Prevalence, Risk, and Risk Factors for Oral and Ocular Dryness with Particular Emphasis on Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine, primarily in rheumatoid arthritis (RA), the prevalence, relative risk, and risk factors for oral and ocular dryness.

Methods. We studied self-reported persistent ocular and oral dryness (PD) present in 2 consecutive observations, and sporadic dryness (SD) present in 1 of 2 consecutive observations, during semiannual assessments in 9921 patients with RA and in 2851 with a noninflammatory rheumatic disorder (NIRD) (not fibromyalgia; FM). We also evaluated prevalence in 2867 patients with FM.

Results. In RA, PD was noted in 11.6% and SD in 17.5%. Compared with NIRD, the age and sex adjusted relative risk (RR) for PD was 1.34 (95% CI 1.17–1.51) and the severity and treatment adjusted RR was 1.46 (95% CI 1.26–1.6). The adjusted RR for FM compared with RA and NIRD was 2.02 (95% CI 1.85–2.20). Dryness prevalence increased 10% to 13% every 10 years, and was associated with therapy. The treatment attributable risk was 27.5%. Fatigue and body pain (Symptom Intensity Scale) was more strongly associated with dryness than was any other clinical scale, including Health Assessment Questionnaire, pain, and Medical Outcomes Study Short Form-36 Health Survey. SD was associated with a covariate adjusted decrease in quality of life of 0.020 (95% CI 0.012–0.029) utility units.

Conclusion. Dryness is increased in RA and is contributed to by severity and therapy. The combination of body pain and fatigue is the strongest clinical correlate of dryness, and is independent of diagnosis of FM. Any factor that increases illness severity or distress results in an increase in dryness. (First Release May 15 2008; J Rheumatol 2008;35:1023–30)

Key Indexing Terms:
DRYNESS RHEUMATOID ARTHRITIS RISK FACTORS
NONINFLAMMATORY RHEUMATIC DISORDERS FIBROMYALGIA

Dryness symptoms, or sicca symptoms, are common. When symptoms reach a certain level of severity and/or when objective ocular involvement is found, the dry eye syndrome (DES) may be diagnosed. When severe oral and ocular symptoms are combined with ocular signs and salivary gland involvement, and often with focal lymphocytic sialoadenitis, Sjögren's syndrome (SS) may be diagnosed[1]. In the presence of another well-defined connective tissue disease, SS is termed secondary SS. SS "...refers to keratoconjunctivitis sicca and xerostomia resulting from immune lymphocytes that infiltrate the lacrimal and salivary glands"[2,3]. Patients with dry eyes and mouth without evidence of SS or another connective tissue disorder have been designated as having dry eye and mouth syndrome (DEMS)[4] and sicca asthenia polyalgia syndrome (SAPS)[5].

Sicca symptoms are common in patients in the general population[6-10]. In a population-based survey, 45% of 2240 persons over the age of 65 years had dry eye symptoms "at least rarely or sometimes"[7]. Of those who had symptoms "often or always," 2.2% had a low Schirmer test result "(≤ 5 mm)." These authors concluded that "although symptoms of ocular irritation are common among the elderly... there is minimal overlap between individuals identified by questionnaire, Schirmer tests, and rose bengal scoring"[11]. A similar lack of objective findings was noted in 341 subjects in a UK general practice, where 24% had dry eye symptoms, 29% dry mouth symptom, and 14% both[8]. These authors also found no association with autoantibodies. In another population based study of 3722 subjects, dry eyes for 3 months or longer was noted in 14.4%. In this group, an increased association with dry eyes was noted for "arthritis." In an Australian population-based study DES was diagnosed as follows: 10.8% by rose bengal, 16.3% by Schirmer's test, 8.6% by tear film breakup time, 1.5% by fluorescein staining, 7.4% with 2 or more signs, and 5.5% with any severe symptom not attributed to hay fever[10]; and "arthritis" was

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associated with dry eye diagnosis. In the Women's Health Study DES was diagnosed in 6.7%[12], and in the Physician's Health Study the percentage was around 3.5%[6]. In summary, dry eye symptoms occur in up to 45% of subjects, depending on the definition, but dry eye syndrome (severe dry eyes) is diagnosed in 2.2%% to 16.3%, depending on the method of diagnosis.

