

CARMEN E. GOTA, MD

Staff, Department of Rheumatologic and Immunologic Disease, and Director, Fibromyalgia Clinic, Orthopaedic and Rheumatologic Institute, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

What you can do for your fibromyalgia patient

ABSTRACT

Patients with fibromyalgia typically have pain “all over,” tender points, generalized weakness and fatigue, non-restorative sleep, and a plethora of other symptoms. In contrast to inflammatory and autoimmune conditions, laboratory tests and physical examination findings are usually normal. American College of Rheumatology guidelines facilitate diagnosis. Management requires a multifaceted, long-term strategy that emphasizes improving function rather than reducing pain.

KEY POINTS

Fibromyalgia is a clinical diagnosis, and specialized testing beyond basic laboratory tests is not indicated.

Antinuclear antibody test results can be confusing, and the test should not be ordered unless a patient has objective features suggesting systemic lupus erythematosus.

Treatment should be tailored to comorbidities such as depression, anxiety, and sleep disturbance. Options include serotonin-norepinephrine reuptake inhibitors (eg, duloxetine), selective serotonin reuptake inhibitors, low-dose tricyclic antidepressants (eg, amitriptyline), and gabapentinoids (pregabalin or gabapentin). These drugs can be used singly or in combination.

Medications that do not work should be discontinued.

“Catastrophizing” by the patient is common in fibromyalgia and can be addressed by education, cognitive behavioral therapy, and anxiolytic or antidepressant drugs.

Sustained, lifelong exercise is the treatment strategy most associated with improvement.

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FIBROMYALGIA may seem like a nebulous diagnosis, with its array of symptoms and pain refractory to medications. But fibromyalgia is a defined syndrome of neuronal dysregulation. It can be diagnosed from the history and physical examination and managed in a primary care setting.

■ CASE 1: MANY SYMPTOMS

A 43-year-old woman presents to her primary care physician with multiple complaints: pain in all joints and in her back and hips, swelling of her hands and feet, morning stiffness, chest pain and shortness of breath (not necessarily related to exertion), fatigue, generalized weakness, headaches, difficulty with memory and concentration, dry mouth and dry eyes, feeling weak and faint in the sun, cold intolerance with purple discoloration of her extremities, a self-described “butterfly” rash on the face, and hair that is thinning and falling out in clumps.

Because many of her symptoms could reflect an inflammatory process or an autoimmune disease,¹ her primary care physician orders multiple tests. Her C-reactive protein level, Westergren sedimentation rate, complete blood cell count, and comprehensive metabolic panel are normal. Urinalysis shows trace leukocyte esterase. Indirect immunofluorescence assay on human laryngeal tumor (HEp-2) cells is positive for antinuclear antibody (ANA), with a titer of 1:320 (reference range ≤ 1:40) and a nuclear dense fine-speckled pattern.

In view of the positive ANA test, the patient is informed that she may have systemic lupus erythematosus (SLE) and will be referred to a rheumatologist. In the days before her rheumatology appointment, she becomes extremely anxious. Obsessively researching SLE online, she becomes convinced that SLE is the correct diagnosis.

Rheumatology evaluation

The rheumatologist assesses the patient’s pain and reports the following:

Location and duration: Hands, wrists, elbows, shoulders, upper and lower back, sides of hips, knees, and feet; has been ongoing for 10 years, but worse in the past 3 months.

Character: The patient describes her pain as “like an ice pick being driven through my joints,” “sometimes unbearable,” and “like being hit by a truck.” She also reports numb, tingling, burning pain in her upper neck and back.

Variation with time, activity, and weather: Worse at night, causing her to wake and toss and turn all night; better with exertion, but after activity or exercise, she is exhausted for the rest of the day and sometimes for up to a week; worse with weather changes, especially during cold or humid weather.

Associated symptoms: Occasional perceived swelling of hands and feet, especially upon wakening in the morning, and 2 to 3 hours of stiffness in the morning that sometimes lasts all day.

Physical examination. Her findings are inconsistent with her symptoms.

The patient exhibits limited range of motion. When asked to bend forward, rotate her neck, or flex and extend her neck and back, she does so only slightly. However, passive range of motion is normal in all joints.

When her joints are examined, she anticipates pain and withdraws her hands. But when she is distracted, examination reveals no evidence of swollen joints or synovitis. She has tenderness in 12 of 18 tender points. Her peripheral pulses are good, strength is normal, and reflexes are brisk.

