

Schizophrenia

SARAH D. HOLDER, DO, *Baylor Family Medicine Residency at Garland, Garland, Texas*

AMELIA WAYHS, MD, MPH, *Dallas, Texas*

Schizophrenia is the most common psychotic disease, with a global prevalence of less than 1%. It affects all ethnicities and is slightly more common in men. Patients with schizophrenia commonly experience debilitating social and occupational impairments, but some are able to function well with proper treatment. Symptom onset is generally between late adolescence and the mid-30s. There are two categories of symptoms: positive and negative. Hallucinations, delusions, and disorganized speech are examples of positive symptoms, whereas decreased emotional expression and lack of motivation are negative symptoms. Antipsychotic medications can treat some symptoms of schizophrenia but are associated with multiple adverse effects, including extrapyramidal symptoms and metabolic changes. Patients receiving antipsychotic medications, especially second-generation (or atypical) antipsychotics, should be monitored regularly for metabolic changes and cardiovascular risk factors. Persons with schizophrenia who undergo psychosocial therapy in addition to medical therapy have better outcomes. Patients diagnosed with schizophrenia have a higher overall mortality rate than the general public, partly because of the increased suicide risk associated with schizophrenia. (*Am Fam Physician*. 2014;90(11):775-782. Copyright © 2014 American Academy of Family Physicians.)

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Schizophrenia is a pervasive, chronic mental disorder with a global prevalence of 0.3% to 0.7%.¹ Although there is no significant difference between sexes, a slight predominance is noted in men.^{1,2} Schizophrenia affects persons in all ethnicities. However, a recent study confirmed that in the United States, blacks are diagnosed with schizophrenia at a disproportionately higher rate compared with non-Hispanic whites.³ This finding could point to a racial or ethnic bias in the diagnosis of schizophrenia in black persons who present with psychosis.³

Schizophrenia is the most common psychotic disease.⁴ Therefore, family physicians should have an overall knowledge of the disease, including the initial presentation, treatment and its challenges, and how to address comorbidities. Whenever possible, family physicians should educate patients and their families about medication reactions and the importance of compliance with treatment. Referral to a psychiatrist is appropriate for patients presenting with psychosis.

Etiology and Risk Factors

Genetics have an important role in the etiology of schizophrenia, even though most patients diagnosed with the disease have no family history of psychosis. The genetic variation responsible for the disease has not

been identified. Relatives of persons with schizophrenia are also at risk of schizoaffective disorder, schizotypal personality disorder, bipolar disorder, depression, and autism spectrum disorder.^{1,5}

Environmental factors may have a role.¹ Possible environmental factors include being born and raised in an urban area, cannabis use, infection with *Toxoplasma gondii*,^{2,6,7} obstetric complications, central nervous system infection in early childhood, and advanced paternal age (older than 55 years).¹

Clinical Presentation

The symptoms of schizophrenia usually begin between late adolescence and the mid-30s. Cases involving children as young as five years have been reported, but these are rare. In men, the symptoms tend to present between 18 and 25 years of age. In women, the onset of symptoms has two peaks, the first between 25 years of age and the mid-30s, and the second after 40 years of age.¹

Patients may have symptoms during a prodromal phase before they become psychotic. These symptoms include social withdrawal, loss of interest in work or school, deterioration of hygiene, angry outbursts, and behavior that is out of character.¹ This phase may be mistaken for depression or other mood disorders. The patient will eventually exhibit active-phase symptoms of the disorder.¹

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Diagnosis

Criteria for schizophrenia include signs and symptoms of at least six months' duration, including at least one month of active-phase positive and negative symptoms (Table 1).¹ Delusions, hallucinations, disorganized speech, and disorganized behavior are examples of positive symptoms. Negative symptoms include a decrease

in the range and intensity of expressed emotions (i.e., affective flattening) and a diminished initiation of goal-directed activities (i.e., avolition).

