-term beneficial effects on pain and health-related quality of life [333].

The lack of fully effective treatments has led patients—and sometimes their healthcare providers—to explore other options to help manage symptoms. Some of these options have no or weak evidence of effectiveness, and the approaches most commonly used by patients are often not recommended practices. For example, the three interventions used most often by the NFA survey respondents were resting (86%); distraction, such as reading or watching television (80%); and heat modalities, such as warm water or hot packs (74%) [49]. The issue is not that these methods are not helpful, rather that the use rates for these approaches are much higher than for many evidence-based recommended strategies [49].

Among the other approaches patients often try are complementary and alternative medicine; between 40% and 90% of individuals with fibromyalgia have tried at least one such method [49; 78; 79]. However, evidence indicates that most of these methods are ineffective. There is limited evidence to support spinal manipulation [335]. Evidence is also lacking on the effectiveness of herbal, nutritional, and dietary supplements (including St. John's wort, ginseng, valerian, melatonin, and botanical oil) for the symptomatic treatment of fibromyalgia [314; 335; 336]. Despite this, approximately 43% to 68% of people with fibromyalgia use such supplements, although they give low ratings for their effectiveness [49; 79]. Given the high rate of individuals with fibromyalgia who seek symptomatic relief from complementary and alternative methods, the American Pain Society guidelines recommend that clinicians ask their patients about their use of such practices and educate them about their effectiveness and possible negative interactions [284].

Methods with greater evidence of benefit include acupuncture and massage therapy. A 2013 Cochrane review found low-to-moderate level evidence that acupuncture (particularly electro-acupuncture) is effective for the treatment of fibromyalgia symptoms compared with no treatment or standard therapy [334]. Acupuncture in general may relieve pain and stiffness, and electro-acupuncture may improve overall well-being, fatigue, and sleep quality. A 2014 meta-analysis of nine randomized controlled trials found that massage therapy (for at least 5 weeks) has beneficial immediate effects on improving pain, anxiety, and depression in fibromyalgia patients [391]. However, no follow-up data are available to show long-term benefit. Long-term data are similarly unavailable for qigong, a somewhat popular Chinese medical exercise, but low-quality evidence exists for the short-term improvement of pain, quality of life, and sleep quality and very low-quality evidence exists for improvement of fatigue [393]. Increased psychologic well-being is often reported by qigong practitioners.

## FOLLOW-UP AND PROGNOSIS

Individuals with fibromyalgia should be followed up routinely to assess response to treatment. Follow-up visits also offer an opportunity for healthcare professionals to encourage their patients to comply with pharmacologic and nonpharmacologic treatment. Reinforcement for the need to exercise is especially important, as 68% to 83% of people with fibromyalgia have been found to not engage in aerobic exercise [49; 330]. Rates of exercise among the general population are below optimum, and people with fibromyalgia need added encouragement because of many symptoms that may be perceived as barriers (e.g., fatigue, pain).

One approach to enhance adherence to an exercise program is to begin pharmacologic treatment targeting the most distressing or severe symptoms and then provide education about exercise as symptoms begin to improve [19; 330]. It is especially important to address sleep disturbances and fatigue. In contrast to recommendations for the general population, increasing lifestyle activity is not effective as exercise for individuals with fibromyalgia; instead, clinicians should encourage their patients with fibromyalgia to conserve their energy in daily life in order to have the ability to comply with prescribed exercises [330].

The authors of one review of nonpharmacologic treatment suggest that clinicians use the acronym ExPRESS to follow principles of nonpharmacologic pain management [314]:

- **Ex**: Exercise
- **P**: Psychiatric (i.e., addressing psychiatric comorbidities to help improve pain and disability)
- **R**: Regain function (helping patients pace activities to avoid doing too much on days they feel well)
- **E**: Education (referral to reliable resources)
- **S**: Sleep hygiene
- **S**: Stress management (such as cognitive-behavioral therapy and relaxation techniques)

### Prognosis

Fibromyalgia symptoms will persist in most individuals, but the majority still report that they feel better overall than at the time of diagnosis [19; 286]. Better outcomes have been associated with greater self-efficacy, help-seeking behavior, increased level of exercise, and pacing of activities [19].