Her facial rash looks more like rosacea than the butterfly rash of SLE. There is no indication of patchy hair loss. Heart and lung examinations are normal. She appears to have a good salivary pool without glossitis.

History reveals long-standing psychological issues

The patient reports a history of panic attacks and a prior diagnosis of anxiety. She is tested with the Generalized Anxiety Disorder 7-item scale (www.mdcalc.com/gad-7-general-anxiety-disorder-7) and scores 17 out of 21, indicating severe anxiety.

DISCUSSION: CHARACTERIZING PAIN

Understanding categories of pain syndromes can help us understand fibromyalgia. Pain can be categorized into 3 types that sometimes overlap²:

Nociceptive or peripheral pain is related to damage of tissue by trauma or inflammation. Syndromes include osteoarthritis, rheumatoid arthritis, and SLE.

Neuropathic pain is associated with damage of peripheral or central nerves. Examples are neuropathy from herpes, diabetes, or spinal stenosis.

Centralized pain has no identifiable nerve or tissue damage and is thought to result from persistent neuronal dysregulation, overactive ascending pain pathways, and a deficiency of descending inhibitory pain pathways. There is evidence of biochemical changes in muscles, possibly related to chronic ischemia and an overactive sympathetic nervous system. Dysregulation of the sympathoadrenal system and hypothalamic-pituitary axis has also been implicated. And genetic predisposition is possible. Examples of centralized pain syndromes include fibromyalgia, irritable bowel syndrome, pelvic pain syndrome, neurogenic bladder, and interstitial cystitis.

Clues to a centralized pain syndrome

For patients with suspected fibromyalgia, distinguishing peripheral pain from centralized pain can be a challenge (Table 1). For example, SLE does not cause inflammation of the spine, so neck or back pain is not typical. Although both nociceptive and centralized pain syndromes improve with exertion, only patients with centralized pain are typically exhausted and bedbound for days after activity. Patients with centralized pain tend to describe their pain in much more dramatic language than do patients with inflammatory pain. Centralized pain tends to be intermittent; inflammatory pain tends to be constant. Patients with centralized pain often have had pain for many years without a diagnosis, but this is rare for patients with an inflammatory condition.

A patient with fibromyalgia typically has a normal physical examination, although allodynia (experiencing pain from normally nonpainful stimulation), hyperalgesia (in-

Patients with centralized pain tend to describe their pain in much more dramatic language than those with inflammatory pain

TABLE 1

Distinguishing inflammatory pain from centralized pain

Feature	Inflammatory pain	Centralized pain
Location	Hands, wrists, cervical spine, knees, hips, ankles, feet	More diffuse, "all over," tender points
Relationship to time of day	Nocturnal, with rest, early morning	Nocturnal, with rest, early morning
Relationship to exertion	Better with exertion	Better during exertion, worse after
Character of pain	Constant, dull, achy	Intermittent, stabbing, burning, "like being hit by a truck," "unbearable"
Duration	Variable	Often many years
General associated symptoms and signs	Fatigue, fever, other organ signs and symptoms	Fatigue, weakness, headaches, irritable bowel syndrome symptoms, cognitive impairment, disturbed sleep, mood disorders, dry eyes and mouth, light sensitivity, difficulty swallowing, sensation of swollen glands in neck, urinary frequency, feeling faint after hot shower or in hot weather
Localized associated symptoms and signs	Stiffness \geq 60 minutes Objective swelling	Stiffness \geq 60 minutes Lack of objective findings Tender points Allodynia (pain from normally nonpainful stimuli), hyperalgesia (increased sensitivity to pain) Acrocyanosis (bluish coloring of hands and feet) Brisk reflexes
Laboratory results	Inflammatory picture: elevated C-reactive protein and Westergren sedimentation rate, anemia, occasionally elevated platelet count, positive serologies (rheumatoid factor, anti-cyclic citrullinated peptide, extractable nuclear antigen panel)	Normal

creased pain perception), and brisk reflexes may be present. Fibromyalgia may involve discoloration of the fingertips resulting from an overactive sympathetic nervous system. Laboratory results are typically normal with fibromyalgia.