DIFFERENTIAL DIAGNOSIS

Other organic and psychiatric diagnoses can present with symptoms of psychosis (Table 2).¹ Initially,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Patients who have been diagnosed with psychosis and/or schizophrenia should be urgently referred for psychiatric evaluation.	C	8
Antipsychotic drugs should be initiated as soon as possible after schizophrenia is diagnosed.	A	1, 8, 10, 11, 13-15, 21, 25
All patients receiving second-generation antipsychotic medications should be monitored at least annually for metabolic changes and cardiovascular risk factors.	C	10, 28-30
Patients with schizophrenia should be offered psychosocial therapies, including cognitive behavior therapy, family interventions, and social skills training, in addition to medical treatment.	B	8-10, 13

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

Table 1. Diagnostic Criteria for Schizophrenia

- A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
 1. Delusions
 2. Hallucinations
 3. Disorganized speech (e.g., frequent derailment or incoherence)
 4. Grossly disorganized or catatonic behavior
 5. Negative symptoms (i.e., diminished emotional expression or avolition)
- B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning)
- C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)
- D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either: (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness
- E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition
- F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated)

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Table 2. Differential Diagnosis of Schizophrenia

<i>Diagnosis</i>	<i>Distinguishing features</i>	<i>Laboratory/imaging findings</i>
Psychiatric conditions		
Brief psychotic disorder	Delusions, hallucinations, and disorganized speech or behavior lasting for at least one day but less than one month	NA
Major depressive or bipolar disorder with psychotic or catatonic features	Psychotic symptoms occur exclusively during periods of mood disturbance	NA
Posttraumatic stress disorder	Traumatic inciting event; symptoms relate to reliving or reacting to the event	NA
Obsessive-compulsive disorder and body dysmorphic disorder	Prominent obsessions, compulsions, and preoccupations with appearance or body odor, hoarding, or body-focused repetitive behaviors	NA
Schizotypal personality disorder	Subthreshold symptoms that are associated with persistent personality features	NA
Autism spectrum disorder or communication disorders	Deficits in social interaction with repetitive and restricted behaviors and other cognitive and communication deficits	NA
Schizoaffective disorder	Mood episode concurrent with active-phase symptoms; mood symptoms present for a substantial portion of the disturbance; delusions present for two weeks without prominent mood symptoms	NA
Schizophreniform disorder	Duration of symptoms is at least one month but less than six months	NA
Delusional disorder	Nonbizarre delusions, absence of hallucinations, disorganized speech or behavior, negative symptoms	NA
Medical conditions		
Substance abuse	Abnormal vital signs, needle marks, poor nutrition	Elevated blood alcohol level, positive results on urine drug screen
Thyroid disorder	Coarse hair and skin, exophthalmos, goiter, pretibial myxedema, tachycardia/bradycardia, tremor	Abnormal thyroid-stimulating hormone level, anemia, hyponatremia
Delirium caused by infection	Altered consciousness, fever, hyporeflexia/hyperreflexia, hypotension, infection source	Abnormal leukocyte count, positive results on human immunodeficiency virus or rapid plasma reagin test
Dementia	Cognitive/memory deficits, abnormal results on Mini-Mental State Examination	NA
Vitamin B ₁₂ deficiency	Ataxia, atrophic glossitis, memory impairment, muscle weakness	Elevated iron and indirect bilirubin levels, low vitamin B ₁₂ levels, macrocytic anemia
Systemic lupus erythematosus	Alopecia, discoid rash, fever, malar rash, oral ulcers, phlebitis, pleural/pericardial rub	Anemia, elevated antinuclear antibody titers, pleural effusion detected on chest radiography, proteinuria
Cushing syndrome	Abdominal striae, buffalo hump, hirsutism, moon face, proximal muscle weakness	Elevated 24-hour urine cortisol level
Temporal lobe epilepsy	Postictal state, abnormal neurologic findings	Abnormal electroencephalography findings
Brain tumor	Focal neurologic deficits	Lesions detected on computed tomography or magnetic resonance imaging of the brain
Wilson disease	Ataxia, dysarthria, hepatomegaly, hyperreflexia, jaundice, Kayser-Fleischer rings in the cornea	Basal ganglia lesions detected on magnetic resonance imaging, Coombs-negative hemolytic anemia, elevated liver enzyme levels
Porphyria	Proximal muscle weakness, tachycardia	Elevated urine porphobilinogen level, hyponatremia

NOTE: Diagnoses are listed from most to least prevalent.