Most persons with dryness symptoms do not satisfy criteria for SS. Uhlig, *et al* found a minimum of 7% of 636 patients with rheumatoid arthritis (RA) satisfied SS criteria, while 20.3% reported daily dry eye, 32.6% daily dry mouth, and 27.3% reported at least 1 symptom from eyes or mouth[13]. A population study from the UK identified a SS prevalence of 3.3% (95% CI 2.2%–4.4%)[14]. Other studies have produced prevalence estimates for SS that ranged between 0.3% and 4.8%[15]. Whatever the actual prevalence of SS is, sicca symptoms are much more common.

Dry eye, which has been studied most, is related to defects in lacrimal film and ocular surface epithelium, and can be caused by one or more age-related, hormonal, pharmacologic, immunopathic, nutritional, genetic, infectious, inflammatory, traumatic, and neurological factors[16].

With respect to RA, it is widely believed that SS is more prevalent in patients with RA than in the general population and, clinically, dryness symptoms in RA are most often attributed to RA. However, dryness is associated with many common medical therapies as well as with aging. In addition, parasympathetic effects on dryness in RA and other conditions have been demonstrated[17-19]. The only large study to examine the issue of dryness in RA did not find it increased compared with the general population[20]. However, this finding may be related to insufficient sample size (71 patients with RA in a sample of 2481 subjects), as the odds ratio (OR) was suggestive of an association, OR 1.8 (0.9 to 3.4). The issue as to whether dryness is increased in RA remains unresolved.

Finally, there is the intriguing association between sicca symptoms and persons diagnosed as having fibromyalgia (FM)[21-24]. The cause of this association remains obscure. We investigated whether dryness symptoms were more common among persons with RA, and we investigated correlates and predictors of dryness and determined decrease in quality of life attributable to dryness symptoms.

MATERIALS AND METHODS

Patient population. We studied participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. NDB participants are recruited from the practices of US rheumatologists, and are followed prospectively with semiannual, detailed, 28-page questionnaires, as described[25,26].

This report examined data from 12,772 adult participants, of whom 9921 had RA and 2851 had a noninflammatory rheumatic disorder (NIRD) that was not FM. The 9921 patients with RA did not include patients with RA in the NDB who were members of safety registries (n = 4763). Safety registry patients are those enrolled at the time they started a specific therapy (e.g., infliximab). Such patients were excluded to insure absence of severity bias and unmeasurable confounding. All patients in the study were enrolled continuously beginning in 1999 and completed at least 2 consecutive semiannual questionnaires between January 1999 and July 2007. Diagnoses were made by the patients' rheumatologists. NIRD included diagnoses such as osteoarthritis, back pain syndromes, tendonitis, etc. In addition, for comparison purposes with respect to prevalence, we also analyzed limited data from 2867 additional patients who had been diagnosed as having FM. Approximately 37% of patients with FM were self-referred but were diagnosed by physicians.

Two sets of observations were used for analyses. For the major analyses we selected a random observation from each patient who completed at least 2 consecutive questionnaires. For specific analyses of the effect of estrogen on dryness symptoms we used all observations in a Cox regression analysis.

Study variables

Outcome variables. In our surveys, we inquired of patients if they had dry eyes and dry mouth in the last 6 months. If both dry eyes and dry mouth were present, we labeled this state as "combined" dryness. Patients who were positive for dryness states at the randomly selected observation but not at the next consecutive observation had these states designated as "sporadic" and when present at both observations had them designated as "persistent." We also asked patients, "Were you ever told by a physician that you had an eye problem caused by rheumatoid arthritis (RA)..." and whether that problem was dry eyes.