Patients with either nociceptive or centralized pain report stiffness, but the cause likely differs. We typically think of stiffness as arising from swollen joints caused by inflammation, but stiffness can also be caused by abnormally tight muscles, as occurs in fibromyalgia.

■ FIBROMYALGIA IS A CLINICAL DIAGNOSIS

Diagnosing fibromyalgia does not require multiple laboratory and imaging tests. The key indicators are derived from the patient history and physical examination.

Diagnostic criteria for fibromyalgia published by the American College of Rheumatology have evolved over the years. The 2011 criteria, in the form of a self-reported patient questionnaire, have 2 components³:

- The Widespread Pain Index measures the extent of pain in 19 areas.

- The Symptom Severity scale assesses 3 key symptoms associated with fibromyalgia, ie, fatigue, cognitive problems, and nonrestorative sleep (scale of 0–3 for each symptom).

There are also questions about symptoms of irritable bowel syndrome, depression, and headache.

Fibromyalgia is diagnosed if a patient reports at least 7 painful areas and has a symptom severity score of at least 5. A patient may also meet the 2011³ and the 2016 criteria⁴ if he or she has 4 painful areas and the pain is perceived in 4 of 5 areas and the Symptom Severity Scale score is 9 or higher.⁴ This questionnaire is not only a rapid diagnostic tool for fibromyalgia, it also helps identify and focus on specific issues—for example, having severe pain in a few localized areas, or having headache as a predominant problem.

These criteria are useful for a variety of patients, eg, a patient with hip arthritis may score high on the questionnaire, indicating that a component of centralized pain is also present. Also, people who have undergone orthopedic surgery who score high tend to require more narcotics to meet the goals of pain improvement.

The 2016 criteria,⁴ the most recent, maintain that pain must be generalized, ie, present in at least 4 of 5 body areas. They also emphasize that fibromyalgia is a valid diagnosis irrespective of other conditions.

■ **CASE 1 CONTINUED:
THE PATIENT REJECTS THE DIAGNOSIS**

Our patient meets the definition of fibromyalgia by each iteration of the American College of Rheumatology clinical criteria. She also has generalized anxiety disorder and a positive ANA test. She is advised to participate in a fibromyalgia educational program, start an aerobic exercise program, and consider taking an antidepressant medication with anxiolytic effects.

However, the patient rejects the diagnosis of fibromyalgia. She believes that the diagnosis of SLE has been overlooked and that her symptom severity is being discounted.

In response, the rheumatologist orders additional tests to evaluate for an autoimmune

disorder: extractable nuclear antigen panel, complement C3 and C4, double-stranded DNA antibodies, and protein electrophoresis. Results are all in the normal range. The patient is still concerned that she has SLE or another autoimmune disease because of her abnormal ANA test result and remains dissatisfied with her evaluation. She states that she will complain to the clinic ombudsman.

■ **SIGNIFICANCE OF ANA TESTING**

Patients with positive test results increasingly go online to get information. The significance of ANA testing can be confusing, and it is critical to understand and be able to explain abnormal results to worried patients. Following are answers to some common questions about ANA testing:

Is ANA positivity specific for SLE or another autoimmune disease?

No. ANA is usually tested by indirect immunofluorescence assay on HEp-2 cells. The test can identify about 150 antigens targeted by antibodies, but only a small percentage are associated with an autoimmune disease, and the others do not have a known clinical association. Enzyme-linked immunosorbent assay (ELISA) ANA testing is also available but is considered less sensitive.

Abeles and Abeles⁵ retrospectively assessed 232 patients between 2007 and 2009 who were referred to rheumatologists for evaluation because of an elevated ANA test result. No ANA-associated rheumatic disease was found in patients who had a result of less than 1:160, and more than 90% of referrals for a positive ANA test had no evidence of ANA-associated disease. The positive predictive value was 9% for any connective tissue disease, and only 2% for SLE. The most common reason for ordering the test was widespread pain (23%). The authors concluded that ANA testing is often ordered inappropriately for patients with a low pretest probability of an ANA-associated rheumatic disease.

Screening with ANA testing generates many false-positive results and unnecessary anxiety for patients. The prevalence of SLE in the general population is about 0.1%, and other autoimmune diseases total about 5% to 7%. By indirect immunofluorescence assay, using a cutoff of 1:80 (the standard at Cleveland

Screening with ANA testing generates many false-positive results and unnecessary anxiety for patients

Clinic), about 15% of the general population test positive. By ELISA, with a cutoff of 20 ELISA units, 25% of healthy controls test positive.