## PATIENT EDUCATION

The goal of patient education is to effect a change in the patient's perception of his or her role in managing and coping with symptoms [19]. As noted, there is strong evidence that patient education is an essential component of effective treatment [284; 312; 313; 315]. Even a single multidisciplinary educational program was associated with significant improvements in pain, fatigue, morning tiredness, stiffness, anxiety, and depression [312]. Education in a variety of formats has been found to be useful, including lectures, written materials, group discussions, demonstrations, and web-based programs

[312; 337]. Healthcare professionals should also encourage their patients to take advantage of many reliable online educational resources.

## CELIAC DISEASE

Celiac disease, also known as celiac sprue, is inflammation of the small intestine caused by gluten proteins, which are found in foods containing rye, wheat, and barley. Gluten proteins are not digested well by digestive enzymes in the upper gastrointestinal tract, and in individuals with a genetic predisposition, the undigested gluten proteins cause an inflammatory reaction in the mucosa of the small intestine.

### EPIDEMIOLOGY

The prevalence of celiac disease is approximately 0.5% to 1% [338; 339]. The true prevalence is thought to be higher than has previously been reported, and the number of so-called silent cases (with few or no symptoms) of the disease has increased [340]. In addition, the incidence pattern has changed, with more cases being diagnosed in adulthood [340]. A 2009 Mayo Clinic study compared stored blood samples taken from male Air Force recruits in 1950 with samples from similarly aged men around the time of the study [360]. The modern samples showed a 4.5-fold increase in the celiac antibody, which correlates with a rate of celiac disease of approximately 1%. This study underscores the fact that the incidence is truly rising, rather than the notion that increased awareness of the disease has led to a spike in its diagnosis [359; 360].

Most U.S. studies have involved predominantly white populations, leaving unclear the prevalence among racial/ethnic groups. European studies (conducted in the United Kingdom, Sweden, the Netherlands, Ireland, and Finland) have indicated that the prevalence may be slightly higher in those countries [22]. Individuals with a family history of celiac disease (first-degree relative) have a higher risk for the disease, with a prevalence of 16% [22]. Serum samples or a self-reported diagnosis from a representative U.S. cohort (7,798 individuals) as part of the National Health and Nutrition Examination Survey 2009–2010 confirmed a prevalence of 1% in the non-Hispanic white population; overall, the prevalence was 0.71%, reflecting the rarity of celiac disease in non-white individuals [361].

### POTENTIAL ENVIRONMENTAL RISK FACTORS

It is not clear how gluten sensitivity begins or how sensitivity is increased by early exposure. The results of studies have suggested that first exposure to dietary gluten before the age of 3 months or after the age of 6 months is a risk factor for disease [68]. Other environmental factors may be a high number of gastrointestinal infections before 6 months of age and frequent rotavirus infections in children younger than 4 years of age [68]. Alternately, the "hygiene hypothesis" posits that an increasingly sterile environment has left the immune system of many individuals unchallenged and, therefore, unfortified by the bacteria, viruses, and parasites that their ancestors faced, causing increased susceptibility to allergic and immune disorders [359].

Some researchers believe that changes in grain itself, rather than increased levels of consumption, are at least partially responsible for the increase in celiac cases [359]. Despite increasing wheat consumption in the last several decades, consumption is still significantly less than it was 100 years ago. In that time, wheat has undergone extensive hybridization as a crop (i.e., modified wheat genetics), and drastic changes during processing, which involves oxidizers, new methods of yeasting, and other chemical processes (e.g., enzymatic modification of wheat prolamins), have occurred in the past 40 years [359; 360]. The effect these changes have had on the immune system is presently unknown; however, human genetic modifications in response to environmental challenges are extremely slow [360].

## ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Autoimmune diseases are three to 10 times more likely in individuals with celiac disease than in the general population [341]. The strongest associations have been found between celiac disease and Sjögren syndrome (4.5% to 14.7%), type 1 diabetes (1% to 12%), Addison disease (1.2% to 8%), primary biliary cirrhosis (1.3 to 7%), autoimmune hepatitis (4% to 6%), and autoimmune thyroid disease (up to 5.8%) [22; 68].