Covariates. At each assessment we recorded demographic variables including age, sex, ethnic origin, marital status, smoking status, household income, and all treatments. Patients reported functional status using the Health Assessment Questionnaire (HAQ)[27,28] and the original Medical Outcomes Study (MOS) Short Form-36 (SF-36) function scale[29]. We also determined pain, global disease severity, and fatigue by visual analog scale (VAS)[30]. The HAQ and VAS for pain intensity and global severity were used to calculate the Patient Activity Scale (PAS)[31]. The PAS is a 0–10 measure of RA disease activity in which higher values indicate greater RA disease activity. It is computed by multiplying the HAQ by 3.33 and then dividing the sum of the VAS pain, VAS global, and HAQ by 3. The PAS is an effective measure of RA activity[32].

The Regional Pain Scale (RPS) is a self-report count of nonarticular regions[33,34]. The Symptom Intensity (SI) scale is derived from 2 separate scales, a VAS for fatigue[35] and the Regional Pain Scale (RPS)[34]. The SI scale uses these 2 measures in continuous form according to the following formula: [VAS fatigue + (RPS/2)]/2. This yields a scale with a 0 to 9.75 range.

The mood scale used in our report represents the normalized Arthritis Impact Measurement Scales (AIMS) anxiety and depression scales if available[36]; otherwise, it represents the SF-36 mental health subscale[29]. Both scales are transformed to a 0-10 scale, with higher values representing greater mood abnormality. To assess quality of life (QOL) by utilities, we administered the EuroQol[37-40], utilizing US tariffs[41], the SF-6D[42], and a transformed VAS[43]. The EuroQol contains 5 questions, 3 of which are about function, 1 about pain, and 1 about psychological status.

Patients reported all medications used within the previous 6 months. Depending on treatment, drugs were classified into the following categories: nonsteroidal antiinflammatory drugs (NSAID), disease modifying antirheumatic drugs (DMARD), biologic agents, prednisone, analgesics, non-serotonin reuptake inhibitors, serotonin reuptake inhibitors, antianxiety medications, sleep medications, H2 antagonists and proton pump inhibitors, diuretics, antihypertensives, other cardiovascular medications, and antiinfectives. For analyses of estrogen effect we used both current and lagged (previous 6 mo) drug use as predictor variables.

Statistical methods. Data analysis included logistic regression in univariable and multivariable analyses as described in the Results section. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated following logistic regression using the method of conditional standardization[44].

Assuming a causal relationship between treatment and dryness, we used logistic regression to determine attributable risk[45].

The associations between combined dryness and RA symptom scales were measured by Kendall's Tau-a. Kendall's tau is related mathematically to the area under the receiver-operating characteristic curve (ROC). Roughly, tau-a allows us to understand the degree to which variables such as combined dryness are simultaneously associated with variables such as HAQ, PAS, and the SI scale. Kendall's tau has a simple interpretation, the percentage concordance between variables. For example, a value of 0.106 (Table 3) indicates that it is 10.6% more likely that a person with a high SI scale score will report dryness than a patient with a low SI scale score will report combined dryness.

Figure 1 represents a running line smooth of the probability of combined dryness as a function of age. The plots of Figure 2, left, were generated by 4 running line smooths of the probability of combined dryness as a function of symptom intensity, fatigue, pain, and sleep, while simultaneously adjusting for age, sex, comorbidity, HAQ, and treatment[46]. Using a simple type of backfitting, the resulting smoother is a locally linear function of the predictors for each observation.

Data were analyzed using Stata (College Station, TX, USA) version 10.0. Statistical significance was set at the 0.05 level, CI were established at 95%, and all tests were 2-tailed.

RESULTS

Prevalence and relative risk. There were 9921 participants with RA. Their mean age was 61.8 (SD 13.3) years, 24.5% were men, and 28.0% had completed college. For the 2851 patients in the NIRD group, the mean age was 67.9 (SD 11.4) years, 20.4% were men, and 30.8% had completed college.

