Over the past 40 years, several experimental mouse model systems have been developed to investigate the pathogenesis of Sjögren’s syndrome (SS). While several animal species have been explored, the greatest experimental activity has centered on mouse models, and they have proven to be valuable resources and generated much data. The question is: How representative are these mouse models of human disease?

Presence of lymphocytic infiltrates within the salivary and lacrimal glands is a characteristic feature of SS. These lymphocytes can recognize ubiquitously present antigens such as SSA and/or antigens that are specific to the salivary and lacrimal glands. Where these lymphocytes are first activated and how they start infiltrating the glands are major issues in SS research.
bid anxiety, depression and pain.

Other causes of poor sleep in patients with Sjögren’s include joint pain, muscle stiffness and discomfort, sicca symptoms and nocturia. Dry mouth and dry eye can interrupt sleep, causing patients to awaken to alleviate these symptoms. Sipping water throughout the night also leads to more frequent awakening for trips to the bathroom.

The peripheral nervous system (PNS) is affected in many Sjögren’s patients and can result in pain which in turn can contribute to sleep difficulties. The reverse can be true as well, as PNS pain may be related to sleep disturbances including myalgias, arthralgias and other small fiber pain sensation. In addition, central nervous system involvement both focal and diffuse has been established in primary Sjögren’s and may contribute to sleep difficulties.

Comorbid diseases also can impact sleep in Sjögren’s patients. As many as 55% of SS patients also may have fibromyalgia (Tishler et al) which by itself is associated with sleep disturbances, particularly insomnia and alpha intrusion. Additionally, restless leg syndrome (RLS) may cause a disruption in sleep and has been reported repeatedly in Sjögren’s patients. In a brief report on rheumatological serologies in secondary restless leg syndrome, it is noted that RLS has been reported in approximately 25% of patients diagnosed with rheumatoid arthritis (RA) and Sjögren’s (Ondo et al).

Specific diagnostic criteria for RLS and sleep disorders in one paper on Sjögren’s (Gudbjörnsson et al) used a single symptom for diagnosing RLS—“Creeping sensations in the legs.” Ten patients with primary Sjögren’s who were not on regular medication for their disease underwent polysomnography and were shown to have a variety of sleep abnormalities. While periodic limb movements of sleep (PLMS) was not specifically mentioned in connection with these patients, they most likely did have this disorder as PLMS often accompanies RLS. PLMS occurs when sudden involuntary jerking or twitching movements occur in the legs during sleep.

The same study found that when compared to both RA patients and healthy controls, the primary Sjögren’s patients reported significantly more incidents of “too little sleep” as well as sleep deficiency, defined as the need for sleep versus actual sleeping time. RA patients with secondary Sjögren’s took significantly longer to fall asleep compared to RA patients without secondary Sjögren’s. And, pSS patients had significantly more trouble initiating and maintaining sleep than RA patients. Frequent awakening in the pSS patients was attributed to pain, headache, shortness of breath, palpitations and sweating and difficulties initiating sleep were attributed to muscular tension, RLS and anxiety.

Inflammation common in Sjögren’s patients may exacerbate sleep disturbance. It is well noted that cytokines may play an important role in sleep disorders. Furthermore, psychiatric abnormalities also have been reported. In an article on sleep disturbances associated with primary Sjögren’s syndrome, it is noted that psychiatric morbidity and personality disorders have frequently been investigated in autoimmune disorders.

Abnormalities seen with Sjögren’s can be varied and subtle, making it difficult to determine the exact cause or causes of sleep disturbance. There may be subclinical variances of sleep disorder as well.

**Clinical Evaluation**

The evaluation of sleep disorders in Sjögren’s starts with a sleep history to include bedtime, estimated time to fall asleep, number and causes of awakenings through the night, final get-up time and how the patient feels early upon awakening, for example, whether the patient is still tired or refreshed. The sleep history includes daytime sleepiness, naps and fatigue as well as discomfort in the legs in the evenings consistent with restless leg syndrome.