NA = not applicable.

Information from reference 1.

Table 3. Antipsychotic Medications

Medication	Dosage (mg per day)	Common adverse effects	Serious adverse effects
First generation			
Chlorpromazine	300 to 1,000	Drowsiness, dry mouth, elevated prolactin levels, extrapyramidal symptoms, glucose intolerance, postural hypotension, weight gain	Neuroleptic malignant syndrome, tardive dyskinesia
Haloperidol	5 to 20	Drowsiness, dry mouth, extrapyramidal symptoms, galactorrhea, hypotension, tachycardia	Neuroleptic malignant syndrome, prolonged QT interval, tardive dyskinesia
Perphenazine	16 to 64	Drowsiness, dry mouth, extrapyramidal symptoms, galactorrhea, hypotension, tachycardia	Neuroleptic malignant syndrome, tardive dyskinesia
Thiothixene	15 to 60	Drowsiness, dry mouth, extrapyramidal symptoms, galactorrhea, hypotension, tachycardia	Neuroleptic malignant syndrome, tardive dyskinesia
Second generation			
Aripiprazole (Abilify)	10 to 30	Anxiety, constipation, dizziness, headache, insomnia, metabolic changes, nausea, vomiting	Agranulocytosis, neuroleptic malignant syndrome, tardive dyskinesia
Clozapine (Clozaril)	150 to 600	Constipation, dizziness, headache, metabolic effects, salivation, sedation, tachycardia, weight gain	Agranulocytosis (complete blood count should be obtained weekly for six months, then every two weeks for six months, then monthly), myocarditis, seizures, tardive dyskinesia
Lurasidone (Latuda)	40 to 160	Akathisia, hyperprolactinemia, metabolic changes, nausea, parkinsonism, somnolence	Neuroleptic malignant syndrome, tardive dyskinesia
Olanzapine (Zyprexa)	10 to 30	Akathisia, constipation, dizziness, hyperprolactinemia, metabolic changes, postural hypotension, weight gain	Agranulocytosis, neuroleptic malignant syndrome, tardive dyskinesia
Paliperidone (Invega)	3 to 12	Hyperprolactinemia, metabolic changes, orthostatic hypotension, priapism, somnolence, weight gain	Neuroleptic malignant syndrome, prolonged QT interval, tardive dyskinesia
Quetiapine (Seroquel)	300 to 800	Agitation, dizziness, dry mouth, headache, metabolic changes, postural hypotension, somnolence, weight gain	Agranulocytosis, neuroleptic malignant syndrome, tardive dyskinesia
Risperidone (Risperdal)	2 to 8	Anxiety, hyperprolactinemia, hypotension, insomnia, metabolic changes, nausea, weight gain	Agranulocytosis, neuroleptic malignant syndrome, tardive dyskinesia
Ziprasidone (Geodon)	120 to 200	Agitation, hypotension, metabolic changes, nausea, somnolence, tachycardia, weight gain	Agranulocytosis, neuroleptic malignant syndrome, tardive dyskinesia

NOTE: The U.S. Food and Drug Administration has issued a boxed warning for all antipsychotics that there is an increased risk of mortality in older adults with dementia-related psychosis.

*—Estimated retail price for one month's treatment based on information obtained at <http://www.goodrx.com> (accessed May 25, 2014).

Information from references 11, and 13 through 21.

patients should be evaluated for any intrinsic cause of psychosis (e.g., delirium, mood disorder with psychosis, Cushing syndrome, drug use [illicit and prescribed]). Ideally, patients should be observed in a controlled setting for an extended time. This allows for differentiation between psychiatric disorders; however, this is not always feasible. In most situations, physicians must rely on a history provided by family members.¹ The physical examination will also help determine organic causes of psychosis.

