

Managing Dry Eyes and Dry Mouth in Sjögren's Syndrome

An interview with Stuart S. Kassan, MD, rheumatologist with Colorado Arthritis Associates, Denver, Colorado, and Clinical Professor of Medicine at the University of Colorado Health Sciences Center. Dr. Kassan's interest in Sjögren's syndrome began with a National Institutes of Health fellowship, a research stint that produced the seminal publication linking Sjögren's to increased risk of lymphoma. Dr. Kassan continued his research at Cornell University in New York and in his current Denver-based rheumatology practice remains active in both research and clinical management of patients with Sjögren's syndrome. In recent years, he acted as Chairman of the Medical Advisory Board for the Sjögren's Syndrome Foundation. We asked Dr. Kassan for his perspective on management of the nonsystemic manifestations of Sjögren's syndrome.

Background

AJMC: You've been active in research and management of Sjögren's syndrome for decades. What was it about Sjögren's syndrome that attracted you to this line of research?

Dr. Kassan: It's a fascinating disorder because it involves a number of overlapping autoimmune diseases and in some cases a progression from a benign to a more malignant disease. For example, patients with Sjögren's syndrome have a 44 times greater chance of developing lymphoma. For a researcher, this means the disease could be critical in figuring out what causes the transformation of cells from benign to malignant. As a clinician, I

find the disease provides a complex challenge, mainly because a significant percentage of patients with Sjögren's syndrome develop other autoimmune conditions.

AJMC: What other conditions?

Dr. Kassan: Primary Sjögren's syndrome is still mostly defined by the classic findings of dry mouth, dry eyes, and dyspareunia, but common systemic features include fatigue and fibromyalgia. Fatigue occurs in as many as 50% of patients with primary Sjögren's syndrome and can be extremely debilitating. The complete list of potential extraglandular manifestations is actually quite long, including rashes, vasculitis, lymphoma, obstructive lung disease, kidney problems, and neurologic manifestations.

AJMC: How prevalent is Sjögren's syndrome in the United States?

Dr. Kassan: In the United States, the prevalence is thought to be anywhere from 2 to 4 million. Approximately 500,000 to 1 million have an official diagnosis but the majority is likely still undiagnosed. The epidemiologic knowledge base for this disease is not solid. We sorely need better data and that was the impetus for recent efforts to develop a consensus for diagnostic criteria.

AJMC: Do rheumatologists usually make the diagnosis of Sjögren's syndrome?

Dr. Kassan: Yes, it's most common for a rheumatologist to make the diagnosis. This is because the diagnosis of Sjögren's syndrome overlaps tremendously with other rheumatologic diseases—like rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, and polymyositis. In some studies, up to 20% to 50% of lupus patients may have what we call secondary Sjögren's. And in rheumatoid arthritis, anywhere from 10% to 30% of patients may have secondary Sjögren's. So, most patients with Sjögren's syndrome are diagnosed after they have a diagnosis for these other rheumatologic conditions.

AJMC: *How common is it for a primary care physician to make the diagnosis of primary Sjögren's syndrome?*

Dr. Kassan: It's less common but it does happen. In most cases, the primary care physician will refer a case to a rheumatologist for the diagnosis. Unfortunately, many physicians still overlook patient complaints related to Sjögren's syndrome. In many cases, the family practitioner and/or the patient will discount the symptoms as trivial or ascribe a woman's various symptoms of dryness to the postmenopausal period. Simple age-related dryness is another common misdiagnosis. All this can lead to long delays in diagnosis.

AJMC: *Who is at highest risk of developing primary Sjögren's syndrome?*

Dr. Kassan: The peak years of developing Sjögren's syndrome are between 40 and 60 years of age. As with many other autoimmune diseases, it occurs more frequently in women, with a female to male ratio of 9:1.

AJMC: *How would you describe the "typical" patient presenting with Sjögren's syndrome?*

Dr. Kassan: Frustrated. She has been suffering from symptoms of Sjögren's syndrome for at least 6 years before diagnosis. And the most common reaction

after diagnosis is relief. She has been living with these symptoms for many years and now she knows it's not all in her head and she might get more effective and specific treatment.

AJMC: *And the typical prognosis?*

Dr. Kassan: For the patient with primary Sjögren's whose symptoms remain primarily local, the prognosis can be good. Over-the-counter and, if necessary, prescription medications can relieve many of the worst symptoms of dry eyes and mouth. Treatment and routine monitoring may also prevent complications such as infections and dental problems. For those patients with organ involvement or systemic manifestations such as fatigue, the path ahead is often harder and the treatment course more complex, but the need for relief of external dryness is no less.

