# Validation of the Sicca Symptoms Inventory for Clinical Studies of Sjögren's Syndrome

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***ABSTRACT.*** ***Objective.*** Oral, ocular, and other dryness are the hallmark features of Sjögren's syndrome (SS). We constructed a new measure of sicca symptoms, the Sicca Symptoms Inventory, for the evaluation of patients with primary SS.

***Methods.*** Female Caucasian groups of patients with primary SS, systemic lupus erythematosus, and rheumatoid arthritis and healthy controls were assessed for tear and saliva production and also completed a symptoms-profiling inventory construct-validated from primary SS patients' own vocabulary, augmented with sicca items from publications and participating clinicians. Multi-item facets of sicca and other discomfort were validated by factor analysis.

***Results.*** Primary SS and other "sicca" conditions were highly discriminated from other rheumatic disorders and healthy controls on each dryness-related facet of oral and ocular discomfort. Selected symptom scores were as sensitive and specific to primary SS as the scores for saliva and tears, respectively, although the severity scores of symptoms and signs were only moderately correlated.

***Conclusion.*** These multiple-question scales distinguish patients with primary SS from controls more precisely than previously used measures. Future studies will test if change in these symptom scores can serve as an outcome measure for clinical trials in SS. (J Rheumatol 2003;30:1259–66)

*Key Indexing Terms:*
SJÖGREN'S SYNDROME SICCA DRYNESS SYMPTOMS
CLINICAL ASSESSMENT MEASURES

Primary Sjögren's syndrome (SS) is a multisystem immune-mediated disorder characterized by chronic inflammation of the exocrine glands (especially salivary and lachrymal glands)[1] that become dysfunctional, leading to the clinical symptoms of dry eyes and dry mouth. Primary SS is found in patients of both sexes of all ages, but mainly affects women during the fourth and fifth decades of life, with a female:male ratio of 9:1. Some patients develop systemic features that can involve the musculoskeletal, pulmonary, gastrointestinal, hepatobiliary, hematologic, vascular, dermatologic, renal, or nervous systems[2]. SS can also occur in association with other autoimmune diseases (secondary SS) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or scleroderma.

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Although symptomatic therapy of dry eyes and dry mouth with artificial tears or saliva may be satisfactory for some patients, for many it is often inadequate, leading to significant disability and reduced quality of life[3]. Recent clinical trials of muscarinic agonists, such as pilocarpine and cevimeline[4,5], offer the possibility of better treatments for severe xerostomia. Immune system modulation by topical ocular use of low dose corticosteroids or cyclosporin[6] may improve dry eye symptoms. Orally administered interferon alpha has been shown to increase salivary flow rates, to relieve oral symptoms, and possibly to reduce the extent of lymphocytic aggregates in glandular tissues[7,8]. More trials with biologic agents are under way.

Sicca features can be assessed using objective tests such as the Schirmer test of tear production or the unstimulated salivary flow rate (USF). Although these are crude measures, they are easily performed in a routine clinical setting, which is their great advantage over other, more precise, ways of assessing gland function, and they are sensitive to change[4]. It is critical that the effects of a reduction in tear/saliva flow on symptom severity vary among individuals[9], most probably because of differences in corneal/oral mucosal sensitivity and/or psychological processes. For this reason, the symptoms experienced need to be measured separately from tests of physical signs of disease.

There are at present no standardized assessment tools specific for sicca symptoms in SS. Measures such as the ocular surface disease severity index (OSDI), which quan-

tify symptoms of ocular dryness in patients with xerophthalmia[10], and the xerostomia inventory (XI) in dry mouth[11] may, however, be useful in SS. This lack of common assessment criteria has made it difficult or impossible to compare efficacies of treatment between studies.

We investigated the structure and distribution of sicca-related symptoms in patients with primary SS and comparison groups in order to validate a questionnaire instrument for measuring the severity of sicca symptoms.

