Journal of Translational Autoimmunity 2 (2019) 100007

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.journals.elsevier.com/journal-of-translational-autoimmunity/

# Potentially inappropriate anticholinergic drug prescriptions for patients with Sjögren's syndrome

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ARTICLE INFO

*Keywords:*
Cholinergic antagonists
Comorbidity
Drug interactions
Sjögren's syndrome
Pharmacoepidemiology

ABSTRACT

Sjögren's syndrome is characterized by the involvement of exocrine glands, manifesting with xerostomia and xerophthalmia. The objective was to determine the treatment received and identify potentially inappropriate prescriptions by estimating the anticholinergic burden generated by medications in patients with Sjögren's syndrome in Colombia. This cross-sectional study was based on a population database that identified patients with Sjögren's syndrome, comorbidities, pharmacological treatment, and medications with anticholinergic properties. The anticholinergic burden was estimated using the Anticholinergic Drug Scale. A total of 4945 patients with Sjögren's syndrome were identified, with a mean age of 64.6 ± 14.04 years and 75.7% women. A total of 79.0% received a topical lubricant, with hyaluronate being the most prescribed (26.8%), while oral pilocarpine was prescribed for 7.4%. The use of biological disease-modifying antirheumatic drugs was identified in 1.3% of cases. A total of 39.1% (n = 1932) of all patients received cholinergic antagonists, especially codeine (6.5%), prednisolone (5.7%), and furosemide (5.3%). The mean anticholinergic burden was 0.91 ± 1.57 (range: 0–24), 17.2% (n = 850) had a score of 1, 7.7% (n = 381) had a score of 2, and 14.2% (n = 701) ≥3 points. Multiple comorbidities were associated with the risk of having cholinergic antagonist medication prescribed. Most patients with Sjögren's syndrome were women whose symptomatic management mainly included ocular lubricants with low use of oral pilocarpine. A large proportion of patients had at least one cholinergic antagonist drug prescribed, increasing its use risk after 40 years of age.

## 1. Introduction

Sjögren's syndrome is the second most frequent autoimmune rheumatic disease [1–3], characterized by lymphocytic infiltration of salivary and tear glands and other exocrine glands, which generates dryness of the skin and mucous membranes, especially of the mouth (xerostomia) and eyes (dry eye), known as sicca symptoms [2,4,5]. The disease can progress and affect other organs, such as the lungs, kidneys, gastrointestinal tract, musculoskeletal system, vessels, and central and peripheral nervous system [4,6,7]. Its prevalence is variable: 0.06% for primary Sjögren's syndrome and 4.8% for primary and secondary forms combined [1,8]. In Colombia, the prevalence of Sjögren's syndrome is 0.12% [5].

Glandular and extra-glandular symptoms are associated with high morbidity and complications of different types. Inadequate production of saliva can cause difficulty swallowing food, chewing or talking and can increase susceptibility to cavities and oral infections, as well as taste disorders, halitosis, and friability of the oral mucosa [3,6,9]. While keratoconjunctivitis sicca is the main ocular manifestation and produces epithelial damage to the cornea and conjunctiva, it manifests as a foreign body sensation, red eyes, irritation, pruritus, visual disturbances, photosensitivity, eye infections, and corneal ulcers [3,6,10].

Treatment of sicca symptoms in patients with Sjögren's syndrome involves general measures such as education, modification of environmental factors, and avoidance of smoking, alcohol consumption, anticholinergic drugs, and contact lenses, in addition to maintaining adequate hydration and avoiding sugary drinks, and is associated with pharmacological measures through tears, artificial saliva, and secretagogues (pilocarpine or cevimeline); the management of severe and acute systemic manifestations requires treatment with corticosteroids or immunosuppressants [6,11,12].

It has been reported that more than 400 drugs can exacerbate the dryness symptoms of Sjögren's syndrome, including antihypertensives,

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https://doi.org/10.1016/j.jtauto.2019.100007
Received 5 June 2019; Accepted 19 June 2019

diuretics, antidepressants, antiparkinson drugs, antipsychotics, antihistamines, centrally acting analgesics, and anticholinergics [6,13–15]. Anticholinergics are among the most frequently prescribed potentially inappropriate medications [16]. The use of this type of medication is associated with an increased risk of falls, delirium, fractures, dry mucosa and skin, blurred vision, and increased intraocular pressure, among others [17–19]. Due to all the above, the use of tools to measure exposure to anticholinergic and sedative medications is advised [20], to reduce polypharmacy and the adverse effects associated with their use [16,21].

Anticholinergic risk scales are tools based on expert consensus that estimate the anticholinergic burden of drugs prescribed to a patient. These scales usually classify drugs in a score range between 0 (none) and 3 (strong potential) according to the anticholinergic potential. For all scales, the total anticholinergic burden is determined by the sum of the scores of each anticholinergic drug [22–24]. The Anticholinergic Drug Scale (ADS) was developed by Carnahan et al. in the US and includes 117 drugs with anticholinergic properties; it was designed to identify the severity of adverse effects of antimuscarinic medication at the central and peripheral levels [20].

Colombia's Health System offers universal coverage to the entire population through two regimes, one contributory or paid by the worker and employer and another subsidized by the state, which has a benefit plan that includes some drugs used for the treatment of rheumatic diseases and approximately 88 of those on the ADS scale. We sought to determine the treatment being received and identify potentially inappropriate prescriptions by estimating the anticholinergic burden generated by the medications in patients with Sjögren's syndrome in Colombia.