After a comprehensive history is obtained, the use of the Mini Sleep Questionnaire (MSQ) might be appropriate for these patients. The MSQ is a 10-item questionnaire that significantly helps in differentiating between different causes of sleep disturbances and between healthy controls and those who suffer from sleep disorders. An overall score is determined that defines the severity of the sleep disturbance.
Treatment

Treatment of sleep problems in Sjögren's patients starts with identification of the most obvious causes of sleep disturbance, such as sicca, anxiety and depression. Attempts to reduce sicca symptoms and obtaining treatment for anxiety and depression can be helpful. Sleep hygiene and cognitive behavioral therapy also may prove beneficial.

Medications such as sedating tricyclic antidepressants can be used in insomnia with comorbid depression. However, these medications could aggravate restless legs, periodic leg movements and sicca syndrome. Non-benzodiazepine agonist receptors such as Zolpidem, Zaleplon, and Eszopiclone can be used along or in combination with antidepressant medications. Ramelteon, a melatonin receptor agonist, can be helpful. Benzodiazepines such as flurazepam, temazepam, triazolam, or estazolam can be used.

Sleep studies are only indicated if other sleep disorders such as sleep apnea, idiopathic hypersomnia, narcolepsy or periodic leg movements are suspected or if a patient has medically refractory or unexplained insomnia.

Conclusion

Sleep disturbances of various types are associated with Sjögren's syndrome, making a comprehensive historical critical for the diagnosis and subsequent treatment. Use of the Mini Sleep Questionnaire and polysomnographic evaluations also can be useful. There may be subclinical involvement in sleep disorders, some of the most common of which are xerostomia, dry eye, restless leg syndrome and fibromyalgia. Additionally, psychiatric disorders including depression and anxiety also may interrupt sleep.

References


Goodchild CE, Treharne GI, Booth DA, Bowman SJ. Daytime patterning of fatigue and its associations with the previous night’s discomfort and poor sleep among women with primary Sjögren’s syndrome or rheumatoid arthritis. Musculoskeletal Care. 2010 Jun;8(2):107-17.


*Mouse Models* Continued from page 1 ▼
a very obvious dry eye in a mouse can become evident by visual examination. However, for most experimental models, rarely has this been the case. Most investigators rely on the Schirmer test, modified for use in mouse models and known as the Phenol Red Thread Test. Although this analysis can show reduced lacrimal gland function, whether the mouse has dry eyes similar to those observed in SS patients is difficult to address. Clearly additional tests such as Rose Bengal staining or Fluorescein staining should be performed. Moreover, biochemical analysis of tears would provide additional evidence for glandular dysfunction.

Two additional criteria focus on oral signs and symptoms. Unlike SS patients, dry mouth in a mouse is difficult to determine. Again, symptoms are not an option. Some investigators have assessed weight loss as a surrogate for reduced food intake presumably due to dry mouth. The problem is that it can take several months before the weight loss is apparent and moreover an underlying autoimmunity or other factors can also contribute towards this. Thus, a direct correlation between dry mouth and weight loss is not always feasible.

Another challenge with evaluation of salivary gland function in a mouse model is the inability to collect unstimulated saliva. Thus, one has to rely on collection of stimulated saliva, which is generally done through the injection of pilocarpine hydrochloride, a muscarinic receptor 3 agonist. Using appropriate dosing of the drug (0.15-1.5 mg/Kg body wt), differences in saliva volumes and flow rates between diseased mice and normal mice can be readily detected. However, one has to exercise caution in interpreting these data. Decreases in saliva volume, particularly if they are small in the range of 10-20% may not be biologically relevant although statistically significant. Varying the pilocarpine dosage may diminish or augment the differences. Further, differences in salivary function may be due to other factors.

Many investigators have used non-autoimmune prone mice as controls when comparing saliva volumes with the diseased mouse. It should be noted that basal saliva volumes in different mouse strains can vary considerably. Thus, a control strain should have similar saliva volume as an age-matched, non-diseased experimental mouse and the growth characteristics of the strains should be similar. Ideally, longitudinal analysis of saliva volumes within the same mouse or cohorts of the same mouse strain should show a progressive drop in volume and flow rate. Moreover, biochemical characterization of saliva should be performed which would provide further evidence for salivary gland dysfunction.