## CLINICAL MANIFESTATIONS

The classic symptoms of celiac disease were once diarrhea and malabsorption, but this presentation is now rare [342]. Although diarrhea, borborygmus (intestinal rumbling), abdominal pain, weight loss, and nutritional deficiencies are the most common gastrointestinal symptoms, many other nonspecific and extraintestinal symptoms often occur [342]. Fatigue is present in nearly 80% of patients, and signs of iron-deficient anemia and osteoporosis are also common [22; 37; 68; 342]. As many as 38% of individuals have silent celiac disease [68; 339].

Dermatitis herpetiformis, a skin disease characterized by blistering lesions that are intensely itchy and often painful, is found in up to 25% of individuals with celiac disease. These lesions are typically located on the extensor surfaces of the elbows, knees, buttocks, and back [343]. Neurologic manifestations develop in about 10% to 12% of individuals with celiac disease, including cerebellar ataxia, peripheral neuropathy, seizures, and myelopathy [68].

## DIAGNOSTIC EVALUATION

The American College of Gastroenterology (ACG) recommends celiac disease diagnostic testing for patients with symptoms, signs, or laboratory evidence suggestive of malabsorption (e.g., chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain and bloating). The ACG also recommends [344]:

- Patients with a first-degree family member who has a confirmed diagnosis of celiac disease should also be tested if they show possible signs/symptoms or laboratory evidence of celiac disease.
- Patients with type 1 diabetes should be tested if they have any digestive symptoms/signs/laboratory evidence suggestive of celiac disease.
- Testing for celiac disease is warranted if the patient has elevated serum aminotransferase levels when no other etiology is found.

All of these are strong recommendations with a high level of evidence [344].

The differential diagnosis of celiac disease involves the exclusion of several conditions with similar characteristics, including anorexia nervosa, bacterial overgrowth, Crohn's disease, and intestinal lymphoma [340]. Irritable bowel syndrome has been diagnosed before the detection of celiac disease in as many as 36% of individuals [340].

The diagnosis of celiac disease should be made on the basis of several factors, including the findings of the history and physical examination, serologic testing, and biopsy of the small intestine [37; 344]. The preferred single test for detection of celiac disease in patients older than 2 years of age is the immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody [344]. Diagnostic testing should be done while the patient's diet includes foods that contain gluten. Children younger than 2 years of age should be screened using the IgA TTG test combined with immunoglobulin G (IgG) based testing (e.g., IgG-deamidated gliadin peptides [DGPs]) [344]. IgG-based testing (IgG DGPs and IgG TTG) should also be used in adult patients in whom low IgA or selective IgA deficiency is identified. Serum IgA endomysial antibodies (EMA) have also been used but are not recommended in the ACG guidelines [22; 37; 344].

| SUGGESTED CRITERIA FOR DIAGNOSIS OF CELIAC DISEASE[a] | |
|---|---|
| **Criteria** | **Description** |
| Typical symptoms | Chronic diarrhea, iron-deficient anemia, weight loss (adults), deficient growth (children) |
| High titers of serum autoantibodies | Both IgA class tTG and EMA in IgA-sufficient patients or IgG class tTG and EMA in IgA-deficient patients |
| HLA-DQ2 or DQ8 genotypes | Found in almost all persons with celiac disease |
| Biopsy findings of celiac enteropathy | Total to partial villous atrophy and crypt lengthening with an increase in lamina propria and intraepithelial lymphocytes |
| Response to gluten-free diet | Positive response to restricted diet |
| [a]Four of these five criteria are needed for diagnosis. | |
| *Source: [346]* | *Table 25* |

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Gastroenterological Association recommends that all diagnostic serologic testing should be done with patients on a gluten-containing diet. (http://www.guideline.gov/content.aspx?id=45327. Last accessed July 29, 2014.)

**Level of Evidence**: High (Further research is unlikely to change our confidence in the estimate of effect)

There is no one universally accepted diagnostic standard, and the diagnosis of celiac disease should be made on the basis of several factors, including the findings of the history and physical examination, serologic testing, and biopsy of the small intestine [37].

Although the sensitivity of IgA TTG antibodies has been good (greater than 95%), the degree depends on the extent of mucosal involvement. The risk of a false-positive result is high; false-negative results may also occur in patients who have celiac disease and IgA deficiency [37]. In general, no further diagnostic testing is needed if serologic testing is negative in a patient at low risk (and without IgA deficiency); further testing (i.e., intestinal biopsy) should be done to confirm the diagnosis when serologic testing is positive [37; 344]. Intestinal biopsy should also be pursued if the suspicion of celiac disease is high, even if serologies are negative [344].