Treatment

Patients diagnosed with psychosis, schizophrenia, or both should be urgently referred for psychiatric evaluation.⁸ Not all patients with acute psychosis require hospitalization, but it should be considered for those who may pose a danger to themselves or others.⁴ The most effective treatment for schizophrenia is a multidisciplinary approach including medication, psychological treatment, and social support.^{5,9-11} The goal of treatment is remission, which is defined as a period of six months

Comments	Monthly cost*
First drug used to treat psychosis	\$235 to \$590
More effective for treating positive symptoms, ¹³ but has a high risk of extrapyramidal symptoms ¹⁴	\$5 to \$30
—	\$55 to \$215
—	\$35 to \$45
Smaller effect on lipids compared with other second-generation antipsychotics ¹⁵	(\$825 to \$1,165 brand)
Reserved for severe, treatment-refractory schizophrenia ¹¹	\$80 to \$200 (\$510 to \$2,010 brand)
Higher incidence of adverse effects with higher dosages ¹⁶	(\$745 to \$1,490 brand)
More weight gain compared with older second-generation antipsychotics, but a lower discontinuation rate ^{17,18}	\$15 to \$45 (\$590 to \$1,760 brand)
Active metabolite of risperidone	(\$775 to \$1,550 brand)
High discontinuation rate compared with other second-generation antipsychotics ¹⁹	\$25 to \$45 (\$530 to \$1,235 brand)
Higher incidence of extrapyramidal effects, increased prolactin levels ^{18,20}	\$10 to \$20 (\$400 to \$1,255 brand)
Least amount of weight gain compared with other second-generation antipsychotics ²¹	\$135 to \$170 (\$830 to \$1,060 brand)

with no symptoms or mild symptoms that do not interfere with a person's behaviors.¹²

ANTIPSYCHOTICS

Antipsychotic agents are the first-line treatment for patients with schizophrenia. There are two general types of antipsychotic drugs: first-generation (typical) and second-generation (atypical) agents. *Table 3* lists commonly used antipsychotic drugs, their adverse effects, typical dosages, and price.^{11,13-21} Multiple

guidelines recommend starting antipsychotic medications as soon as possible after psychotic symptoms are recognized and/or the patient is diagnosed with schizophrenia.^{8,10,11,13,21,22} The National Institute for Health and Care Excellence suggests urgent referral to mental health services when a person presents with psychotic symptoms, and recommends that primary care physicians initiate antipsychotic medications only in consultation with a psychiatrist (*Table 4*).⁸ Initial medication choice should be individualized, taking into account financial considerations, adverse effect profiles, dosing regimens, and patient preferences.

Antipsychotic medications are more effective than placebo in reducing overall symptoms of schizophrenia and preventing relapse.¹³⁻¹⁵ Patients with schizophrenia who

Table 4. National Institute for Health and Care Excellence Guidelines for Management of Schizophrenia

All persons presenting with psychotic symptoms should be urgently referred to mental health services
Antipsychotic medication for a first presentation of sustained psychotic symptoms should not be initiated in the primary care setting unless it is done in consultation with a psychiatrist
Patients should be offered an antipsychotic medication when they are initially diagnosed with schizophrenia
The risks and benefits of the medication should be discussed with the patient
Potential adverse effects should be considered when deciding on a medication
A combination of antipsychotics should not be prescribed
A loading dose of antipsychotics should not be prescribed
Oral antipsychotics should be offered to patients with acute exacerbations or recurrences of psychotic symptoms
Patients with schizophrenia should be informed of the high risk of relapse if medical therapy is discontinued within one to two years
Physical examinations and cardiovascular risk assessment should be performed at least annually in patients with schizophrenia, and results should be shared with the psychiatrist
Cognitive behavior therapy should be offered to all persons with schizophrenia
Patients whose symptoms have responded to treatment and remain stable should be given the option of returning to their primary care physician for continued management
Physicians should consider re-referral to mental health services if there is poor treatment response, nonadherence to treatment, intolerable adverse effects of medications, or comorbid substance use, or if the patient is a threat to him- or herself or others

Information from reference 8.