SS has a strong autoimmune component, and one criterion deals with the demonstration of serum autoantibodies to Ro/SSA or La/SSB. A high titer of these autoantibodies is present in the majority of patients. However, in mice, even in spontaneous mouse models for lupus (some of these also develop SS-like disease), these autoantibodies are not readily detected. This occurs despite the presence of other anti-nuclear autoantibodies in high titers. To detect the Ro/SSA and La/SSB autoantibodies in mice, recombinant antigens are used in ELISA or western blots. In our experience, this format detects polyreactive low affinity autoantibodies. Thus, use of immunoprecipitation assays employing antigen in its native form should be used for the detection of Ro/SSA and La/SSB antibodies in mice. Alternatively, if autoimmune response to other antigens is demonstrated in a convincing manner, the insistence for demonstration of anti-Ro/SSA and anti-La/SSB autoantibodies in mouse needs to be re-examined.

The criterion for histopathologic changes in salivary glands can be readily investigated in mice. The biggest strength of mouse models for SS research is the ability to investigate early events that initiate inflammatory cell infiltration within the exocrine glands and, thereby, mechanisms of disease induction. Like other autoimmune disorders, genetic predisposition alone is not sufficient for manifestation of SS. Interaction with environmental factors is a critical requirement for disease development. Microbial infections, particularly viral infections, have been long suspected as a major environmental factor. Since no specific infection has been conclusively associated with SS, it is possible that multiple infections with different viruses provide a trigger for SS development in genetically susceptible individuals. The earliest consequence of a viral infection is the activation of innate immunity. Thus, we can hypothesize that chronic activation of innate immunity in genetically-susceptible individuals is a major event for SS development.

Our recent studies in the New Zealand Black X New Zealand White F1 (NZB/W F1) mice provide evidence for this theory. As a surrogate for viral infection, we repeatedly treated NZB/W F1 mice with a Toll-like receptor 3 agonist, poly (IC). This treatment caused a rapid infiltration of inflammatory cell infiltrates within the submandibular glands of mice. The sialoadenitis in poly(IC)-treated mice was much more severe and accelerated by 2-3 months over the PBS-treated controls. Our studies further show that rapid upregulation in the expression of multiple chemokines within the submandibular glands of poly(IC)-treated mice.
EVOXAC works at the source.

EVOXAC treats dry-mouth symptoms at the source.

- A cholinergic agonist that binds to muscarinic receptors
- EVOXAC stimulates the natural flow of saliva
- Clinically proven to help relieve the dry-mouth symptoms from Sjögren’s syndrome

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IMPORTANT SAFETY INFORMATION

EVOXAC (cevimeline HCl) is indicated to treat the symptoms of dry mouth in patients with Sjögren’s syndrome.

- Cevimeline HCl is contraindicated in patients with uncontrolled asthma, known hypersensitivity to the drug, and when miosis is undesirable, e.g., in acute iritis and narrow-angle (angle-closure) glaucoma
- Cevimeline HCl can potentially alter cardiac conduction and heart rate and produce transient changes in hemodynamics. Cevimeline HCl should be administered with caution and under close medical supervision to patients with a history of cardiac disease, controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease
- Cevimeline HCl should be administered with caution to patients taking beta-adrenergic antagonists because of the possibility of conduction disturbances and to patients with a history of nephrolithiasis or cholelithiasis
- If a patient sweats excessively while taking cevimeline HCl, dehydration may develop
- Caution should be advised while driving at night or performing hazardous activities in reduced lighting
- Safety and effectiveness in pediatric patients have not been established
- Cevimeline HCl is metabolized by the P-450 isozymes CYP2D6 and CYP3A4. Thus, there may be potential for interaction between cevimeline HCl and other compounds
- Special care should be exercised when cevimeline HCl is taken by geriatric patients, considering the greater frequency of decreased hepatic, renal, or cardiac function
- The most frequently reported adverse events associated with the pharmacologic action of a muscarinic agonist (>10% incidence) in clinical trials of cevimeline HCl were: excessive sweating, nausea, rhinitis, and diarrhea. Consult the full Prescribing Information for other adverse events


Please see next page for brief summary of the full Prescribing Information about EVOXAC.
Attendees at the California Dental Association (CDA) conference packed the room to overflowing to hear the educational session on dry mouth and Sjögren’s. In fact, many had to be turned away because all 400 seats were filled. The Sjögren’s Syndrome Foundation (SSF) co-sponsored the CE course together with the CDA Foundation, and the two organizations are considering future programs on the topic because of the high level of enthusiasm. In addition, the SSF is pleased that the Florida Dental Association is interested in holding a similar program in 2012.