Upper endoscopy with biopsy of the small intestine has been considered the criterion standard for confirmation of diagnosis of celiac disease [344]. Evaluation of a biopsy specimen will demonstrate celiac enteropathy in almost 100% of patients who have typical symptoms in combination with high titers of IgA TTG [345]. However, there is a spectrum of characteristic histologic changes in the small intestinal mucosa; villous atrophy may vary from partial to total, and other mucosal changes may include subtle crypt lengthening or increased epithelial lymphocytes. Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for celiac disease, and other causes should be considered [344]. Because changes may be intermittent along the mucosa, it is recommended that at least four tissue samples be obtained for evaluation from the distal duodenum and one or two from the bulb [37; 344]. Findings on biopsy are not 100% sensitive or specific, as evidence of celiac disease may be similar to that of infection, enteritis, lymphoma, or bacterial overgrowth.

Given the potential difficulty in confirming the diagnosis of celiac disease with use of serologic testing and biopsy, some authors have suggested that a diagnosis can be made when four of five criteria are present (***Table 25***) [346]. It should be noted that these criteria are different from the ACG clinical guidelines for the diagnosis and management of celiac disease.

The ACG guidelines state that HLA-DQ2/DQ8 genotyping testing should not be routinely used in the initial diagnosis of celiac disease, but it is recommended to effectively rule out the disease in selected clinical situations [344]. These include, but are not limited to, patients with Down syndrome, patients on a gluten-free diet in whom no celiac disease testing was done before the diet, patients with discrepant celiac-specific serology and histology, and patients with suspicion of refractory celiac disease where the original diagnosis of celiac remains in question [344]. HLA-DQ2/DQ8 genotyping testing should be used in an attempt to rule out celiac disease in patients already on a gluten-free diet before a formal gluten challenge, but a formal gluten challenge should be considered in order to obtain an accurate diagnosis.

## TREATMENT OPTIONS

Celiac disease is treated with a lifetime gluten-free diet, as avoidance of gluten proteins from wheat, barley, and rye can help mucosal lesions to heal and reverse the effects of the disease. In addition to alleviating gastrointestinal symptoms, long-term compliance with a gluten-free diet can also improve outcomes related to bone density, iron-deficiency anemia, and dermatitis herpetiformis [347; 348]. For example, anemia and iron-deficiency generally improve in 6 months and 1 year, respectively [347]. Some neurologic manifestations may remain despite adherence to a gluten-free diet [349].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Dietetic Association, individuals with celiac disease should be advised to consume whole or enriched, gluten-free grains and products such as brown rice, wild rice, buckwheat, quinoa, amaranth, millet, sorghum, and teff. Research reports that adherence to the gluten-free dietary pattern may result in a diet that is low in carbohydrates, iron, folate, niacin, zinc, and fiber. If usual food intake shows nutritional inadequacies that cannot be alleviated through improved eating habits, individuals with celiac disease should consume a daily, gluten-free, age- and sex-specific multivitamin and mineral supplement.

(http://www.guideline.gov/content.aspx?id=14854. Last accessed July 29, 2014.)

**Level of Evidence**: II (Fair—studies of strong design with minor methodological concerns OR only studies of weaker study design)

A multidisciplinary approach to treatment is needed and may involve gastroenterologists, endocrinologists, allergists, dermatologists, hepatologists, pharmacists, and social workers. Central to the team is a registered dietician. In addition to assessing the food/nutrition-related history, the results of diagnostic testing, factors affecting quality of life, gastrointestinal symptoms, and other diseases, the dietician provides medical nutrition therapy and is responsible for educating the patient about how to adhere to a gluten-free diet [344; 347]. Testing and treatment for micronutrient deficiencies (particularly folic acid, iron, vitamin D, and vitamin B12) may be warranted in newly diagnosed patients. Treatment with medication and aggressive nutritional support (including parenteral nutrition) is indicated for patients with refractory celiac disease [344].