## MATERIALS AND METHODS

*Subjects*. With Multicentre Research Ethics Committee approval and with informed consent, 130 consecutive female Caucasian patients with primary SS, fulfilling at least 4 out of 6 of the European Community (EC) diagnostic criteria[12,13], including either anti-Ro/La antibodies and/or a positive labial gland biopsy (focus score > 1), were recruited from 12 participating centers in the UK from January to September 2000. For the RA group, 93 consecutive patients fulfilling the 1987 revised American Rheumatism Association criteria for the classification of RA[14] were recruited from a general rheumatology clinic in Birmingham, UK. For the SLE group, 83 consecutive patients fulfilling the 1982 revised criteria for the classification of SLE[15] were recruited from a specialist clinic at the University of Birmingham, UK. Diagnostic criteria for definite or probable secondary SS were met by 19 of the RA patients and 21 of the SLE patients. On the basis of the demographics of primary SS patients attending rheumatology clinics in Birmingham, the inclusion criterion for all groups was that they be female Caucasians aged 35–75 years. A community control group included 103 healthy women without medically significant conditions, who did not have oral or ocular dryness and who were recruited by postal invitation from 2 general practitioners' lists from the Birmingham area. An additional control group was recruited from oral medicine, ophthalmology, or rheumatology clinics, consisting of 26 consecutive female Caucasian patients aged 28–83 years with symptomatic and/or objective xerostomia/xerophthalmia (termed "sicca" here). These individuals were negative for anti-Ro/La antibodies and did not fulfil the diagnostic criteria for primary SS. These 5 groups were sent the inventory reported here as a followup study at 6–9 months after the initial phase of this project.

*Methods*. The original diagnostic category was checked during the study by reported oral and ocular symptoms according to the EC criteria, performance of a Schirmer I test, unstimulated salivary flow rate, and anti-Ro/La antibodies (by ELISA; Binding Site, Birmingham, UK). Data on labial gland biopsy results were utilized if performed.

A small number of recruits were found to be outside the originally specified age range but were included in the study: 7 with primary SS, 8 SLE, 2 RA, and 4 controls were under age 35 years; 5 of the RA group were over 75.

*Questionnaire instruments*. Each member of the 4 groups self-administered a research inventory that included an instrument developed during this project, to measure the severity of facets of somatic and mental fatigue and of general discomfort and pain, using terms elicited from patients with primary SS in freely worded diaries. Questions were added about localized discomfort, previously assessed by a checklist (Booth DA, *et al*, unpublished data), including a number of sicca-related items derived from patients and from previous publications[4,10,16,17] and a questionnaire developed by the Department of Oral Medicine at the University of Liverpool (Field A, Rostron J, personal communication) to assess dryness (sicca) symptoms. Data from the checklist phase of the project (Booth DA, unpublished data) were used to construct frequency tables for the presence or absence of each sicca symptom in each patient and control group. Those items with a positive response frequency of over 30% in the primary SS group (above the 25th centile) were included in the sicca questions. Respondents were asked to give the frequency of experience of each symptom item over the previous 2 weeks as one of 5 categories represented by a line of integers, with zero labeled "never" and 4 labeled "all the time." Respondents were also asked to rate the overall severity of each group of symptoms over the last 2 weeks, on a line of integers from zero to 7, with zero labeled "no problem at all" and 7 categorized "as bad as imaginable."

*Procedure*. All participants in the initial phase in 2000 were sent the inventory by post in March-September 2001, together with a duplicate questionnaire with instructions for use after 24 hours.

*Data analysis*. Completed questionnaires were returned by 112 (86%) of 130 participants with primary SS, 65 RA (70%) (14 with secondary SS), 69 SLE (83%) (16 with secondary SS), 77 (75%) controls, and 18 sicca (69%). Returns of completed retest questionnaires were slightly lower: 108 (83%) participants with primary SS, 59 RA (63%) (12 with secondary SS), 65 SLE (78%) (14 with secondary SS), 72 (70%) controls, and 16 sicca (62%). The total of missing replies for the 9 fatigue and discomfort severity ratings was low (0.7%). Missing responses for the 50 single-symptom frequency items were 2.1% of total possible replies and 2.2% for the 8 grouped-symptom severity items. The total missing responses on the 24 hour retest questionnaire were slightly higher at 2.8% and 3.8%, respectively. When possible, missing responses on the first inventory were replaced with ratings given on the 24 hour retest.

Except where specifically indicated, the analysis of RA and SLE groups excluded patients with definite or probable secondary SS. Statistical analyses were conducted in SPSS for Windows (version 6.1.3).

Principal components analysis was used to confirm the structures of the grouped-symptom severity scores and single-symptom frequency scores by Varimax rotation of the number of factors corresponding to the hypothesized domains or facets of discomfort or fatigue.