Ava Wu, DDS, Michael Brennan, DDS, MHS and Vidya Sankar, DMD, MHS developed a Continuing Education program that covered: 1) How to identify dry mouth; 2) How to identify possible causes of a patient’s dry mouth; and 3) How to manage, treat and prevent complications from dry mouth. Educating oral professionals about dry mouth and Sjögren’s is critical in order to prevent the many complications that can occur in dry mouth, manage complications when they do occur, and ensure that Sjögren’s patients are identified and obtain regular care from their dentist and other specialists such as a rheumatologist and ophthalmologist.

About 25 million Americans suffer from dry mouth, the top three causes for which are medications, Sjögren’s, and radiation therapy to the head and neck. Dry mouth is more prevalent in women than in men and occurs more frequently in Caucasians. Advanced age is not related to salivary gland dysfunction and dry mouth, but dry mouth occurs more frequently in older adults largely due to side effects of medications.

Dr. Wu is a Clinical Professor and Director of the Salivary Gland Dysfunction Clinic at the University of California, San Francisco, School of Dentistry, San Francisco, California; Dr. Brennan is Associate Chairman of the Department of Oral Medicine and Director of the Sjögren’s Syndrome and Salivary Disorders Center at the Carolinas Medical Center, Charlotte, North Carolina; and Dr. Sankar is an Associate Professor in the Department of Comprehensive Dentistry at the University of Texas Health Science Center, San Antonio Dental School. San Antonio, Texas.

Clinicians can ask their patients key questions to determine whether dry mouth, and potentially Sjögren’s, might be a problem.

- Does the amount of saliva in your mouth seem too little, too much, or do you not notice it?
- Do you have difficulties swallowing?
- Does your mouth feel dry when eating a meal?
- Do you sip liquids to aid in swallowing dry food?

treated mice are responsible for initiating lymphocytic infiltration. Clearly these studies have significant implications for understanding the etiopathogenesis of SS and demonstrate the utility of mouse models in SS research.

Many genetic defects in mice (induced or spontaneous) can lead to some features of SS. However, a careful evaluation of each mouse model needs to be conducted, keeping in mind the inherent pitfalls, before it can be accepted as a relevant model for SS. The recent advances in gene expression studies and genome wide associations in SS patients have opened up a vast area of research. Clearly, exploring how different gene polymorphisms observed in SS patients contribute toward disease development in experimental mouse model systems will be a more efficient strategy than the reverse approach of investigating whether a certain mutation observed in mice is present in SS patients. We feel that the former strategy might lead to the development of biomarkers for SS and suggest novel therapeutic strategies to treat human disease.

In summary, the mouse models for SS are a valuable resource for investigating the mechanisms of disease pathogenesis, although there is no single model which is ideal for all investigations or fully replicates the human disease. Further research is needed to define more completely the existing mouse models and to develop new models. Further, mouse models will provide a valuable test of emerging concepts of mechanisms of disease development and new therapies.

Editor’s Note: Co-author Dr. Umesh Deshmukh received the SSF Innovative Concept Grant in 2008 and 2009 for his project, “Adenosine receptor agonists: Novel therapeutic agents for Sjögren’s syndrome.” His grant was made possible by support from the Leach Family. He recently received an R21 research grant from the National Institutes of Health to continue his work in innate immunity activation in the pathogenesis of Sjögren’s.

Further Reading:

Acknowledgements
Grant support by SSF and the National Institutes of Health. We are thankful to Dr Philip C. Fox for helpful suggestions for this article.