The treatment of celiac disease also includes the management of complications. Dapsone can be used to treat dermatitis herpetiformis until the gluten-free diet has had effect; the drug typically relieves symptoms within 1 to 3 days [343]. Because of the potential for dapsone to cause hemolysis in some individuals, a baseline CBC and periodic follow-up testing are recommended [343]. Calcium and vitamin D supplements may also be necessary

to ensure bone health [37]. The use of bisphosphonates for osteoporosis may be appropriate, although their use for osteoporosis related to celiac disease has not been studied extensively [37].

## FOLLOW-UP AND PROGNOSIS

Follow-up for individuals with celiac disease should focus on four components [22; 350]:

- Monitoring adherence to a gluten-free diet
- Treatment of nutritional deficiencies
- Assessment of bone mineral density
- Evaluation for signs of lymphoma

Healthcare professionals should ensure that patients and their families have the resources, education, motivation, and support to comply with a gluten-free diet. Serologic testing should be done to monitor compliance with a gluten-free diet; strict adherence usually leads to antibody levels becoming normal within 3 to 12 months after starting the diet [37]. A lack of response according to serologic testing may indicate continued exposure to gluten; if the patient has been adhering to the gluten-free diet, the clinician should explore other diagnoses. Among other diseases that appear similar to celiac disease are microscopic colitis, pancreatic insufficiency, inflammatory bowel disease, ulcerative jejunoileitis, collagenous sprue, and T-cell lymphoma [37].

Follow-up should also include monitoring of nutritional deficiencies to ensure adequate levels of iron, folate, and vitamin B12. Bone mineral density usually resolves in children who adhere to a gluten-free diet, but it may not resolve in adults. Thus, bone density testing may be appropriate to determine whether treatment for osteopenia or osteoporosis is needed [37]. Children should be monitored for normal growth and development [344].

**COMMERCIAL AND PROCESSED FOOD THAT MAY CONTAIN GLUTEN**

| |
|---|
| Baked beans (canned) |
| Bouillon cubes |
| Candy |
| Canned meats |
| Coffee (flavored instant) |
| Cold cuts, hot dogs, salami, sausage |
| Communion wafers |
| French fries |
| Fruit pie fillings |
| Gravy, sauces |
| Herbal teas |
| Hot cocoa mixes |
| Imitation fish |
| Matzo |
| Nondairy cream substitutes |
| Rice mixes |
| Potato chips |
| Prepared salad dressings |
| Seasoned tortilla chips |
| Self-basting turkey |
| Soups (canned) |
| Soy sauce |
| Vegetables in sauce |
| Yogurt (flavored or frozen) |

*Source: [37; 355]* *Table 26*

Celiac disease is associated with a risk of non-Hodgkin lymphoma that is three to six times higher than that for the general population, and the risk for lymphoma is higher for individuals in whom celiac disease is diagnosed later in adulthood [351; 352]. Data have suggested that the risk of lymphoma decreases over time on a strict gluten-free diet [22]. New gastrointestinal symptoms or other signs of lymphoma should prompt further evaluation. Studies have indicated that the risk of other gastrointestinal malignancies, such as esophageal, gastric, and colorectal cancer, are not increased among individuals with celiac disease [351; 353; 354].

## PATIENT EDUCATION

Patient education is key to the success of treatment and must focus on strict adherence to a gluten-free diet. A registered dietician should talk to patients and family members on ways to be compliant, noting the importance of addressing potential nutritional deficiencies through eating whole/enriched gluten-free grains and taking a multivitamin or mineral supplement [347]. Especially important is education about possible cross-contamination in food manufacturers and restaurants as well as at home and the careful reading of food labels to identify foods containing gluten (***Table 26***) [37; 347; 355].

# CASE STUDY

Patient A is a woman, 25 years of age, who recently gave birth to her second child. She visits her primary care provider because of the gradual onset of fatigue, anxiety, and a feeling of her "heart pounding." The physician finds nothing remarkable on physical examination; a CBC indicates slight anemia. The physician tells her he believes the symptoms are related to slight anemia and the stress of giving birth in addition to caring for a toddler. The physician recommends that Patient A try to rest more, take a daily multivitamin with iron, and obtain some help caring for her two small children.