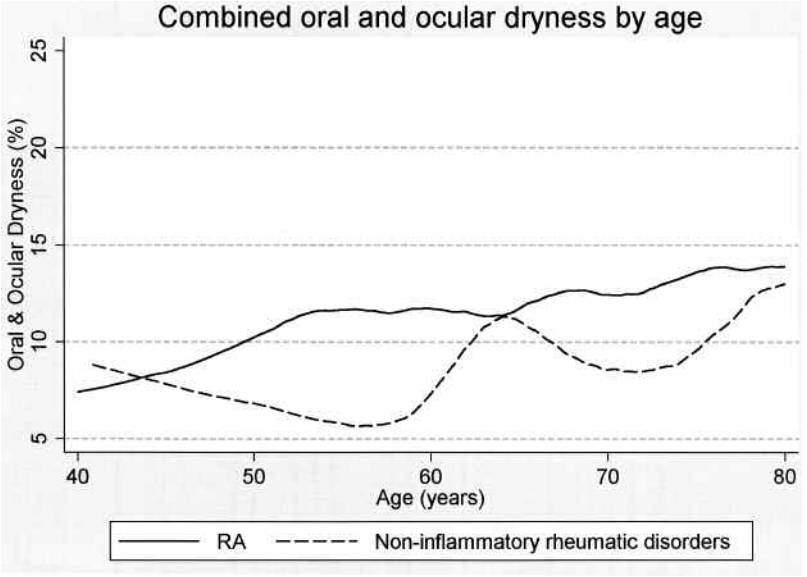

Figure 1. Oral and ocular dryness by age for RA and noninflammatory disorders.

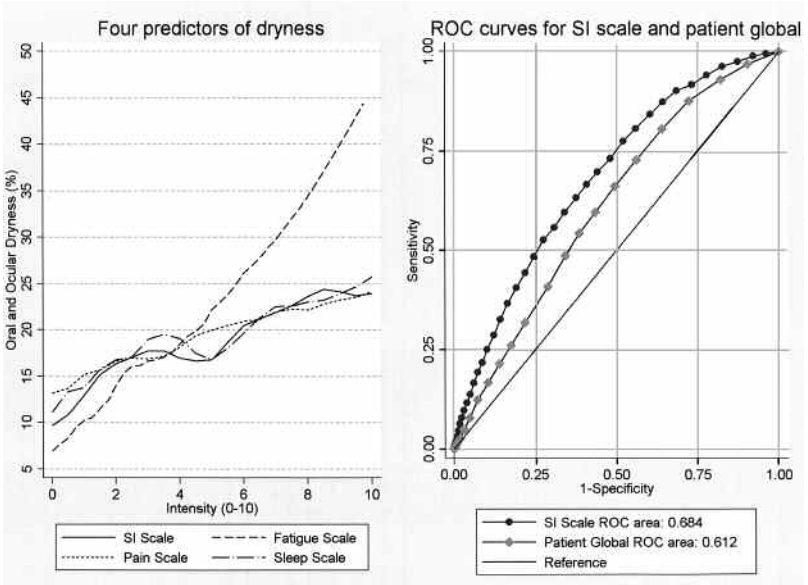

Figure 2. Left panel. Predicted percentage of RA patients with oral and ocular dryness by 4 clinical scales, adjusted for age, sex, comorbidity, and HAQ, and for treatments in Table 2. Right panel. Area under receiver-operating curves for SI scale and patient-global.

Table 1 shows that persistent and sporadic symptoms were more common among persons with RA than those with NIRD, with RR between 1.34 (95% CI 1.17–1.51) and 1.23 (95% CI 1.11–1.35) for persistent and sporadic combined oral and ocular dryness, respectively. Persistent dry eye and dry mouth occurred in 11.6% of subjects with RA and sporadic dry eye and dry mouth occurred in 17.5%. Persistent dry eye in RA occurred in 25.2% and sporadic dry eye in RA occurred in 33.8%. Of those RA patients with persistent and sporadic dry eye, 62.2% and 57.9% reported that their physicians told them their symptoms were due to RA.