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are receiving antipsychotic drugs report a better quality of life, but have a higher incidence of weight gain, sedation, and movement disorders.¹⁵ As such, all patients who report symptom relief while receiving medication should be offered maintenance therapy with antipsychotics.¹¹ A patient's response to treatment during the first two to four weeks is highly predictive of long-term response, although it may take several months to achieve maximal effect.¹⁷ Patients should be given an adequate trial of therapy (at least four weeks at a therapeutic dose) before discontinuing the drug or transitioning to a different medication.²²

Studies have shown that there is no difference in effectiveness between first- and second-generation antipsychotics.^{23,24} Quality of life is also similar at one year between groups of patients treated with each drug class.²³ The main difference between these medications is their adverse effect profiles; first-generation antipsychotics most commonly cause extrapyramidal symptoms, whereas second-generation agents most commonly cause weight gain and metabolic changes.^{22,25-27} Adverse reactions and previous response to antipsychotic medications should be taken into account when deciding which class of medication to initiate.

ADVERSE EFFECTS AND MONITORING

Extrapyramidal symptoms such as pseudoparkinsonism, akathisia (a sensation of inner restlessness and inability to be still), and dystonia are associated with first-generation antipsychotics. Patients receiving these medications should be routinely monitored for adverse effects and maintained on the lowest effective dose that controls their symptoms. Medications such as propranolol, lorazepam (Ativan), amantadine, benztrapine, and diphenhydramine (Benadryl) are used to treat extrapyramidal symptoms.²⁵ Tardive dyskinesia involving facial muscles generally occurs after the patient has been taking antipsychotic medications for a prolonged time. Symptoms include puffing of the cheeks, protrusion of the tongue, chewing motions, and pursing of the lips. The condition is typically irreversible, but symptoms may lessen after the medication is discontinued. Laboratory monitoring is not necessary for patients receiving first-generation antipsychotics. Patients receiving the

Table 5. Recommended Screening Frequency for Patients Receiving Atypical Antipsychotics

Screening component	Baseline	Every six weeks	Every 12 weeks	Quarterly	Annually
Blood pressure	X	X	X	X	X
Body mass index	X	X	X	X	X
Fasting glucose level	X	X	X		X
Fasting lipid levels	X	X	X		X
Lifestyle counseling	X	X	X	X	X
Medical history	X				X
Waist circumference	X				X

Information from references 28 and 30.

BEST PRACTICES IN PSYCHIATRY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	Sponsoring organization
Do not prescribe antipsychotic medications to patients for any indication without appropriate initial evaluation and appropriate ongoing monitoring.	American Psychiatric Association
Do not routinely prescribe two or more antipsychotic medications concurrently.	American Psychiatric Association

Source: For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <http://www.aafp.org/afp/recommendations/search.htm>.

second-generation antipsychotic clozapine (Clozaril) are at high risk of agranulocytosis, and the package insert recommends a complete blood count weekly for six months, then every two weeks for an additional six months, then monthly. Clozapine is reserved for patients with severe refractory symptoms because of its increased risk of adverse effects; it should be prescribed only by a psychiatrist.¹¹

The most worrisome adverse effects associated with second-generation antipsychotics are metabolic changes, such as weight gain, insulin resistance, hyperglycemia, and lipid abnormalities.^{15,25,27,28} All second-generation antipsychotics confer varying degrees of risk

for metabolic changes,²⁸ and these effects are not dose-dependent.²⁹ Weight gain is usually rapid in the first few weeks of treatment, then plateaus; however, this can take a year or more to occur.²⁷ Therefore, patients should be examined frequently after initiating treatment with second-generation antipsychotics, and at least annually if they have normal baseline values. Patients with cardiovascular risk factors require more frequent monitoring.^{28,30} *Table 5* outlines the recommended frequency of monitoring for patients receiving second-generation antipsychotics.^{28,30} Primary care physicians should regularly assess body mass index, fasting glucose levels, and lipid profiles, and work toward minimizing these and other cardiovascular risk factors.^{8,30,31}