Over the next year, Patient A's symptoms wax and wane. Her family is supportive as she tries to reduce the stress in her life, but her symptoms do not resolve completely. At a routine physician office visit, she describes continued extreme fatigue as well as muscle weakness. On physical examination, her skin feels warm and moist and her pulse is slightly elevated (80 beats per minute). During the history-taking, the physician learns that Patient A's mother has Graves' disease. On further physical examination, the physician notes that the thyroid gland feels normal, that her eyes and eyelids appear normal, and that she has no fine finger tremor. However, based on the family history and Patient A's desire to have another child in the near future, the physician orders thyroid function studies. The TSH level is normal, as are the T3 and T4 levels. The physician reiterates the need for lifestyle modifications, including enhanced nutrition, exercise, better sleep, and over-the-counter analgesics as needed.

***Rationale and comments****: Several factors indicate the possibility of Graves' disease, although some do not. Patient A is younger than the typical woman in whom Graves' disease first occurs (40 to 60 years). But in individuals with genetic susceptibility, stress and recent childbirth have been identified as potential environmental triggers for the disease. Her symptoms of fatigue, anxiety, and palpitations are among the common symptoms of Graves' disease, as is her warm, moist skin. However, the lack of thyroid enlargement, a pulse of less than 90 beats per minute, and the absence of finger tremor are findings with the most significance in ruling out hyperthyroidism.*

*It seems appropriate to rule out a diagnosis of Graves' disease given that Patient A wants to have another child. The American Association of Clinical Endocrinologists recommends TSH with measurement of total T4 or a free T4 index testing for women of childbearing age before or during pregnancy. Laboratory testing confirmed that she did not have Graves' disease, as a low TSH level with increased T4 levels indicates hyperthyroidism.*

Patient A's symptoms continue, and she becomes increasingly frustrated by the lack of symptomatic relief. Among the new symptoms that have developed are dry eyes, intermittent headaches, and pain in the finger joints of both hands, all of which she attributes to too much time working on the computer at her job. The pain in her fingers resolves with rest. She also begins to have occasional pain and stiffness in both hips, especially in the morning. She starts to take large doses of over-the-counter analgesics as well as nutritional supplements. She continues to feel fatigue so overwhelming that she must call in sick to work at least once or twice every month. She wants to have another child but does not feel as though she would be able to physically handle a pregnancy and the care of a third child. She begins to have mood swings, and she feels depressed "sometimes."

She makes an appointment with her primary care provider to discuss her increasing symptoms. Based on her description of new symptoms, the physician orders a rheumatoid factor test, and the result is a low positive. He refers her to a rheumatologist for possible rheumatoid arthritis.

On examining Patient A, the rheumatologist finds normal vital signs, except for a low-grade fever. There is slight limitation in the range of motion of both hips, with some decreased muscle strength in the left leg. In taking the history, the rheumatologist learns that Patient A's joint pain has been present for about 1 month and that her pain/stiffness in the hip lasts for about 30 to 60 minutes each morning. The physician orders a CBC, platelet count, ACPA, ESR, and CRP; the results of all are normal, except for continued slight anemia. Radiographs of the hips show slight degeneration in the left hip. The rheumatologist tells Patient A that her pain may be related to early osteoarthritis, and he prescribes a COX-2 inhibitor for pain relief, prescribes an antidepressant, and recommends regular exercise, more rest, and counseling for stress reduction. Patient A interprets the suggestion of counseling and an antidepressant as meaning that her physical symptoms are "in her head," and she becomes even more frustrated.

***Rationale and comments**: Again, some of the details of Patient A's case fit with a diagnosis of rheumatoid arthritis and others do not. The proximal interphalangeal and metacarpophalangeal joints are among the most commonly involved joints, and they are not usually painful at rest. Joint symptoms are usually bilateral. As is the case for most individuals, the symptoms of rheumatoid arthritis develop over a long period of time (weeks to months). Her other symptoms-fatigue, weakness, and generalized muscular aches-are also suggestive of rheumatoid arthritis. Approximately 46% of individuals with rheumatoid arthritis have extra-articular manifestations, and among the most common are dry eye syndrome and anemia of chronic disease. Depression is also common, occurring in about one-third of individuals. In addition, the findings of a low-grade fever, limitation in the range of motion of the hip, and decreased muscle strength near an affected joint are consistent with rheumatoid arthritis.*