For comparison purposes and general interest, we also determined the proportion of the 2867 patients diagnosed as having FM who satisfied the above definitions. Persistent dry eye and dry mouth occurred in FM in 23.7% and sporadic dry eye and dry mouth occurred in 33.3%. Persistent dry eye in FM occurred in 37.2% and sporadic dry eye occurred in 48.0%. Persistent dry mouth in FM occurred in 41.2% and sporadic dry mouth occurred in 53.2%. Compared with RA and NIRD subjects, the RR for these symptom groups in patients with FM was as follows: persistent combined dryness 2.02 (95% CI 1.85–2.20), persistent dry eyes 1.46 (95% CI 1.38–1.55), persistent dry mouth 2.00 (95% CI 1.89–2.12), sporadic combined dryness 1.91 (95% CI 1.78–2.04), sporadic dry eye 1.42 (95% CI 1.35–1.49), and sporadic dry mouth 1.79 (95% CI 1.70–1.87). Patients with FM diagnosed by rheumatologists did not differ as to the proportion with persistent or sporadic dryness ($p > 0.05$) compared with self-referred patients with FM. We did not perform any other analyses that included subjects with FM.

Association with age in RA. Combined sporadic oral and ocular dryness increased by about 10% to 13% every 10 years (Figure 1 and Table 2), and was less common in men, with unadjusted OR 0.50 (96% CI 0.44–0.58) and multivariable adjusted OR 0.57 (95% CI 0.49–0.66) (Table 2).

Correlates of dryness in RA. Table 2 displays the RA age and sex adjusted and the multivariable correlates of sporadic oral and ocular dryness. With the exception of NSAID and DMARD, all variables in the age and sex adjusted analyses are significantly associated with dryness. The largest OR for treatment variables can be seen for analgesics, antidepressants, anxiolytics, sleep medications, and anti-ulcer treatments. In the multivariable analyses, OR are reduced, as expected. However, the above treatments remain statistically significant. Assuming dryness is related to treatment, the attributable risk of treatment is 27.5% (95% CI 22.5%–32.1%). Comorbidity remains a significant predictor in the multivariable model (Table 2) as does HAQ functional score. However, prednisone and biologic therapy are no longer significant.

Not included in Table 2 is the use of estrogen compounds; we did not include them because they are used only by women. However, in analyses restricted to women, we found the age and sex adjusted risk of persistent and sporadic combined dryness and persistent and sporadic dry eye in those taking estrogen compared with nonusers to be as follows: sporadic dry eyes OR 1.25 (95% CI 1.12–1.38), persistent dry eyes OR 1.29 (95% CI 1.15–1.44), sporadic combined dryness OR 1.27 (95% CI 1.12–1.43), and persistent combined dryness OR 1.32 (95% CI 1.15–1.52). Unlike analgesics, antidepressants, anxiolytics, sleep medications, and anti-ulcer treatments, which are known to cause dryness as adverse effects, estrogen might be prescribed to treat dryness and the resulting association might be confounded. Therefore we performed additional analyses in women not reporting any dryness at their baseline observation using Cox regression and used lagged estrogen use as the predictor variable. To maximize the sample size we combined RA and NIRD in the analyses. This resulted in analysis of 5286 patients. However, the results were not different when patients with RA were studied alone. Use of estrogen in the 6-month period prior to assessment of dryness was not associated with subsequent sporadic dry eyes (OR 1.05, 95% CI 1.00–1.01, p = 0.267) or sporadic combined dryness (OR 1.01, 95% CI 1.00–1.01, p = 0.267). The results were sim-

Table 1. Persistent and sporadic dry eye and mouth symptoms in rheumatoid arthritis (RA) and noninflammatory rheumatic disorders (NIRD).

	RA (n = 9921)		NIRD (n = 2851)		
	Crude %	Adjusted %* (95% CI)	Crude %	Adjusted %* (95% CI)	Adjusted Relative Risk* (95% CI)
Persistent					
Dry eye and mouth	11.6	11.2 (10.5–11.8)	9.7	8.3 (7.4–9.4)	1.34 (1.17–1.51)
Dry eye	25.2	25.1 (24.2–26.0)	23.0	20.8 (19.3–22.4)	1.20 (1.11–1.30)
Dry mouth	21.0	21.0 (20.1–21.8)	20.3	18.3 (17.0–19.8)	1.14 (1.04–1.24)
Sporadic					
Dry eye and mouth	17.5	17.3 (16.6–18.1)	15.8	14.1 (12.9–15.4)	1.23 (1.11–1.35)
Dry eye	33.6	33.8 (32.8–34.7)	32.0	29.8 (28.1–31.5)	1.13 (1.06–1.21)
Dry mouth	30.2	30.4 (29.5–31.4)	30.3	28.1 (26.4–29.8)	1.08 (1.01–1.16)

* Adjusted for age and sex. Persistent: present in 2 of 2 consecutive observations; sporadic: present in at least 1 of 2 consecutive observations.