Table 1 Mouse Models Mimicking Different Aspects of Human Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Mouse Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>NZB/WF1, MRL lpr/lpr, IQI/Jic, Aly, NOD, NOD based (C57BL/6-Aec1Aec2, NOD.B10-H-2b)</td>
</tr>
<tr>
<td>Induced</td>
<td></td>
</tr>
<tr>
<td>Transgenic</td>
<td>Baff, RbAp48, Il-10, Il-12, Il-14, HTLV-tax</td>
</tr>
<tr>
<td>Gene knockouts</td>
<td>Tgfβ, Pik3, Foxp3, Aromatase, kB enhancer, Act1, Tsp-1, Id3, NOD based (Ccr5, E2f2, Ifnr, Ifng, Il-4, Stat6, Aire)</td>
</tr>
<tr>
<td>Immunization</td>
<td>Tissue extracts, Carbonic anhydrase II, Ro60 peptides</td>
</tr>
<tr>
<td>Other</td>
<td>NFS/sld d3Tx, MCMV infection, Retrovirus, Estrogen deficiency, GVHD</td>
</tr>
</tbody>
</table>

New Director Takes the Helm of the NIDCR in August

The Sjögren’s Syndrome Foundation welcomes Martha J. Somerman, DDS, PhD as the new Director of the National Institute of Dental and Craniofacial Research (NIDCR) at the National Institutes of Health (NIH). Dr. Somerman begins her new position on August 29, 2011. Dr. Somerman brings a background in periodontics as well as geriatrics and leaves her position as Dean at the University of Washington School of Dentistry in Seattle, Washington.

Dr. Isabel Garcia has held the interim position since August 2010, when Larry Tabak, former Director of NIDCR, left the directorship at the NIDCR to become second in command at the NIH as Deputy Director under Dr. Francis Collins. Both Drs. Tabak and Garcia have been excellent partners with the SSF and outstanding leaders, and the Sjögren’s Syndrome Foundation looks forward to continuing its relationship with Dr. Somerman and the exceptional staff at the NIDCR.

The NIDCR is home to the NIH Sjögren’s Syndrome Clinic and a leader in Sjögren’s research intramurally and through its extramural grants award system. SSF Vice President Katherine Hammitt completed her tenure on the NIDCR national advisory council the end of 2010.

Lindsey Criswell, MD, MPH, Dsc becomes UCSF Chief of Rheumatology

Lindsey Criswell, MD, MPH, Dsc has been appointed Chief of Rheumatology at the University of California

Continued on page 11 ▼
Clinicians: Patient Education Sheets are available on the SSF website to download

Clinicians: Patient Education Sheets are available on the SSF website to download for your patients at www.sjogrens.org/home/about-sjogrens-syndrome/brochures-and-fact-sheets.

These sheets provide tips for coping and/or basic information about a particular problem or symptom in Sjögren’s that your patients will find useful.

Naturally help relieve symptoms of Dry Eye.

The new tranquileyes Moisture Release Eyewear (available in clear or sunglass lenses) were developed by a Board Certified Ophthalmologist and create a moisture rich environment while your eyes are open. Experience extended relief day and night.

For a limited time, friends of the Sjogren’s syndrome foundation receive a 15% discount off any purchase. An additional 15% of your purchase will be donated back to SSF in support of finding a cure.

For more information or to order, visit www.eyeeco.com. Use promotional code ‘SSF’ online to receive discount or call toll free 1-888-730-7999.
SSF Partners with Professional Organizations for a Second Year to Award Student Fellowships

Current Sjogren’s Syndrome Foundation (SSF) partnerships with professional organizations to award student fellowships are proving so successful for all parties that the SSF will be collaborating with these groups again this year. In 2010 and 2011, the SSF provided student awards through the American College of Rheumatology (ACR) REF Preceptorship Program, the Contact Lens Association of Ophthalmologists Education and Research Foundation (CLAO ERF), and the American Association for Dental Research (AADR). These partnerships allow the SSF to increase awareness of Sjögren’s and the SSF, reach more students and their mentors, and, overall, offer more funding than ever before.

This expansion of the SSF student fellowship program has been made possible by The Bannon Humphrey Foundation of Charleston, South Carolina, which joins the SSF in believing in the importance of fostering future scientists and clinicians in Sjögren’s. The SSF will once again appoint a Sjögren’s expert to join each organization’s review committee.