ADJUNCTIVE TREATMENTS

In addition to medication, patients with schizophrenia should be offered adjunctive therapies such as cognitive behavior therapy, family interventions, and social skills training.^{8-10,13} Cognitive behavior therapy is the most commonly used adjunctive therapy, but a Cochrane review found no clear evidence that it is superior to other talking therapies, although it may be helpful in dealing with emotions and distressing feelings.³² A Chinese study found that psychosocial treatment combined with medication improved treatment adherence, insight, and quality of life, and decreased hospital admissions.⁹ Patients receiving combined treatment were less likely to discontinue their medication or to relapse (absolute risk reduction = 14% and 8%; number needed to treat = 7 and 12, respectively).

There is a higher incidence of anxiety disorders, panic symptoms, posttraumatic stress disorder, and obsessive compulsive disorder in patients with schizophrenia compared with the general public.³³ Medications such as selective serotonin reuptake inhibitors and anxiolytics can be helpful in treating comorbid mood disorders in these patients, but do not treat the symptoms of schizophrenia.³⁴

Clinical Course and Prognosis

Patients with schizophrenia have a varied clinical course that may include remission, exacerbations, or a more persistent chronic illness. Among patients who remain ill despite therapy, some have a stable clinical course, whereas others experience worsening symptoms and functioning. Factors that predict the clinical course and prognosis of these patients are not understood, and there is no reliable way to predict outcomes. Approximately 20% of patients can be expected to have a positive outcome.¹

Suicide is a concern when treating patients with schizophrenia. The risk of suicide is 13 times greater

in persons diagnosed with schizophrenia compared with the general public, with a lifetime risk of about 5%.^{1,4,35} Patients with auditory hallucinations, delusions, substance abuse, or a history of suicide attempts are at higher risk. Adequate treatment of schizophrenia and its comorbidities, along with diligent screening for risk factors, reduces the likelihood of suicide.³⁵ The overall mortality rate for patients with schizophrenia is two to three times higher than that of the general public.^{1,36} Most deaths are related to an increased rate of cardiovascular and respiratory diseases, stroke, cancer, and thromboembolic events.³⁶

In the past, schizophrenia was viewed as a disease with a poor prognosis. Currently, the disease course and response to treatment are marked by heterogeneity; differences in treatment response, disease course, and prognosis are to be expected.^{5,12} Despite adequate treatment, one-third of patients will remain symptomatic. Although most patients need some form of support, most are able to live independently and actively participate in their lives.⁵

Data Sources: We were provided a search from Essential Evidence Plus using the search term schizophrenia. We searched the National Institute for Health and Care Excellence, U.S. Preventive Services Task Force, and Agency for Healthcare Research and Quality. A PubMed search was completed using the search subjects schizophrenia, schizophrenia diagnosis, schizophrenia treatment, and schizophrenia prognosis. Search dates: March and September 2012, and August 2014.

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The Authors

SARAH D. HOLDER, DO, is the associate program director at the Baylor Family Medicine Residency at Garland (Tex.). She is also a clinical assistant professor at Texas A&M Health Science Center College of Medicine, Dallas campus. At the time this article was written, she was medical director of the QuickCare Clinic and a volunteer faculty member at the Methodist Family Medicine Residency Program in Dallas, and an adjunct clinical assistant professor at the University of North Texas Health Science Center—Texas College of Osteopathic Medicine, Fort Worth.

AMELIA WAYHS, MD, MPH, is a family physician in private practice in Dallas. At the time this article was written, she was a faculty member at the Methodist Family Medicine Residency Program.

Address correspondence to Sarah D. Holder, DO, Baylor Family Medicine Residency at Garland, 601 Clara Barton Blvd., Suite 340, Garland, TX 75042 (e-mail: sarah.holder@baylorhealth.edu). Reprints are not available from the authors.

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