Table 2. Associations of demographic, functional, comorbidity, and treatment variables with combined ocular and oral dryness in rheumatoid arthritis.

	% Used	Adjusted for Age and Sex OR (95% CI)	Multivariable Analysis* OR (95% CI)
Age (per 10 yr increase)		1.13 (1.08–1.17)	1.10 (1.05–1.15)
Male sex		0.50 (0.44–0.58)	0.57 (0.49–0.66)
HAQ (0–3)		1.77 (1.65–1.90)	1.44 (1.33–1.56)
Comorbidity Index (0–9)		1.31 (1.27–1.36)	1.19 (1.15–1.24)
NSAID	62.2	1.05 (0.94–1.17)	1.08 (0.96–1.20)
DMARD	25.7	1.01 (0.89–1.14)	1.02 (0.90–1.16)
Biologic agents	75.4	1.23 (1.09–1.38)	1.08 (0.95–1.22)
Prednisone	33.4	1.30 (1.17–1.45)	1.03 (0.91–1.15)
Analgesics	40.9	1.90 (1.71–2.12)	1.41 (1.26–1.58)
Non-SRI antidepressants	5.0	2.24 (1.84–2.73)	1.49 (1.20–1.84)
SRI antidepressants	6.2	2.22 (1.85–2.66)	1.55 (1.27–1.89)
Anti-anxiety medications	2.8	2.00 (1.54–2.60)	1.08 (0.81–1.44)
Sleep medications	3.0	1.78 (1.38–2.31)	1.21 (0.92–1.60)
H_2 and PPI antagonists	26.8	1.90 (1.70–2.12)	1.44 (1.28–1.62)
Diuretics	18.9	1.31 (1.16–1.49)	0.97 (0.84–1.11)
Antihypertensives	38.0	1.19 (1.06–1.32)	0.84 (0.75–0.95)
CV medications (other)	22.2	1.49 (1.32–1.68)	1.14 (1.00–1.31)
Antiinfectives	3.5	1.64 (1.28–2.09)	1.13 (0.87–1.47)

* Adjusted for all other variables in the table except for age and sex, which are unadjusted. HAQ: Health Assessment Questionnaire; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease modifying antirheumatic drugs; SRI: serotonin reuptake inhibitor; PPI: proton pump inhibitor; CV: cardiovascular.

ilarly nonsignificant when non-lagged estrogen (current) use was studied.

Which clinical measures are most strongly associated with dryness? We next investigated the relation between clinical measures and combined dryness in RA. Figure 2, left, adjusted for age, sex, comorbidity, HAQ, and all treatment variables, demonstrates that high scores on the SI scale are associated with greater probabilities of combined sporadic dryness. Figure 2, right, shows the stronger association of combined dryness with the SI scale compared with patient global. The SI scale is a measure of "fibromyalgianess" (pain extent and fatigue), and persons with levels about 6 or above on the SI scale generally satisfy American College of Rheumatology criteria for FM. Table 3 provides specific results on the strength of association between combined dryness in RA and specific clinical scales using Kendall's tau-a. The SI scale is the strongest correlate of dryness, and its correlation with dryness is significantly stronger than the correlation with dryness of any other variable in the table ($p = 0.011$). Taken as a whole, these data indicate that fibromyalgianess is the most important clinical measure of dryness in RA, even after controlling for RA severity and treatment factors.

Do clinical and treatment variables explain the RA dryness

Table 3. The association of combined dryness and clinical variables as measured by Kendall's Tau-a in 9921 persons with rheumatoid arthritis.