The single symptoms and grouped symptoms (facets) most predictive of disorder were identified by the percentage of the disease group whose severity of symptom was more than the cutoff score (sensitivity) and percentage of the healthy controls who were less than cutoff score (specificity). Case cutoffs were specified from the 95% confidence intervals for healthy controls at a grouped-symptom severity rating of one or above, except for the Wetting Mouth and Arthralgia/Systemic facets, where a score of 2 or above was used.

Spearman's correlations of ranked values were used to test the repeatability of ratings between initial test and retest one day later and to compare severity ratings of grouped sicca symptoms and secretory measures in individuals falling within the cutoff ranges.

## RESULTS

*Characteristics of patients*. Anti-Ro and/or anti-La antibodies were found in 82% of the patients with primary SS, 51% of SLE patients, and 3% of RA patients and controls, but none of the 26 sicca patients. Of the 73 primary SS patients who previously had a labial gland biopsy, it was positive in 69 and nondiagnostic in 4. Labial gland biopsy had also been performed in 20 of the 26 sicca patients and it was negative in all 20. No patient with SLE or RA or control had a lip biopsy. The SLE group was significantly younger (mean 48.6 yrs, SD 10.9) than the primary SS, RA, and control groups (means 57.0–60.8 yrs, SD 10.0–12.3; $p < 0.005$ for the 3 groups combined). This group's disparity in age does not affect the interpretation of the data and so it is not addressed further.

*Domains of localized discomfort from severities of grouped symptoms*. The first stage of analyzing the data used factor analysis to identify correlations between grouped oral and ocular symptom scores (and individual symptoms at other sites) in order to divide the symptoms into a number of main

components (domains). Seven such domains were confirmed in each group of patients and controls when loadings were maximized in rotations of 6–8 factors (Table 1). These domains distinguished ocular, oral, vaginal, and cutaneous symptoms of dryness, split the symptoms of arthritis between large and small joints, and isolated Raynaud's symptoms from all other discomfort. The Painful Limbs facet in this study may largely correspond to the General Discomfort domain used in our initial study (Booth DA, unpublished data).

*Facets of ocular sicca from symptom frequencies*. Having established the broad domain structure, we examined the correlations between individual questions about localized discomfort. The rated frequencies of single ocular symptoms formed 3 highly consistent multi-item components in factor analysis (data not shown). These components corresponded well to the facets (Sore Eyes, Eye Irritation, and Poor Vision) of the Ocular Sicca domain (Tables 1 and 2) and to the 3 subscales of the OSDI[10].

In primary SS, 14 of the 17 individual symptoms of ocular sicca included in the research inventory (listed in Table 2) loaded highly (> 70%) on their respective factors. Of the other 3 items "sensitivity to light" and "dazzled by sunlight" were invalid as Eye Irritation in SLE (percentage loadings 16% and 25%, respectively) as well as in primary SS (37% and 41%), although not in RA (78% and 75%). In the healthy controls, these 2 items also loaded strongly on a factor that was quite separate from irritation attributed to the air. These items were therefore rejected from the Eye Irritation facet of the Ocular Sicca domain in the sicca symptom inventory (SSI).

The third of these 3 items with a low loading (53%) on its respective factor (Poor Vision) in primary SS was "limited vision when driving at night." This item might, however, be particularly susceptible to variation arising from a relatively low incidence of night-driving over the previous 2 weeks (especially in the summer period surveyed). Since this item was robust in this facet for the other groups, it was retained in the subscale for the Poor Vision facet of the SSI.

The Sore Eyes component had a high loading of the frequency of "burning eyes" in primary SS only. In SLE, this item loaded strongly (78%) on the Eye Irritation factor instead. Loadings were modest for either factor in patients with RA and controls. Nevertheless, since primary SS is the condition characterized by tear gland degeneration, the item was retained in the Sore Eyes facet of the SSI.

*Facets of oral sicca*. The frequency scores for single symptoms of Oral Sicca were structured into 5 components in factor analysis in each of the 4 groups, namely, Difficult Eating, Dry Throat, Bad Breath, Wetting Mouth, and Oral Problems (listed in Table 2), with variances accounted for ranging from 57% to 3%.