It is true that ANA positivity may precede the onset of SLE.^{6,7} Arbuckle et al⁸ evaluated serum samples from the US Department of Defense Serum Repository obtained from 130 people before they received a diagnosis of SLE; in 115 (88%), at least 1 SLE-related autoantibody was present before diagnosis (up to 9.4 years earlier). However, in those who test positive for ANA, the percentage who eventually develop autoimmune disease is small.⁵

Is the titer of ANA significant and of diagnostic value?

The likelihood of autoimmune disease increases with increasing titer. But high titers can be seen in healthy people. Mariz et al⁹ examined ANA test results from 918 healthy controls and 153 patients with an autoimmune rheumatic disease. Of these, ANA was positive in 13% of healthy people and 90% of patients with an autoimmune disease. High titers were more likely in patients with an autoimmune disease, but also occurred in healthy controls.

Does the immunofluorescence pattern provide diagnostic information?

It can. There are 28 identified patterns of ANA, including nuclear, cytoplasmic, and mitotic patterns. The most common, the nuclear fine-speckled pattern, is seen in healthy controls and patients with an autoimmune disease. But other patterns are either characteristic of an autoimmune disease or, conversely, of not having an autoimmune disease (Table 2).⁹

Our patient has a nuclear dense fine-speckled pattern, further reducing the likelihood that she has an autoimmune disease.

■ CASE 2: POORLY CONTROLLED, LONG-STANDING FIBROMYALGIA

A 43-year-old woman who has had fibromyalgia for 15 years is referred to a new primary care provider. She reports severe pain all over, low back pain, fatigue, nonrefreshing sleep, chronic migraine, constipation alternating with diarrhea, heartburn, intermittent numbness and tingling in her hands and feet, and

TABLE 2

Significance of ANA immunofluorescence patterns

Associated with autoimmune disease

Nuclear homogeneous

Nuclear coarse-speckled

Nuclear centromeric

Associated with healthy individuals

Nuclear dense fine-speckled

Most common, found in both groups

Nuclear fine-speckled

Based on information in reference 9.

depression. At this time, she rates her pain on a visual analog scale as 9 out of 10, and her fatigue as 8 out of 10.

During the past 6 months, she has made 25 visits to specialists in 8 departments: spine, pain management, anesthesia, neurology, headache clinic, gastroenterology, sleep medicine, and physical therapy.

Her daily medications are duloxetine 120 mg, bupropion 300 mg, pregabalin 450 mg, cyclobenzaprine 30 mg, tramadol 200 mg, zolpidem 10 mg, nortriptyline 50 mg, acetaminophen 3,000 mg, and oxycodone 30 mg. She has also tried gabapentin and milnacipran without success. She reported previously taking different selective serotonin reuptake inhibitors and tricyclic antidepressants but cannot remember why they were stopped.

How should this complex patient be managed?

■ BIOPSYCHOSOCIAL MANAGEMENT

Managing the pain of fibromyalgia requires a different model than used for peripheral pain from injury, in which the source of pain can be identified and treated with injections or oral therapy.

Neuronal dysregulation is not amenable to clinical measurement or treatment by medications at this time. But fortunately, many factors associated with fibromyalgia can be addressed: stressful life events, sleep disturbance,

Managing the pain of fibromyalgia requires a different model than that for peripheral pain

physical deconditioning, mood disorders, and maladaptive pain responses, including “catastrophizing” behavior (coping with pain in a highly dramatic and obsessive way). Modifying these factors can be much more productive than focusing on treating pain.

The goal for care providers is to change the focus from reducing pain to a biopsychosocial model of pain control aimed at increasing function.¹⁰

Mood modification

Not only are mood disorders common in patients with fibromyalgia, but the prevalence of complex psychiatric conditions is also elevated. Up to 80% of patients with fibromyalgia meet criteria for axis I (clinical psychological) disorders, and up to about 30% of patients meet criteria for axis II (personality) disorders. About 22% of patients have existing major depression, and about 58% develop it during their lifetime. In a study of 678 patients with fibromyalgia, 21% had bipolar disorder.^{11–15}