2011/2012 Student Fellowships

<table>
<thead>
<tr>
<th>Application Deadline</th>
<th>Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR REF 08/01/2011</td>
<td>Medical or graduate student in rheumatology</td>
</tr>
<tr>
<td>11/01/2011</td>
<td></td>
</tr>
<tr>
<td>03/01/2012</td>
<td>Man is the recipient of a 2010 and 2011 SSF research grant entitled “Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren’s Syndrome.”</td>
</tr>
<tr>
<td>AADR 10/14/2011</td>
<td>Graduate or undergraduate student working toward a DDS, DMD or PhD</td>
</tr>
<tr>
<td>CLAO ERF 10/30/2011</td>
<td>May be an ophthalmology resident, fellow or medical student; an optometry student; or ophthalmologist, optometrist, technician or nurse working toward an advanced degree.</td>
</tr>
</tbody>
</table>

Once an award is made, no more applications for future cycles will be considered.

For more information, visit the SSF website at www.sjogrens.org/home/research-programs/student fellowships or email research@sjogrens.org

"Transitions" Continued from page 9

San Francisco (UCSF). Having joined the faculty in 1992, Dr. Criswell has excelled in the research areas of genetics and epidemiology, focusing on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and most recently on Sjögren’s. She is the recipient of a 2010 and 2011 SSF research grant entitled “Epigenetic Profiling of Multiple Cell and Tissue Types in Sjögren’s Syndrome.”

In addition, in August 2010, Dr. Criswell became Co-Director of the international registry on Sjögren’s (the Sjögren’s Syndrome International Collaborative Clinical Alliance or SICCA) based at UCSF. She also has spoken at numerous national and international meetings, including the recent SSF luncheon meeting at the fall 2010 American College of Rheumatology annual meeting for the program, “The Role of Human Genetics and Epigenetics in the Identification of Relevant Clinical Targets for the Development of Novel Therapies in Autoimmune Disease – Particularly Sjögren’s: A Critical Review.”
Nutrients and support the health of cells.

Research into new treatments and a possible cure.

What is Sjögren's syndrome?

Warning Signs and Symptoms of Dry Mouth

Severe and progressive tooth decay, oral infections (parodontal disease), and a painful ulceration of the mouth. As a result, detecting the early signs of dry mouth is critical.

Symptoms of dry mouth can include difficulty swallow-
ing, swallowing—such as dry mouth, difficulty talking or eating certain foods, or some discomfort when swallowing dry foods. The effects of dry mouth may be worsened by dental decay located at the necks of teeth next to the gumline. The patient may feel a burning sensation or a rough or peeling sensation on the tongue, and may have a dry, gritty, or burning sensation in the eyes. In some cases, symptoms of dry mouth may be worse in the morning before the patient is even aware of his or her dry mouth.

It is important to determine if dry mouth is caused by systemic disease or by medications. Medications such as antihistamines, diuretics, antidepressants, and anticholinergics can cause dry mouth. It is also important to look for symptoms of systemic disease such as rheumatoid arthritis, fibromyalgia, Sjögren's syndrome, and other medical conditions such as lupus, diabetes, and menopause, which can all cause dry mouth.

Sjögren's syndrome is a systemic autoimmune disorder that affects multiple organ systems, including the nervous system, blood vessels, lungs, liver, and pancreas. It affects the entire body, and a person may experience symptoms in multiple body parts. The symptoms of Sjögren's syndrome may include dry eyes and dry mouth, as well as fatigue, joint pain, and increased risk of arthritis. The disease can affect both sexes equally, and the average age of diagnosis is the late 40s. In some cases, Sjögren's syndrome may mimic symptoms of other medical conditions such as diabetes, rheumatoid arthritis, or lupus. Sjögren's syndrome may also be associated with other immune-related diseases such as lymphoma. The symptoms of Sjögren's syndrome are often misdiagnosed, and it can take years to diagnose the disease.