Dry Eyes and Mouth: Not Trivial

AJMC: *What are the actual symptoms of dry eyes? How do patients describe this to you?*

Dr. Kassan: In most cases, the deficiency in the tear film related to Sjögren's syndrome produces eye irritation, which is felt by patients as a gritty, sandy, or burning feeling in the eye. This mucosal dryness and irritation is called keratoconjunctivitis sicca. Patients can also report eye fatigue or they might develop rope-like thickened strands of mucus. In some cases this irritation can lead to corneal ulceration and/or infection.

AJMC: *How do dry eyes impact the patient's everyday life? Is it a nuisance or does it really limit what they can and can't do?*

Dr. Kassan: For many patients, the impact can be significant. In addition to the constant irritation, they may have trouble with simple activities like watching television or reading. The discomfort

or blurred vision might also lead to difficulty at work on the computer or driving. In some patients, the biggest problem is that they can't cry.

AJMC: *Do all Sjögren's patients with dryness also have inflammation and infection?*

Dr. Kassan: We believe that most patients do have an autoimmune-driven inflammatory process of the lacrimal glands. This is indicated by the presence of lymphocytes and findings of keratoconjunctivitis sicca on examination. The level of inflammation varies from patient to patient. When extreme, corneal ulcers can occur. Although noninfectious inflammation is most common, both viral and bacterial infections of the eye can also occur. These can be associated with severe scarring and vision loss if not treated.

AJMC: *How do the symptoms of dry mouth manifest?*

Dr. Kassan: First there is a dramatic discomfort or soreness caused by the constantly dry mouth. The sides of the mouth and tongue and the lips often become cracked because of the lack of salivary action. Mucus in the mouth may be dry and sticky. All this dryness causes a burning sensation in the mouth and the lack of salivary lubrication can even make it difficult for patients to talk normally. They are often hoarse. It also causes the cheeks to stick to the teeth and get caught during chewing, which explains the scars and sores from cheek biting that are often seen in these patients. But beyond the persistent dryness and burning, the biggest problem in patients with dry mouth is the trouble they have eating. These patients need to take a fair amount of liquid with meals to be able to chew and swallow food. Without this extra liquid, eating is extremely difficult and choking is a real possibility.

AJMC: *What are other problems related to dry mouth?*

Dr. Kassan: Rampant dental caries and loss of teeth are other major problems. All people carry some level of natural predisposition to dental caries but in patients with Sjögren's this tendency is greatly amplified. The tooth demineralization associated with Sjögren's can be extreme, with tooth decay developing and progressing rapidly in many patients. Patients also often have difficulty wearing dentures. Some studies now indicate that gum disease may also be more prevalent in patients with Sjögren's syndrome. For all these reasons, regular visits to the dentist and close attention to brushing and fluoride applications are critical in patients with Sjögren's syndrome. A distinct form of erythematous oral candidiasis is also fairly common in these patients, with many individuals developing not the classic white patches of thrush but instead a red burning oral mucosa that must be treated with topical antifungal medication.

Issues in Diagnosis

AJMC: *What are the most important factors in making the diagnosis of Sjögren's syndrome?*

Dr. Kassan: Most rheumatologists acknowledge 3 main diagnostic criteria. The primary finding required for diagnosis is dry eyes and dry mouth. The second strong indicator is a positive antinuclear antibody (ANA) blood test. This ANA test is positive in many patients with autoimmune diseases including the majority, though not all, of patients with Sjögren's syndrome. The third element of the diagnosis is the lip biopsy, where a small sample from the inside of the lip is taken and examined under the microscope for evidence of lymphocytes, which indicates an inflammatory process.

AJMC: *Are there specified tests and exact cut-offs required to make the diagnosis?*

Dr. Kassan: In the early 1990s, separate groups of American and European special-

ists developed diagnostic guidelines and although these are generally similar, the American protocols tended to be more rigorous in their requirements. For example, the European criteria allowed a diagnosis to be made even in the absence of biopsy or autoantibodies. The 2 systems are fairly detailed and establish different standards for determining a “definite” or “probable” diagnosis of Sjögren's syndrome.