*The positive rheumatoid factor would also seem to suggest rheumatoid arthritis, as this finding has long been known as an indicator of rheumatoid arthritis, and studies have shown that it is positive in approximately 69% to 90% of people with the disease. However, the test may be positive in healthy individuals as well as in individuals with other rheumatic diseases (e.g., Sjögren syndrome, systemic sclerosis, systemic lupus), with chronic infections, or with pulmonary disease. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis call for a rheumatoid factor as well as an ACPA, which has a higher specificity. The negative ACPA and normal ESR and CRP level, along with her other signs and symptoms, yield a score of 5 on the diagnostic criteria, one point lower than the 6 needed for a diagnosis of "definite" rheumatoid arthritis. The radiographic evidence of degeneration in the left hip and the morning stiffness that lasts less than 1 hour suggest osteoarthritis.*

*The rheumatologist's treatment plan is appropriate. There is good evidence that nonselective NSAIDs and COX-2 inhibitors have comparable efficacy, and a COX-2 inhibitor has been associated with lower risks of gastrointestinal adverse events than a nonselective NSAID plus a proton-pump inhibitor. The recommendations for nonpharmacologic treatment are also in line with established recommendations.*

Patient A adheres to her medication treatment, and the pain in her hips is somewhat relieved. However, more new symptoms appear over the course of the next year. During the winter, she becomes intolerant to cold weather, with her hands and feet becoming painful and discolored when she is exposed to cold. When she sees her primary care provider, he tells her that she may have Raynaud phenomenon. Her other symptoms continue, and he reiterates the need for her to continue with the rheumatologist's treatment plan. The following summer, she has a strange red, raised rash on her cheeks after being out in the sun. In addition, small, raised sores begin to develop on her legs and arms. The joint pain, swelling, and fatigue continue. She returns to her primary care provider who is himself frustrated by Patient A's continuing symptoms. He suggests that she return to the rheumatologist, but

she says she did not have a good experience with him and wants to see a different rheumatologist. He refers her to another local rheumatologist and notes in her chart that she has been a "chronic complainer."

At the first visit, the new rheumatologist elicits Patient A's long medical history and description of her numerous symptoms. On physical examination, the vital signs are normal, except for a low-grade fever. The physician notices small ulcers in her mouth, pain and swelling in both hips, and a slight pleural rub. He orders a CBC and platelet count, an ANA titer, an anti-double-stranded DNA titer, and antiphospholipid antibodies. He also obtains biopsy samples from the lesions on her legs. The results of the lab work show a normal white blood cell count, a low platelet count (<100,000/$mm^3$), and positive ANA titer, anti-double-stranded DNA titer, and antiphospholipid antibodies. The findings of the skin biopsy indicate small vessel vasculitis. The rheumatologist diagnoses systemic lupus erythematosus, explaining to Patient A that all of her symptoms over the past 4 years can be attributed to the disease.

***Rationale and comments**: Patient A's constellation of symptoms indicates systemic lupus. The classic sign of a butterfly-shaped rash in the malar area of the face is present in up to 90% of cases. Other common symptoms include the discoid rash elsewhere on the body, photosensitivity, Raynaud phenomenon, joint pain (especially in proximal joints of the fingers), fatigue, dry eye syndrome, low-grade fever, small oral ulcers, pain and swelling in both hips, and slight pleural rub. The ANA titer is highly sensitive for systemic lupus, with a positive result in approximately 93% to 100% of individuals with the disease. An anti-double-stranded DNA test can help confirm a diagnosis of systemic lupus, as it has greater specificity than the ANA titer. About 20% to 30% of people with systemic lupus have antiphospholipid antibodies, which increases the risk for thromboembolism and pregnancy loss. The clinical findings, coupled with the results of laboratory testing, fulfill nine of the 11 criteria for the diagnosis of systemic lupus; four criteria are needed for a definite diagnosis.*

The rheumatologist emphasizes the need for both pharmacologic and nonpharmacologic measures. He begins treatment with hydroxychloroquine (200 mg PO) twice daily and 5 mg of prednisone daily, after obtaining baseline dual x-ray absorptiometry, measuring her height, and determining the serum 25-hydroxyvitamin D level. The rheumatologist also makes several recommendations:

- Use artificial tear drops.
- Take supplemental calcium and vitamin D.
- Engage in regular exercise.
- Schedule a comprehensive eye examination.
- Schedule routine gynecologic examinations.
- Modify lifestyle factors to reduce the risk of cardiovascular disease.
- Protect skin against exposure to ultraviolet rays.
- Maintain follow-up visits at 6-month intervals.