The symptoms of Sjögren's syndrome may include:

- Dry eyes
- Dry mouth
- Fatigue
- Joint pain
- Increased risk of arthritis
- Increased risk of other autoimmune diseases, such as lupus or rheumatoid arthritis

Sjögren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4,000,000 Americans. The average age of diagnosis is the late 40s, but Sjögren's syndrome can occur at any age. The disease is diagnosed by both dentists and physicians. It is important to determine if dry mouth is caused by systemic disease or by medications. Medications such as antihistamines, diuretics, antidepressants, and anticholinergics can cause dry mouth. It is also important to look for symptoms of systemic disease such as rheumatoid arthritis, fibromyalgia, Sjögren's syndrome, and other medical conditions such as lupus, diabetes, and menopause, which can all cause dry mouth.

Sjögren's Syndrome: A Place To Begin

A listing of products that may be helpful for people with Sjögren's syndrome.

Healthcare professionals: Call to order complimentary materials to share with your patients!

Contact us for more information: 800-475-6473 • www.sjogrens.org
Two Ophthalmic Companies with Therapies for Sjögren’s Are Sold

TheraTears® Acquired by Akorn, Inc.

The company that produces TheraTears®, Advanced Vision Research (AVR), Inc., was acquired this spring by Akorn, Inc. TheraTears® has long been a key supporter of the Sjögren’s Syndrome Foundation and produces a wide range of products for dry eye, including moisture drops and gels, eyelid cleansers and nutritional supplements containing omega 3s. The SSF mourned the loss of AVR Founder and CEO Jeffrey Gilbard, MD in 2009. Akorn, Inc. is a niche pharmaceutical dealing mostly in generic drugs and also supplies lissamine green dye and strips and threads to evaluate tear production.

Inspire Pharmaceuticals, Inc. Acquired by Merck & Co., Inc.

Merck & Company, Inc. this spring purchased the ophthalmic company, Inspire Pharmaceuticals, Inc. Inspire receives a royalty on two therapies for dry eye disease – Restasis® (cyclosporine) and Diquas® (diquafosol tetrasodium). The company also developed Azasite® (azithromycin ophthalmic solution) for bacterial conjunctivitis and was in the process of conducting trials for the drug’s use in blepharitis, which commonly occurs in dry eye and Sjögren’s.

Approval in Europe Follows U.S. Approval for New Anti-BLYS Drug

After winning approval by the U.S. Food and Drug Administration in March, the first lupus therapy in over 50 years just won approval in May in Europe. Benlysta®, the first of its kind in a class of B-lymphocyte stimulator (BLYS) inhibitors, was developed by Human Genome Sciences (HGS), and partners HGS and GlaxoSmithKline are working together to market the therapy. Preliminary trials are underway for use of Benlysta® in Sjögren’s in France and Italy.

New Market Study on Dry Mouth Treatment

Invado Pharmaceuticals of Pomona, New York announced in May that a recent market research study demonstrated significant symptomatic relief of dry mouth in 90% of Sjögren’s patients using their prescription oral rinse. Forty Sjögren’s patients with xerostomia participated in the study of NeutraSal®. No adverse effects were reported. The average dose was 2.3 times a day and average duration of relief was 71 minutes. NeutraSal® is a supersaturated calcium phosphate rinse.

Award Given for Proposed New Treatment for Dry Mouth

Georgia Health Sciences University College of Dental Medicine investigators have received one of three International Innovation in Oral Care Awards for their study of a new lozenge for dry mouth. Co-investigators Drs. Stephen Hsu and Douglas Dickinson have launched a clinical trial to study a lozenge containing green tea polyphenols, xylitol and jaborandi leaf extract from a plant in South and Central America and providing a slow-extended release of the formula in the mouth. The award is sponsored by the International Association of Dental Research and GlaxoSmithKline.
The 11th International Symposium on Sjögren’s Syndrome (ISSS) will be held September 28 – October 1, 2011 in Athens, Greece. Visit the ISSS website at www.sjogrensyympodium-athens2011.org to register for this major international event in the Sjögren’s world and view the scientific program.

The 11th ISSS is organized by the Department of Pathophysiology, School of Medicine, University of Athens, Greece.
Patient Education Sheet
Peripheral Neuropathy and Sjögren’s

The SSF thanks Julius Birnbaum, MD for authoring this Patient Education Sheet. A rheumatologist and neurologist, Dr. Birnbaum is Assistant Director of the Johns Hopkins Jerome L. Greene Sjögren’s Syndrome, Baltimore, Maryland.