AJMC: *Have these variations in diagnostic criteria led to any differences in how patients are managed in the United States versus Europe?*

Dr. Kassan: Probably not. In practice, most rheumatologists will focus on dealing with the local manifestations of dry eye and mouth as needed. But having a uniform set of diagnostic criteria will be critical in helping define the full scope of this disease and then improving management. The current lack of uniformity in diagnosis makes it very difficult to track disease demographics and outcomes and to find answers to many of the basic questions we are discussing here—like how many patients have this disease, who's at highest risk, what are the rates of serious complications such as lymphoma, and which treatments work best.

AJMC: *When will a uniform set of diagnostic guidelines be available?*

Dr. Kassan: Consensus guidelines have been discussed recently and will be available soon. [*Ann Rheum Dis*, in press]

AJMC: *Are specific tests needed to confirm the severity of a patient's dry eyes and dry mouth?*

Dr. Kassan: The patient's history and the physical examination usually provide most of the evidence needed. But in some cases, specific tests aid in the evaluation of these symptoms. For example, salivary flow can be stimulated and measured with several techniques including injection of radioactive dyes into the salivary glands

followed by X ray. None of these methods for measuring salivary flow is particularly precise. The simpler tests for dry eye are much more commonly employed. In the Schirmer test, a small piece of filter paper placed under the lower lid for 5 minutes gives a rough estimate of tear production. A slit lamp exam is another simple ophthalmological office test to measure tear volume. Dyes such as rose bengal and lissamine green can also be applied directly to the ocular surface to visualize devitalized cells.

AJMC: *What should be considered in the differential diagnosis of primary Sjögren's syndrome?*

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—Stuart S. Kassan, MD

Dr. Kassan: Dry eyes and mouth can be caused by a number of conditions. Perhaps the most common thing to watch for is treatment with medications such as cold remedies, antihistamines, antidepressants, antihypertensives, or anti-inflammatory drugs. Temporary causes such as dehydration, anxiousness, or other psychological or physiological changes may also contribute to episodes of salivary or lacrimal dryness. Patients with undiagnosed conditions such as viral infections, hepatitis C infection, depression, multiple sclerosis, and amyloidosis may also have dry mouth or eyes.

AJMC: *Dry eyes and mouth are in fact very common complaints. Is there any*

danger of overdiagnosis as awareness of Sjögren's syndrome grows?

Dr. Kassan: No I don't believe that will happen. Sjögren's is unlike some other controversial conditions such as fibromyalgia or Lyme disease in that the elements needed for diagnosis are relatively clear. Certain details of diagnosis still need to be standardized, yes, but the core tools for defining the disease—the symptoms, the ANA test, and the biopsy—are established. Also, Sjögren's tends to be a disease for which patients with mild disease do not actively seek a diagnosis. They tend to be prompted to seek care only when their symptoms reach a certain level.

AJMC: *What's the quickest way for the primary care physician to screen for Sjögren's syndrome in a patient with slight symptoms of dry eyes and mouth?*

Dr. Kassan: The Schirmer test is probably the best quick test of tear production. This can be done in any office, although the results are more reliable the more often it's done.

AJMC: *Is it always necessary for patients with possible primary Sjögren's to be referred to a rheumatologist for diagnosis?*

Dr. Kassan: That is certainly preferable. From both a clinical and a cost standpoint, it makes sense to evaluate the patient thoroughly for the full range of local and systemic conditions associated with Sjögren's syndrome. In some cases, referral to an ophthalmologist, dentist, or oral pathologist may also be beneficial but in almost all cases, referral to a rheumatologist makes good sense. The rheumatologist can perform a full evaluation, including the special blood tests for antibodies and immunoglobulins that may help determine the presence of an associated autoimmune condition. This specialist is best equipped to determine whether the manifestations are local, for example, limited to dry eyes or oral candidiasis, or systemic such as arthritis, nephritis, or pneumonitis.

Treatment Options

AJMC: *What are the main over-the-counter (OTC) treatment options for patients with dry eyes and mouth related to Sjögren's syndrome?*

Dr. Kassan: Most patients use moisture replacement products such as artificial tears, artificial salivas, skin lotions, nasal sprays, and vaginal lubricants. These can actually be very effective for those patients with mild or moderate symptoms. Sugar-free chewing gum can also be effective in stimulating salivary flow. Newer artificial tears, such as those without preservatives or with longer-lasting formulations, now provide patients with even better OTC options.

AJMC: *At what point do you consider switching patients to a prescription product for their symptoms?*

Dr. Kassan: Patients are normally very good at telling us when it's time. Nonetheless, most prescription treatments are currently underutilized. Many more patients should be benefiting from these effective options. That's why regular visits should be scheduled not only to monitor the patient's satisfaction with eyes and mouth symptom relief but also to check for development of complications. Obviously, an oral fungal infection or an ocular bacterial infection would require immediate specific therapy.