The severity of fibromyalgia increases linearly with the severity of depression.¹⁶ Patients with fibromyalgia and a “depressive affect balance style” have worse outcomes across all Outcome Measures in Rheumatology (OMERACT) core symptom domains, reporting more pain, fatigue, insomnia, anxiety, depression, and function.^{17,18}

Fibromyalgia combined with mood disorders can also be costly. In one study, the mean annual employer payments (direct and indirect costs) per patient were \$5,200 for patients with fibromyalgia only, \$8,100 for patients with depression only, and \$11,900 for patients with both.¹⁹

Obtaining a psychiatric history is important when evaluating a patient with fibromyalgia symptoms. Patients should be asked if they have a history of depression, anxiety, posttraumatic stress disorder, or other conditions. The Patient Health Questionnaire – Depression 9 and the Generalized Anxiety Disorder Assessment (GAD-7) (both available at www.mdcalc.com) can be useful for evaluating mood disorders.

Patients with moderate depression and fibromyalgia who have not yet been treated should be prescribed duloxetine for its potential benefits for both conditions.

Patients who have already been treated with multiple drugs at high doses without benefit, such as our patient, should be referred to a psychiatrist. There is no additional benefit to referring this patient to a rheumatologist or spine clinic.

Addressing sleep problems

Sleep problems are not easy to manage but can often be helped. Epidemiologic studies indicate that poor sleep quality leads to chronic widespread pain in otherwise healthy people.^{20–22} In addition, experimental sleep deprivation leads to fatigue, cognitive difficulty, and a reduced pain threshold.²³ In our patients with fibromyalgia, we have observed an inverse relationship between the number of hours slept and the severity of depression.

Sleep quantity and quality can be assessed by asking patients whether they have trouble sleeping, how many hours they sleep, and whether they have been diagnosed with a sleep disorder.

Because many patients with fibromyalgia are overweight or obese, they should also be evaluated for sleep apnea, narcolepsy, and restless leg syndrome.^{24,25}

Medications shown to improve sleep include pregabalin or gabapentin (taken at bedtime), low-dose amitriptyline, trazodone, cyclobenzaprine, melatonin, and nabilone.^{26–29}

Patients should be counseled about sleep hygiene.³⁰ Exercise can also help sleep.

Targeting maladaptive pain responses

Patients who catastrophize tend to have higher tender point counts, a hyperalgesic response, more depression and anxiety, and more self-reported disability. They are also less likely to return to work.³¹ They usually respond poorly to medications and are good candidates for cognitive behavioral therapy.

A high score on a self-reported Pain Catastrophizing Scale³² can help determine whether a multidisciplinary approach is advisable, although no threshold defines an abnormal score.

Educating patients about the neurobiology underlying their pain can be therapeutic.^{33–37} Cognitive behavioral therapy can help patients recognize their faulty thought processes and the relationship between pain and stress, and

The severity of fibromyalgia increases linearly with the severity of depression

TABLE 3

Evaluating fibromyalgia for management

Domains	Key questions and characteristics	Tests
Mood	Ever diagnosed with depression, anxiety, or other psychiatric condition?	Depression (PHQ-9) Anxiety (GAD-7) Bipolar screen (MDQ)
Sleep	Difficulty falling or staying asleep? Average hours slept, daytime sleepiness, snoring, apnea? Prior diagnosis of narcolepsy, sleep apnea, or restless leg syndrome?	
Physical conditioning	Moderate aerobic exercise at least 30 minutes 3 times a week?	
Stressful life events	Past stressors: born premature, unhappy childhood, history of mental, physical, or sexual abuse? Current stressors: financial, family, health, social?	
Maladaptive pain responses, catastrophizing	Does patient use a lot of drama to describe symptoms?	Pain Catastrophizing Scale
Function	Are you working? Have you applied for disability benefits?	

GAD-7 = Generalized Anxiety Disorder Assessment; MDQ = Mood Disorder Questionnaire; PHQ-9 = Patient Health Questionnaire-Depression 9

learn better coping mechanisms.^{38,39} Patients who achieve the highest improvements in pain catastrophizing tend to derive the greatest benefit from cognitive behavioral therapy.⁴⁰

Exercise improves symptoms

Exercise improves fibromyalgia on many fronts and is associated with a host of positive effects in the brain and peripheral muscles. Exercise improves Fibromyalgia Impact Questionnaire scores, increases physical function and fitness, and reduces tender point counts, depression, and catastrophizing.⁴¹⁻⁵² There is no consensus on the best type of exercise, but both strengthening and aerobic exercises appear to be important.