Variable	Mean	SD	Z-score	p	Tau-a (95% CI)
Symptom Intensity Scale (0–10)	3.3	2.2	24.72	< 0.001	0.106 (0.098 to 0.115)
Regional Pain Scale (0–19)	5.1	4.8	22.75	< 0.001	0.099 (0.091 to 0.108)
Fatigue Scale (0–10)	4.1	2.9	19.91	< 0.001	0.084 (0.076 to 0.093)
Patient activity scale (0–10)	3.5	2.2	19.46	< 0.001	0.083 (0.074 to 0.091)
HAQ disability scale (0–10)	1.0	0.7	18.49	< 0.001	0.079 (0.071 to 0.087)
Pain scale (0–10)	3.6	2.7	17.44	< 0.001	0.075 (0.066 to 0.083)
Sleep scale (0–10)	3.4	3.0	16.00	< 0.001	0.070 (0.061 to 0.078)
Patient global severity (0-10)	3.4	2.5	15.37	< 0.001	0.065 (0.057 to 0.073)
Mood (0–10)	2.8	1.7	14.96	< 0.001	0.065 (0.056 to 0.074)
SF-36 mental component scale*	51.6	11.0	17.47	< 0.001	0.077 (0.068 to 0.086)
SF-36 physical component scale*	33.3	10.6	17.47	< 0.001	0.076 (0.068 to 0.085)

* N = 9161. HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36 Health Survey.

relationship? We then regressed RA diagnosis on age, sex, comorbidity, SI scale, HAQ, and all non-RA treatment variables to determine if these factors altered the association for combined sporadic dryness with RA noted in Table 1. The relative risk of RA for sporadic combined dryness was 1.33 (95% CI 1.19–1.47) and was 1.46 (95% CI 1.26–1.6) for persistent combined dryness. The area under the ROC for sporadic combined dryness was 0.724 and for persistent combined dryness was 0.747. Therefore, adjustment for treatment and severity factors leads to stronger associations between RA and dryness.

Dryness and utility quality of life measure. We investigated the extent to which dryness was associated with impaired quality of life. In a multivariable linear regression model that included all of the variables of Table 2, persons with sporadic combined dryness had utility scores that were 0.020 (95% CI 0.012–0.029) units lower using the EuroQOL scale and 0.019 (95% CI 0.014–0.025) units lower using the SF-6D. The SI scale was not included in these analyses to prevent overadjusting. However, when it was added, the EuroQOL difference became nonsignificant (p = 0.570) and the SF-6D difference dropped to 0.01 (95% CI 0.00–0.01).

DISCUSSION

We have shown that dryness symptoms are increased in patients with RA, that they increase with age, that they are associated with certain medications, that they are associated with illness severity, and that they have a special predilection for fatigue and fatigue/regional pain (fibromyalgianess)-type symptoms.

The data suggest that RA contributes to sicca, as evidenced by the increase in the relative risk of persistent oral and ocular dryness in RA compared with NIRD. After adjustment for demographics, comorbidity, patient arthritis symptoms, and all treatments germane to RA and NIRD, the relative risk of RA for sporadic combined dryness was 1.33 (95% CI 1.19–1.47) and was 1.46 (95% CI 1.26–1.6) for persistent combined dryness. Therefore, treatment and clinical factors evaluated in our study do not explain the risk increase in RA. Interestingly, RA may be (appropriately) assumed to be associated with dryness by many, but this association has not been demonstrated in epidemiological studies[20].

Our methods do not allow measurement of true SS or objectively define dry eye syndrome, even though roughly 60% of patients reported that their physicians told them their eye symptoms were due to RA. However, about 25% of RA patients with combined dryness symptoms have been shown to satisfy SS criteria[13]. And, in agreement with other studies[6], our data also demonstrate an age-related increase in dryness, as illustrated in Figure 1.

If immunological abnormalities and age explain only a small part of dryness complaints, what other factors contribute to sicca? With respect to treatment variables, a series of therapies that have been shown to cause dryness as an adverse effect in controlled clinical trials were also identified in our study. These include analgesics, anxiolytics, antidepressants, sleeping medications, H2 antagonists and proton pump inhibitors, diuretics, and antihypertensives. When all such medications were considered, their multivariable attributable risk was 27.5% (95% CI 22.5%–32.1%). In a population-based but not clinical study, the prevalence of sicca symptoms attributed to drying medications was 62% for combined eye and mouth symptoms[20].