He also warns her of the risk of pregnancy loss related to the presence of antiphospholipid antibodies and encourages her to learn all she can about the disease, providing her with educational materials, a list of reliable websites, and a list of local support groups.

***Rationale and comments**: The rheumatologist's treatment and follow-up plan meet all the recommendations in established guidelines. The preferred first-line treatment of systemic lupus without major organ involvement is an antimalarial drug and a low-dose glucocorticoid (usually prednisone), two of only three drugs approved by the FDA for use in systemic lupus. Antimalarial agents offer many benefits. They can alleviate joint-related, cutaneous, constitutional, and serosal manifestations of systemic lupus; they can prevent disease flares; they are well tolerated; they have been associated with a lower risk of infection than other treatment approaches; and they have a protective effect on survival. Artificial tear drops are recommended for the treatment of mild dry eye syndrome related to systemic lupus. Glucocorticoid-induced osteoporosis occurs in 4% to 24% of individuals with systemic lupus, and the ACR recommends a daily calcium intake of*

*1,200 to 1,500 mg and supplemental vitamin D, as well as a baseline dual x-ray absorptiometry, height, and serum 25-hydroxyvitamin D level. Hydroxychloroquine increases the risk for retinopathy, although this side effect is rare at Patient A's dose. Still, ophthalmologic follow-up is important, and the American Academy of Ophthalmology recommends a complete ophthalmologic examination within the first year after treatment. Systemic lupus is associated with an increased risk for HPV infection and cervical dysplasia, making it necessary to have regular gynecologic evaluations. In addition, the risk of cardiovascular disease is increased, and steps should be taken to reduce the risk. Lastly, systemic lupus is associated with an increased risk for other autoimmune diseases, and healthcare professionals should carefully consider the possibility of these diseases during follow-up. Providing educational resources in a variety of formats helps to ensure that patients better understand their disease and its management, which is an essential component in the treatment of a chronic disorder.*

Over the next month, Patient A's rash gradually resolves, and her pain and fatigue improve. She feels well enough to comply better with an exercise program, and her symptoms further improve. Her rheumatologist sees her for follow-up every 6 months. One year after the initiation of treatment, she continues to feel much better than she "has in a long time" and has made several new friends in her local support group.

***Rationale and comments:*** *This case reflects the challenges in diagnosing an autoimmune disease because of vague, overlapping symptoms. The absence of characteristic features on physical examination does not necessarily rule out an autoimmune disease, because signs and symptoms tend to wax and wane. As was the situation for Patient A, most individuals consult many healthcare providers, often over the course of several years, before a diagnosis is made. In addition, the attitude of Patient A's physicians represent a common reaction. More than 45% of individuals with an autoimmune disease have reported that they had been labeled as a chronic complainer in the early stages of their disease because no cause for their symptoms could be determined.*

## CONCLUSION

When considered collectively, autoimmune diseases affect more individuals than heart disease and cancer combined. However, because these diseases have been studied separately, their health burden has been underappreciated. As chronic illnesses with no cure, autoimmune diseases and fibromyalgia require lifelong treatment and many are associated with substantial morbidity, disability, and mortality. Healthcare professionals, especially primary care providers, face many challenges in diagnosing and treating autoimmune diseases. First, because the prevalence of each autoimmune disease is low, a typical primary care provider will not have experience with the diagnosis and care recommended for every disease. Second, many autoimmune diseases (as well as fibromyalgia) lack objective testing to confirm the diagnosis. Third, the initial symptoms of most autoimmune diseases are vague and are common across many autoimmune diseases and/or fibromyalgia. Lastly, few guidelines are available for diagnosis and management, especially guidelines with up-to-date evidence bases. As a result, it often takes several years before a definitive diagnosis is made. Even after diagnosis, the most effective treatments are not always used. Most individuals with autoimmune diseases or fibromyalgia need close follow-up to assess response to treatment, to monitor side effects of treatment, and to prevent comorbidities. At every follow-up visit, healthcare professionals should encourage their patients to participate actively in decision making and self-management. Although a variety of specialists is often involved in the care of individuals with an autoimmune disease or fibromyalgia, the primary care team has a pivotal role in the overall management of these patients.

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