I tell patients that fibromyalgia is an exercise-deprivation syndrome. Many are afraid to exercise because they associate it with pain and exhaustion afterwards. Patients should be encouraged to start with something very low-impact, such as gentle exercise in a warm-water pool. It should be emphasized that exercise is a lifelong treatment.

Drug therapy

The US Food and Drug Administration has approved 3 drugs for fibromyalgia management: 2 serotonin-norepinephrine reuptake inhibitors (duloxetine and milnacipran) and 1 gabapentinoid (pregabalin). Our patient in Case 2 is taking 2 of them without apparent benefit and has previously had no success with the third. This is not surprising. A summary of published treatment research on these drugs found that only 50% to 60% of patients tested reported more than 30% pain reduction.⁵³ The studies also showed a placebo response of 30% to 40%. Depending on the study, the number needed to treat to see a benefit from these drugs is 8 to 14.⁵³

EVALUATING THE SEVERITY OF FIBROMYALGIA

Focusing on key characteristics of the patient's history can help evaluate fibromyalgia and determine a treatment strategy (Table 3). The Fibromyalgia Impact Questionnaire is also a useful evaluation tool.

I tell patients that fibromyalgia is an exercise-deprivation syndrome

It is important to assess the severity of fibromyalgia because patients with severe fibromyalgia are not good candidates for further referral to other specialists. They instead need chronic rehabilitation services, where they can learn to better function with a chronic pain syndrome.

In general, patients with the following features have conditions with high severity:

Symptoms: High burden and intensity

Function: Disabled, unemployed, interference with activities of daily living

Mood: Severe depression, bipolar disorder, axis II disorder, posttraumatic stress disorder

Medications: Polypharmacy, opioid drugs, multiple failed interventions

Maladaptive attitudes: High catastrophizing, refusal to accept diagnosis

Fibromyalgia Impact Questionnaire score: 60 or above.

The fibromyalgia of our patient in Case 2 would be categorized as severe.

■ MULTIFACETED MANAGEMENT

Patients with fibromyalgia are a heterogeneous group, and the syndrome does not lend itself to a single management strategy.⁵⁴ Multiple guidelines have been published for managing fibromyalgia.^{55–57} Thieme et al⁵⁸ reviewed existing guidelines and the strength of their recommendations. The guidelines unanimously strongly favor exercise, and most also strongly favor cognitive behavioral therapy. Most favor treating with amitriptyline and duloxetine; recommendations for other antidepressants vary. Nonsteroidal anti-inflammatory drugs, opioid drugs, and benzodiazepines are not recommended.

We offer a monthly 1-day clinic for patients and family members to provide education about fibromyalgia, discuss the impor-

tance of exercise, counsel on maladaptive responses, and demonstrate mindfulness techniques. We focus on function rather than pain. Interactive online-based interventions using cognitive behavioral techniques, such as *FibroGuide: A Symptom Management Program for People Living With Fibromyalgia*, developed at the University of Michigan, have proven helpful.⁵⁹

■ RECOMMENDATIONS

For most patients, do not focus on pain reduction, as that is ineffective. Instead, target reversible factors, eg, mood, sleep, exercise status, stressors, and maladaptive attitudes toward pain. Possible treatment combinations include:

- A serotonin and norepinephrine reuptake inhibitor (eg, duloxetine)
- A low-dose tricyclic antidepressant at bedtime (eg, amitriptyline)
- A gabapentinoid (pregabalin or gabapentin).

If a medication within a class does not work, stop it and try another rather than add on.

Treat mild to moderate fibromyalgia with multidisciplinary interventions, with or without centrally acting medications. Treat severe fibromyalgia with more intensive psychiatric or psychologic interventions, multidisciplinary care, and medications targeted at comorbidities. Provide all patients with education and advice on exercise.

Keep laboratory tests and imaging studies to a minimum: a complete blood cell count with differential, comprehensive metabolic panel, thyroid-stimulating hormone, C-reactive protein, and Westergren sedimentation rate. Do not test for ANA unless the patient has objective features suggesting SLE. ■

Guidelines strongly endorse exercise, and most also favor cognitive behavioral therapy

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- ADDRESS:** Carmen Gota, MD, Department of Rheumatologic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; gotac@ccf.org