Controls, however, provided a less robust structure than the primary SS group for the whole Oral Sicca domain in the SSI. The Difficult Eating facet was less clearly structured in

*Table 1*. Construct validation of domains of local discomfort from factor-analytic loadings × 100 of symptom severity and frequency scores. Question items for grouped symptoms rated for severity have initial capitals; single symptoms rated for frequency have lower-case initial letters. The percentage loading of each item is given for the rotated factor analysis of each group, with the variance accounted for by each factor given below.

| Domain Name | Symptom | Primary SS | SLE | RA | Controls |
|---|---|---|---|---|---|
| Ocular Sicca | Sore Eyes | 89 | 77 | 85 | 71 |
| | Eye Irritation | 86 | 91 | 83 | 42 |
| | Poor Vision | 48 | 61 | 83 | 92 |
| Variance, % | | 6.7 | 8.1 | 26.8 | 7.3 |
| Oral Sicca | Difficult Eating | 85 | 79 | 39 | 89 |
| | Dry Throat; Bad Breath | 75 | 8 | 40 | 63 |
| | Wetting Mouth | 77 | 87 | 86 | 17 |
| | Oral Problems | 72 | 60 | 91 | 53 |
| Variance, % | | 8.3 | 6.5 | 6.0 | 13.1 |
| Vaginal Dryness | painful sex | 91 | 92 | 87 | 96 |
| Variance, % | | 4.5 | 3.2 | 3.2 | 4.8 |
| Skin Dryness | dry skin | 88 | 92 | 89 | 88 |
| | itchy skin | 88 | 78 | 86 | 91 |
| Variance, % | | 14.0 | 16.1 | 50.5 | 13.2 |
| Cold Hands | uncomfortably cold hands | 95 | 92 | 94 | 96 |
| Variance, % | | 9.4 | 6.2 | 7.8 | 8.8 |
| Painful Limbs | discomfort in big joints | 87 | 91 | 80 | 83 |
| | discomfort in muscles | 85 | 92 | 87 | 87 |
| Variance, % | | 53.9 | 58.8 | 8.7 | 47.1 |
| Painful Hands | discomfort in fingers | 73 | 58 | 86 | 91 |
| | swollen wrists/fingers | 93 | 93 | 90 | 85 |
| Variance, % | | 11.4 | 6.5 | 23.3 | 20.0 |

*Table 2*. Sensitivity to disease groups and specificity to controls of grouped-symptom severity scores and single-symptom frequencies of localized discomfort above cut off score and clinical signs of ocular and oral sicca.