AJMC: *What are the main pharmacologic or surgical options for relieving the symptoms of dry eyes and mouth?*

Dr. Kassan: Beyond the specific therapies for infections, there are a couple of main options. To limit the outflow of tears through the puncta and nasolacrimal ducts, punctal plugs can be inserted by the ophthalmologist. A cyclosporine eye drop may also soon be available to treat the eye inflammation. And in those patients who continue to have extreme difficulty in chewing and swallowing food, the muscarinic agonists pilocarpine and cevimeline now often provide considerable relief.

AJMC: *How can these muscarinic stimulants be effective if the patient's secretory glands have been destroyed by an autoimmune process?*

Dr. Kassan: It's true that this may seem like trying to get water from a stone, but in many patients, many secretory glands may remain intact. Pilocarpine has been used for many years to stimulate both lacrimal and salivary gland output, and cevimeline is a newer longer-lasting muscarinic that does that as well. Both may be effective in some Sjögren's syndrome patients.

AJMC: *Are there any special considerations with dosing or side effects for these agents?*

Dr. Kassan: The basic strategy is to start with a low dose and build up. The main side effects to watch for with the muscarinic agents are sweating and gastrointestinal intolerance.

AJMC: *If approximately half of all Sjögren's patients have the secondary form of disease, we can presume many of them are already taking anti-inflammatory, immunosuppressive, or analgesic drugs. Is there any evidence that these drugs affect the symptoms of dry eyes or mouth?*

Dr. Kassan: Yes, in fact, some of the drugs being taken by patients with rheumatoid arthritis or SLE may worsen the symptoms of dry eyes and mouth. The best examples of this are pain medications such as the narcotics or the tricyclics sometimes used to treat secondary fibromyalgia and/or depression. This can be a difficult situation if the patient is otherwise doing well on the systemic agent—a clinician is reluctant to reduce the dose simply to limit the eye and mouth problems. This is where a more effective topical agent can contribute substantially to the overall therapeutic plan.

Management of Care

AJMC: *Have there been any attempts to measure the total economic burden relat-*

ed to Sjögren's syndrome in the United States?

Dr. Kassan: No. The difficulty, again, has been inconsistency in reporting and tracking patients who have this disease. Most of our data are anecdotal.

AJMC: *Based on your experience, what seems to be the major cost driver in primary Sjögren's syndrome?*

Dr. Kassan: The profound fatigue that occurs in as many as 50% of all Sjögren's cases may in fact be one of the most debilitating and, ultimately, expensive components of this disease. Treatment of fatigue often involves hydroxychloroquine. The fibromyalgia accompanying the disease is also costly in terms of care seeking and treatment attempts, not to mention quality of life and potential lost productivity at work or school. The dental complications associated with the dry mouth symptom can also be fairly expensive.

AJMC: *Can treatment reduce these costs?*

Dr. Kassan: Careful management, which includes appropriate treatment, can definitely relieve symptoms and reduce complications. Will this reduce total health system costs? We simply don't have the data to prove that total costs for managing these patients can be reduced.

AJMC: *What can managed care organizations and health maintenance organizations do to improve their approach to patients with Sjögren's syndrome?*

Dr. Kassan: The first thing they can do is improve diagnosis. This will require increased awareness among staff or participating primary care physicians. Where it's appropriate, education of dentists and ophthalmologists can also increase early detection rates for the disease. Access to rheumatologists and to the full range of prescription options for the symptom relief is also important.

AJMC: *Are there any other opportunities for managed care?*

Dr. Kassan: As in many other areas of rheumatology, increased patient education is absolutely vital to improved outcomes with Sjögren's. Because so many patients with Sjögren's syndrome are actually diagnosed while receiving care for another chronic condition like rheumatoid arthritis or lupus, adding some patient education to existing disease management programs is one possibility. Because of their strength in patient education and proactive disease management of chronic conditions, this is one area where managed care organizations may have an advantage in tackling the problem of Sjögren's syndrome.

AJMC: *Sjögren's syndrome is the first or second most prevalent autoimmune disease and yet ranks ninth in research funding. How did it become such a "large orphan disease?"*

Dr. Kassan: Over the years, research priorities have changed, whereby those studying Sjögren's syndrome have decreased in number. Hopefully, by making Congress and the public more aware of the significant prevalence of Sjögren's syndrome in the population, more research funds will be made available to study this disease further.