One might also consider that RA activity or severity contributes to sicca, as dryness is associated with increased (abnormal) scores for HAQ, pain, and global severity. In addition, sicca is more common in those with adverse outcomes, such as total joint replacement and work disability (data not shown). The trouble with simply attributing RA activity or severity to these factors is that the same factors are also important in NIRD. Therefore, it appears that illness severity, or some consequences of illness severity, rather than RA alone is the important determinant of dryness.

Certain symptoms and conditions have been of particular interest to SS investigators, including fatigue, sleep disturbance, depression, autonomic neuropathy, and FM; these are associated with an increase in sicca symptoms[3,5] and confound SS care and research. A recent research conference on SS described fatigue and quality of life as core measures in the evaluation of SS[47]. We investigated a number of these symptoms.

We found that certain symptoms are related to dryness (Table 3 and Figure 2). In particular, we found that the Fatigue-Regional Pain Scale (SI Scale) was the strongest correlate of dryness, followed by the Regional Pain Scale (RPS), fatigue alone, HAQ, and comorbidity. The relation between dryness and these variables is shown in Figure 2. We have shown that the SI scale is the strongest correlate of RA and non-RA severity[48]. This scale appears to be a unifying measure of illness severity. Importantly, it is composed of the central component abnormalities of the FM syndrome, and at high values (about 6 or above) identifies those who satisfy FM criteria. However, it is not necessary to invoke FM to notice the dryness and fatigue/regional pain association because the association is linear at all levels of the SI scale. We have indicated elsewhere that FM represents the end of a fatigue–pain continuum and is not a distinct disorder[48], and we have shown that the association between fatigue and regional pain is a universal phenomenon and that it exists at all levels of the SI scale. Of interest, among persons in a population survey who had chronic widespread pain (CWP), oral and ocular dryness was a predictor of CWP 7 years later[49].

We think that the SI scale results indicate that fatigue and musculoskeletal pain are a universal mechanism associated with physical and mental distress, and that dryness is also a

manifestation of that distress. One might say that in NIRD, musculoskeletal illness "causes" dryness; and that in RA, musculoskeletal illness and an immunological component "cause" dryness; and that in SS, the syndrome and its distress consequences both act to cause the symptoms. We put "cause" in quotes because the relationship is causal only in the broadest sense.

Based on the SI scale, it follows that symptoms such as fatigue or sleep problems or even dryness will always be increased in persons with a chronic illness compared with population and "normal" controls[50]. The mechanism by which dryness occurs in the absence of lacrimal and salivary gland abnormality is not clear, but could occur through parasympathetic[18] or other neural or even hormonal mechanisms[18,50-52].

Although we found increased dryness in women who used estrogens, as reported by Schaumberg, *et al*[52], this association disappeared in our Cox regression analyses when we restricted our sample to women who did not report dryness at the first study observation. The above authors commented that, "Since we were not able to determine if initiation of HRT [hormone replacement therapy] preceded the onset of dry eye syndrome, the relationship may reflect a higher tendency of women with dry eye syndrome to be prescribed HRT"[52]. Our data suggest that such confounding may have occurred. The issues are further complicated for our analyses, however, because estrogen use has decreased substantially with recent reports of associated adverse effects. We examined that issue (data not shown) in different time periods in our cohort, but we did not see any indications of estrogen effect on dryness in prospective analyses.

Severe dryness symptoms (as in dry eye syndrome) are "associated with a measurable adverse impact on several common and important tasks of daily living"[53], and patients with SS have more abnormal SF-36 scores, as well[5,14]. Indeed, it would be hard to find any report of chronic symptoms that would not be associated with alteration in quality of life. Our study evaluated all levels of dryness severity, and we found a severity-adjusted utility difference of ~0.02 units between those with and those without dryness. However, one should be cautious of attributing a clear causal relationship to such results because of the possibility of unmeasured confounding.

Dryness is increased in RA and is contributed to by RA, illness severity, and therapy. The combination of body pain and fatigue is the strongest clinical correlate of dryness, and is independent of a diagnosis of FM. Any factor that increases illness severity or distress results in an increase in dryness.

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