| Grouped Symptom | Single Symptom | Sensitivity Primary SS | SLE | RA | Specificity Controls |
|---|---|---|---|---|---|
| Sore Eyes | | 96 | 57 | 41 | 74 |
| (Ocular facet 1) | gritty eyes | 81 | 36 | 40 | 82 |
| | eyes sore, painful | 85 | 40 | 40 | 81 |
| | itchy eyes | 76 | 40 | 43 | 76 |
| | irritation in eyes | 80 | 36 | 37 | 78 |
| | burning eyes | 64 | 21 | 24 | 91 |
| Eye Irritation | | 90 | 62 | 53 | 65 |
| (Ocular facet 2) | eyes uncomfortable in wind | 80 | 34 | 47 | 75 |
| | ... with air-conditioning | 80 | 40 | 25 | 82 |
| | ... in low-humidity places | 86 | 33 | 29 | 87 |
| | * irritated by smoky atmosphere | 82 | 30 | 37 | 90 |
| | [sensitivity to light] | 76 | 57 | 37 | 78 |
| | [dazzled by sunlight] | 76 | 62 | 55 | 65 |
| Poor Vision | | 85 | 45 | 42 | 69 |
| (Ocular facet 3) | blurred vision | 63 | 34 | 30 | 81 |
| | limited reading | 69 | 36 | 39 | 78 |
| | limited driving at night | 49 | 21 | 11 | 88 |
| | hard to see computer screen | 48 | 30 | 25 | 92 |
| | hard to watch TV | 63 | 32 | 29 | 91 |
| | poor vision | 63 | 31 | 27 | 79 |
| Difficult Eating | | 96 | 38 | 28 | 91 |
| (Oral facet 1) | mouth felt dry when eating | 92 | 38 | 23 | 97 |
| | difficulty eating certain foods | 88 | 34 | 22 | 97 |
| | difficult swallowing dry food | 91 | 30 | 23 | 88 |
| | liquid helps to swallow | 95 | 43 | 27 | 87 |
| | food stuck in mouth | 92 | 34 | 23 | 94 |
| | need to rinse away food | 92 | 32 | 25 | 92 |
| | appreciated food less | 69 | 24 | 22 | 96 |
| Dry Throat/Bad Breath† | | 93 | 58 | 38 | 81 |
| (Oral facets 2/3) | mouth felt dry when breathing | 90 | 51 | 35 | 82 |
| | difficulty talking | 85 | 40 | 22 | 88 |
| | had to drink to speak easily | 78 | 34 | 16 | 92 |
| | nose felt dry | 86 | 53 | 41 | 83 |
| | throat/windpipe dry | 91 | 51 | 41 | 84 |
| | air-conditioning dries mouth | 82 | 45 | 29 | 85 |
| | [dry cough] | 64 | 41 | 37 | 84 |
| | saliva felt sticky† | 76 | 28 | 18 | 92 |
| | breath smelt† | 70 | 43 | 31 | 78 |
| Wetting Mouth | | 96 | 53 | 71 | 68 |
| (Oral facet 4) | [carried fluid during the day] | 73 | 26 | 28 | 86 |
| | * carried drink to bed | 81 | 40 | 36 | 70 |
| | * needed drink during the night | 77 | 38 | 34 | 79 |
| | * woke at night to pass urine | 82 | 58 | 68 | 74 |
| | * urgent need to pass urine | 86 | 42 | 50 | 66 |
| Oral Problems | | 92 | 43 | 38 | 81 |
| (Oral facet 5) | ulcers in the mouth | 50 | 34 | 35 | 90 |
| | swollen salivary glands | 43 | 17 | 14 | 99 |
| | felt as though choking | 69 | 28 | 25 | 95 |
| | change in flavors or taste | 63 | 24 | 20 | 90 |
| | visited the dentist | 47 | 23 | 20 | 90 |
| Vaginal Dryness | painful sex | 76 | 35 | 33 | 79 |
| Skin Dryness | dry skin | 78 | 61 | 56 | 75 |
| | itchy skin | 77 | 57 | 52 | 79 |
| Systemic Discomfort / Arthralgia | | 94 | 90 | 98 | 28 |
| | cold hands | 76 | 62 | 42 | 80 |
| | * Discomfort in big joints | 64 | 51 | 82 | 75 |
| | * Discomfort in muscles | 63 | 45 | 66 | 83 |
| | Discomfort in fingers, wrist ache | 79 | 64 | 92 | 96 |
| | Swollen fingers, wrists | 56 | 51 | 88 | 79 |
| Ocular Clinical Test | Schirmer test (0 < average ≤ 5.0 mm) | 75 | 14 | 19 | 79 |
| Oral Clinical Test | USF (> 0 ≤ 1.5 ml) | 86 | 71 | 12 | 83 |

* Caseness cutoff at a frequency score of 1 or zero, where 4 means all the time; the cutoff score for the other items was zero frequency. Single-symptom items in brackets [ ] were excluded from the final inventory to measure sicca symptoms in primary SS. † Bad Breath facet and question items. USF: unstimulated salivary flow rate.

controls than in any of the 3 disease groups: several items had very low loadings on the component corresponding to this facet. This may indicate that xerostomia from causes other than rheumatic disorders has a quite different symptom profile.

In primary SS, the item "appreciated food less" loaded weakly on Difficult Eating (percentage loading 47), unlike in SLE (80) and RA (64). This may indicate that the effects of saliva deficits in primary SS on the enjoyment of eating are separated in the minds of these patients from other factors, whereas dryness is a major contributor to unpalatability without this exocrine pathology.

The items "dry cough" and "carried fluid during the day" were dropped from the Dry Throat domain of the SSI because they did not load at all on their respective components in primary SS (11% and –9%, respectively), and their loadings varied from modest to very low in groups not expected to suffer from chronic dryness of the mouth. Further, symptoms of respiratory infection could confound such a symptom cluster of Oral Sicca.

The question items in the facet composed of other Oral Problems (listed in Table 2) formed a rather fragile component in the factor analyses, possibly because these problems are insufficiently frequent to be represented reliably by the 2 week period prior to questioning. In support of this hypothesis, each item other than "swollen salivary glands" had a very high loading on this component in one of the groups other than primary SS (80–91%).