There are many different types of neuropathies in Sjögren’s syndrome. These neuropathies can have different causes and may require different diagnostic techniques and different therapeutic strategies. Unlike other autoimmune disorders, in which the neuropathies predominantly cause weakness, the neuropathies in Sjögren’s primarily affects sensation and also can cause severe pain. Recognition of unique patterns and causes of neuropathies in Sjögren’s is important in arriving at appropriate therapies.

- Recognize that neuropathic pain is a chronic disease. Just as most causes of neuropathies and neuropathic pain in Sjögren’s do not come on suddenly, reduction of neuropathic pain can take a while.

- Initial and predominant neuropathies in Sjögren’s can occur anywhere – in the feet, thighs, hands, arms, torso and/or face.

- Many different symptomatic therapies for neuropathic pain are available. Both physician and patient awareness of potential benefits and side-effects can help tailor an appropriate approach.

- While the class of tricyclic anti-depressants (TCAs) often constitute a first-line tier of therapy in other neuropathy syndromes, the TCAs can increase mouth and eye dryness and therefore are not routinely used as front-line therapies in most Sjögren’s patients.

- Electrophysiologic tests may help in the diagnosis of neuropathies affecting larger nerves which are coated by an insulator called myelin. However, neuropathies affecting smaller-fiber nerves that lack this myelin coating cannot be detected with these tests.

- Special diagnostic tests, including the technique of superficial, punch skin biopsies (small biopsies of 3 millimeters and not requiring any stitches), can help in the diagnosis.

- A relatively rare neuropathy can cause significant weakness in Sjögren’s patients. In contrast to other neuropathies which develop slowly, this neuropathy can present with very abrupt-onset of weakness. This so-called “mononeuritis multiplex” occurs because the blood flow through vessels which nourishes nerves is suddenly compromised.

- In general, immunosuppressive medications are almost always warranted to treat “mononeuritis multiplex” neuropathy. In contrast, the role of immunosuppressives is not well-established in other neuropathies, including neuropathies that cause pain but are not associated with weakness.

- Sjögren’s patients frequently wonder whether pain associated with a neuropathy means they are at an increased risk for more severe motor weakness. While there are exceptions, if weakness is not present at onset, it most likely will not occur.

- Neuropathic pain can be alleviated and assuaged, although there may initially be a “trial-and-error” process with different and perhaps multiple agents.
Clinicians now can offer patients a new product specifically for Meibomian Gland Dysfunction (MGD) which often accompanies the dry eye that occurs in Sjögren’s patients. The maker of SYSTANE®, Alcon Labs, has introduced SYSTANE® BALANCE Lubricant Eye Drops to restore the natural tear’s lipid layer and provide long-lasting dry eye relief. MGD may diminish the oily component in tears, causing tear film instability and the tears to evaporate too quickly.

For more information on Meibomian Gland Dysfunction, see the article in the Spring 2011 issue of Sjögren’s Quarterly on the release of the Meibomian Gland Report from the workshop sponsored by the Tear Film and Ocular Surface Society (TFOS). Also watch for a future Clinician’s Corner article in the Quarterly treatment of MGD.

Patients are needed for a double blind study of patients with severe dry eye. Led by Steven P. Dunn, MD, Division Head, Cornea and External Diseases, Department of Ophthalmology, William Beaumont Hospital/Oakland University, Royal Oak, Michigan, the study will assess the agent Thymosin Beta 4 which has been shown to promote healing of the corneal surface and has been studied in patients with recalcitrant corneal ulcers and erosions with significant success (Dunn SP, Heidemann DG, Chow CY, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Arch Ophthalmol. 2010 May;128(5):636-8; Dunn SP, Heidemann DG, Chow CY, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Treatment of chronic nonhealing neurotrophic corneal epithelial defects with thymosin beta4. Ann N Y Acad Sci. 2010 Apr;1194:199-206.) Thymosin Beta 4 is found in serum and, thus, might be one of the key “ingredients” of serum tears which are often used as a last resort in patients with severe ocular surface disease.

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