*Sensitivity of above-zero symptoms of discomfort and signs of ocular or oral sicca.* Both the 3 grouped symptoms and nearly all the single symptoms in the facets of the Ocular Sicca domain showed greater sensitivity for primary SS than did the clinical sign of tear production assessed by Schirmer test (Table 2). As expected, the sensitivity percentages for SLE and RA were poor. Specificity of the single symptoms of xerophthalmia for healthy controls was often better than the Schirmer test at the cutoff of 5 mm, but the grouped symptoms were not as specific as the sign.

In Oral Sicca as well, the grouped-symptom severity scores had a higher sensitivity for primary SS than an unstimulated salivary flow (USF) rate of 1.5 ml or less (Table 2). USF had a relatively high sensitivity for SLE also, but was very insensitive to RA. The sensitivity percentages of the symptoms for SLE and RA were poor (all < 60 except 71 for Wetting Mouth in RA).

*Sensitivity and specificity of other sicca and other discomfort.* In all groups, the question item "painful sex" that (for these female patients) makes up the Vaginal Dryness facet and domain was structured by factor analysis as a separate component from the Oral and Ocular Sicca domains and from the symptoms of skin dryness and "cold hands" (Table 1). The vaginal symptom was moderately sensitive and specific for primary SS (Table 2).

The severity scores in response to the single question that grouped symptoms of Systemic Discomfort and Arthralgia had high sensitivity for primary SS, SLE, and RA, but no specificity to health (Table 2). The frequency scores for the 7 single symptoms in the domains of Skin Dryness, Cold Hands, Painful Limbs, and Painful Hands (Table 1) had moderate specificity in excluding health and varied in sensitivity among the diseases (Table 2). The symptoms of "dry skin," "itchy skin," and "cold hands" were unexpectedly more specific to primary SS than to SLE, although least specific to RA. The symptoms of "discomfort in big joints," "discomfort in finger and/or ache in wrist," and "swollen fingers and/or wrists" had high sensitivity for RA (Table 2). The frequency of the symptom "discomfort in muscles" had no sensitivity for the 3 disease groups, although it was specific at excluding healthy controls.

*Correlation of symptom scores with measures of secretion.* In agreement with previous studies[9], the correlations between symptom scores and clinical signs (Schirmer test and USF rates) for groups of patients with sicca symptoms were poor (Table 3). In the Ocular Sicca domain, only Eye Irritation in sicca patients and Poor Vision in RA showed the expected negative correlation with Schirmer test findings with an absolute value above r = 0.3 (Table 3), but these values did not approach significance. In contrast, for symptoms in the Oral Sicca domain, a majority of negative correlations with USF exceeded 0.3 (Table 3). In primary SS, the correlations of USF values with severity scores of grouped symptoms of Difficult Eating and Oral Problems were highly significant ($p < 0.001$), while Dry Throat/Bad Breath had $p < 0.01$ and Wetting Mouth $p < 0.10$. In the smaller groups, correlation of USF with Difficult Eating and Wetting Mouth in SLE with secondary SS were the only instances to reach significance ($p < 0.05$).

Of note, in primary SS, severity scores for the grouped symptom Difficult Eating were weakly associated with USF ($p < 0.07$) when values above zero were split at the standard clinical cutoff rate of 1.5 ml, but the correlation became significant ($p < 0.03$) when split at 1.0 ml and highly so at 0.9 ml ($p < 0.001$).

*Repeatability of measurements of Local Discomfort.* The evidence from the differences between the initial administration of the research inventory and a retest 24 hours later was that the scores are generally high in precision. First, the grand mean (SD) of the mean differences in frequency scores for single symptoms across all 5 groups was virtually zero (0.1). Second, no 24 hour difference in scores for any item reached statistical significance to an alpha criterion of 0.05, allowing for the large number of comparisons made. Third, the differences in severity scores of grouped symptoms from initial test to 24 hour retest included both increases and decreases in each of the 4 groups; there was no significant difference across all groups between the number of increases and the number of decreases (chi-square = 0.77, p = 0.38).

*Table 3*. Percentage rank correlations (r × 100) between grouped-symptom ratings and clinical signs for disease groups.

| Clinical Sign | Grouped Symptom | Primary SS, N = 88–103 | SLE 2SS, N = 12–16 | RA 2SS, N = 10–12 | Sicca, N = 11–13 |
|---|---|---|---|---|---|
| Schirmer test averaged | Score Eyes | –11 | +3 | –6 | –23 |
| | Eye Irritation | –15 | –11 | +12 | –31 |
| | Poor Vision | –16 | –6 | –37 | –21 |
| USF | Difficult Eating | **–40** | **–64** | –21 | –24 |
| | Dry Throat/Bad Breath | **–25** | –42 | –42 | –20 |
| | Wetting Mouth | –17 | **–72** | +20 | –48 |
| | Oral Problems | **–33** | –38 | –6 | –2 |

Values in bold type: $p \leq 0.05$. SLE 2SS, RA 2SS: Secondary SS in SLE and RA. Patients who gave severity ratings of zero were excluded from the analyses. USF: unstimulated salivary flow rate.

In addition, the structuring of severity scores of the grouped symptoms as the domains of Ocular and Oral Sicca, Vaginal Dryness, and Systemic Discomfort/Arthralgia in the initial test was replicated in factor analysis of the data from retest after 24 hours. The weakly loaded items from the initial ratings had low loadings again on their respective factors from the 24 hour retest ratings, a replicated contrast that further confirms the construct validity of the SSI's domains.

*Profiles of severity.* On average, the group of patients with primary SS rated each of the 8 groupings of sicca symptoms (Table 1) as twice as or more severe than did the groups with SLE and RA (Figure 1). The 4 facets of Oral Sicca and Sore Eyes separated primary SS from SLE and RA by at least two 95% confidence intervals. The validity of the construct of Sicca Symptoms in primary SS was confirmed by the contrast with the symptoms of arthralgia and systemic discomfort in RA: the RA group rated the severity of this grouping of symptoms highest, without an overlap of 95% confidence intervals with primary SS (Figure 1). It is of interest that both SLE and RA consistently scored higher than healthy controls on all facets of sicca, with overlap of 95% confidence intervals only for Vaginal Dryness, Oral Problems, and Poor Vision, even though secondary SS was excluded from these SLE and RA groups. Therefore the short form of this instrument, consisting of these grouped symptoms of dryness, appears to be sensitive enough to pick up undiagnosed infiltration of lacrimal and salivary glands.

Only small numbers of patients with secondary SS or with "sicca syndrome" were studied (RA with secondary SS, returned questionnaires n = 14; SLE with secondary SS, n = 16; sicca syndrome, n = 16). Nevertheless, for all facets of

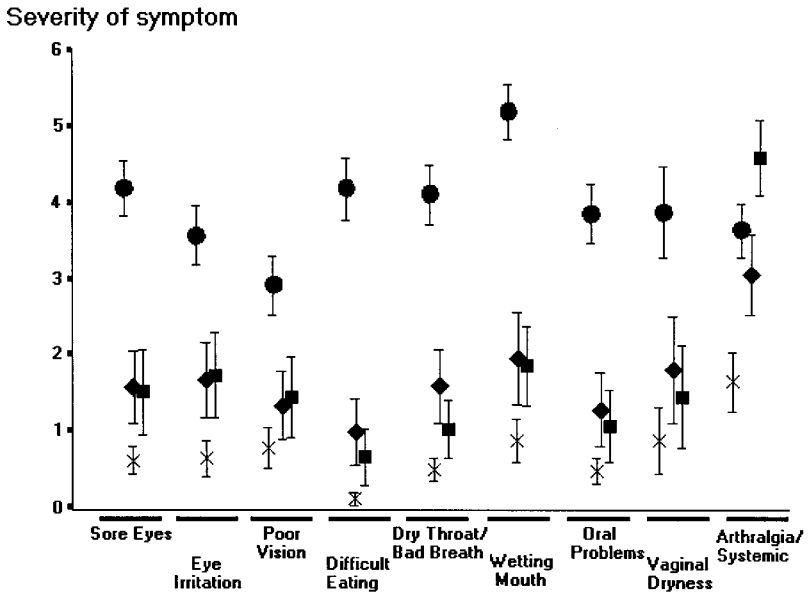


*Figure 1*. Mean and 95% CI for ratings of discomfort at their worst over the last 2 weeks (7 = worst discomfort imaginable) for groups diagnosed with primary SS, SLE, and RA and healthy controls. ●: primary SS (N = 78–112); ◆: SLE (N = 48–53); ■: RA (N = 39–50); ×: controls (N = 58–77).

sicca, the average severity scores were similar among these groups and patients with primary SS (data not shown), suggesting that any differences between these conditions derived from studying larger groups are likely to be modest.

## DISCUSSION

Dryness of the eyes and mouth is the predominant complaint of patients with SS and can vary substantially in severity and the extent of consequent disability[18]. Assessment of the severity and/or frequency of sicca symptoms at any one time is therefore critical to the evaluation of patients with SS and to measurements of their response to therapy. To date there is no consensus on symptom assessment for this purpose. There are many ad-hoc question wordings and response layouts devised by local expert consensus for specific clinical trials or longitudinal studies[4,16,17]. The ocular surface disease severity index (OSDI)[10] was recently constructed to assess symptoms in patients with idiopathic (nonimmune) xerophthalmia, but this has not been tested in SS and does not cover oral symptoms. A xerostomia inventory (XI) has also been constructed and tested in older individuals with xerostomia[11], but not in those with SS, and does not cover different facets of ocular sicca (although it does contain a single summative item, "My eyes feel dry"). Establishing a "gold standard" measure of ocular and oral sicca in SS would strengthen the methodology of future longitudinal studies and clinical trials and enable their findings to be compared in a similar manner to that current in RA[19].

The results reported here are for sicca symptoms that are moderately prevalent in primary SS. Frequency scores for the individual symptoms formed principal components in factor analysis that closely matched the facets of symptoms to which the items appeared to contribute. Rated severity scores of symptoms grouped in accord with each of these major facets of sicca further factored into distinct domains of ocular, oral, vaginal, and cutaneous symptomatology. Both the severity scores of grouped symptoms and the frequencies of single symptoms of sicca discriminated the patients with primary SS from healthy controls and also secondary SS in those with RA and SLE. Scores on these facets and items were precise and repeatable over a 24 hour period. They related at least as well to tear production and unstimulated salivation as other reported symptom assessments[9]. The facets of dryness of the eyes confirmed by factor analysis were similar to the 3 subscales of the recently published OSDI, distinguishing among visual difficulty, soreness of the eyes arising with provocation, and irritation by atmospheres or bright light. The XI[11] consists of 11 items scored in a single scale rather than the subscaled-facets structure of the SSI and the OSDI, hence a similar comparison against facets of the Oral Sicca domain of the SSI cannot be made. Six of the 11 items of the XI, however, correspond roughly to individual items of the SSI, predominantly within the Difficult Eating facet.

Patients with primary SS were clearly discriminated from healthy controls by each facet of the domains of oral and ocular sicca, other dryness, and other local discomfort, such as arthralgia and cool hands (Raynaud's), and also by the facets of the bodily fatigue domain in our first study (Booth DA, unpublished data). Scores on this Profile of Fatigue and Discomfort also differed between patients with primary SS and other diseases, especially for the components of sicca. Hence these components have been separated into an instrument for the sicca symptoms alone.

The 42 single symptoms of ocular, oral, vaginal, and cutaneous dryness (Table 2) constitute the long form of a Sicca Symptoms Inventory, scored in 4 domains of Ocular Sicca (with 3 facets: Sore Eyes, Eye Irritation, and Poor Vision), Oral Sicca (5 facets: Difficult Eating, Dry Throat, Bad Breath, Wetting Mouth, and Oral Problems), Vaginal Dryness (a one-question facet and domain), and Skin Dryness (one facet and domain with 2 items) (Table 1). The cross-validated short form of the SSI consists of 10 grouped symptoms of dryness (each equating to a facet in the long form), scored in 10 facets in 4 domains.

Both forms of the SSI use ratings of severity over the previous 2 weeks. The frequency ratings used in this study for single symptoms gave the same symptomatological structure as the severity ratings used on grouped symptoms. Severity judgments are likely to encompass both frequency and intensity and it is more convenient to raters and investigators to use a single format for responses.

Thus the self-assessment profiles described in this report and one other (Booth DA, unpublished data) are construct-valid measures of the most important symptoms associated with SS. Current work is testing whether these measures can detect changes in symptom severity over time, in which case the SSI and the full Profile of Fatigue and Discomfort will be useful for measuring outcome in clinical therapeutic trials and other longitudinal studies of primary SS. We recommend use of the long form instrument when the most precise measurements are needed. However, when only quick profiling is required or there is concern about possible "questionnaire fatigue," then the short form should be satisfactory.

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## APPENDIX

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