## 2. Materials and methods

An observational cross-sectional study was conducted on prescription patterns for drugs with anticholinergic properties in patients diagnosed with Sjögren's syndrome based on a population database. The database contains information collected from approximately 6.5 million people affiliated with the contributory regime of the Colombian Health System and five Health-Promoting Companies, corresponding to approximately 30.0% of the active affiliate population of this regimen in the country and 14.3% of the Colombian population between November 1, 2018, and January 31, 2019.

We analyzed the prescriptions for patients diagnosed with Sjögren's syndrome using the International Classification of Diseases (ICD-10) codes: Dry syndrome (Sjögren): M350; drugs for its management and drugs with anticholinergic properties were identified using the ADS scale. Patients of both sexes, 18 years of age or older, and seen in an outpatient clinic were selected.

Based on the information regarding consumption of medications by the affiliated population, systematically obtained by a dispensing company (Audifarma SA), a database was designed to collect the following groups of patient variables:

1. Sociodemographic: sex, age, city of care, and Health-Promoting Companies;
2. Comorbidities were identified from the main and secondary diagnoses reported by the ICD-10 within three months prior to study dates, between August 1, 2018, and January 31, 2019, in patients with Sjögren's syndrome;
3. Conventional disease-modifying antirheumatic drugs (cDMARDs): methotrexate, sulfasalazine, chloroquine, hydroxychloroquine, azathioprine, and leflunomide;
4. Biological disease-modifying antirheumatic drugs (bDMARDs): rituximab, abatacept, etanercept, infliximab, tocilizumab, certolizumab, golimumab, and adalimumab;
5. Medications used for the symptomatic management of xerostomia/xerophthalmia:
   - Local: artificial tears (ophthalmic hydroxymethyl cellulose, ophthalmic hyaluronate, hydroxypropyl methyl cellulose), ophthalmic cyclosporine, polyacrylic acid, and artificial saliva; and
   - Systemic: oral pilocarpine and cevimeline (not available in Colombia);
6. Anticholinergic drugs: A search was conducted for the 117 drugs included in the ADS scale, of which 88 are commercialized in Colombia according to the National Institute of Food and Drug Surveillance (Instituto Nacional de Vigilancia de Medicamentos and Alimentos - INVIMA). The total anticholinergic burden was determined by the sum of the risk of each of the prescribed medications. Accordingly, patients were classified into four groups: 1. patients with an ADS score of 0 (no anticholinergic activity); 2. patients with an ADS score of 1 (mild anticholinergic activity); 3. patients with an ADS score of 2 (moderate anticholinergic activity); and 4. patients with an ADS score $\geq$3 (high anticholinergic activity);
7. Drug interactions: Potential interactions were identified in patients who had an anticholinergic burden $\geq$1 and who were receiving concomitant symptomatic treatment for Sjögren's syndrome and in those who were receiving antimuscarinic drugs but not humectants/lubricants or pilocarpine; and
8. Comedications were grouped into the following categories: a) antidiabetic, b) antihypertensive, c) hypolipidemics, d) antiulcer, e) antidepressants, f) antiglaucomatous, g) non-opiod analgesics, h) antipsychotics (typical and atypical), i) antiepileptics, j) antihistamines (first and second generation), k) antiparkinson, l) antidementia, m) diuretics, n) opioid analgesics, o) thyroid hormone, and p) platelet antiaggregants.

The protocol was approved by the Bioethics Committee of the Universidad Tecnologica de Pereira in the risk-free research category. The ethical principles established by the Declaration of Helsinki were respected. Patient personal data were not considered.

The data were analyzed using the statistical package SPSS Statistics, version 24.0 for Windows (IBM, USA). A descriptive analysis was performed with frequencies and proportions for the qualitative variables and measures of central tendency and dispersion for the quantitative variables. The comparison of quantitative variables was determined using Student's t-test or ANOVA and $X^2$ for categorical variables. Binary logistic regression models were performed using as a dependent variable receiving medications with a mild-moderate or high anticholinergic burden (ADS scores 1–2 and $\geq$3, respectively) and as covariables those medications that were significantly associated with these higher ADS scores in the bivariate analyses. $p < 0.05$ was determined as the level of statistical significance.

## 3. Results

We identified 4945 patients diagnosed with Sjögren's syndrome, distributed in 47 different cities. The mean age was 64.6 $\pm$ 14.0 years (range: 18.3–101.8 years), and 75.7% (n = 3745) were women. The female:male ratio in the study population was 3.1:1. A total of 83.6% (n = 4134) were receiving pharmacological treatment for Sjögren's syndrome, with hyaluronate (n = 1326, 26.8%) being the most prescribed ocular lubricant, while oral pilocarpine was prescribed in 7.4% (n = 365) of the cases. The use of cDMARDs was identified in 11.9% (n = 587) of the patients, while the use of bDMARDs was identified in 1.3% (n = 62) (Table 1).

Of all the patients identified, approximately 1932 (39.1%) were prescribed at least one drug with anticholinergic properties, distributed in 60 different drugs. Of these, 23.4% (n = 1156) received a single drug, 10.0% (n = 493) received two drugs, and 5.7% (n = 283) received three drugs or more. The average anticholinergic burden according to the ADS scale was 0.91 $\pm$ 1.57 (range: 0–24), 17.2% (n = 850) had a score of 1, 7.7% (n = 381) had a score of 2, and 14.2% (n = 701) had a score $\geq$3 points. The most frequently prescribed drugs with anticholinergic properties were codeine, prednisolone, and furosemide (see Table 2).

**Table 1**
Prescription pattern of pilocarpine, humectants/lubricants for topical use and disease-modifying antirheumatic drugs for patients diagnosed with Sjögren's syndrome, Colombia.

| Drug | Frequency (n = 4945) | % |
|---|---|---|
| **Symptomatic treatment** | 4134 | 83.6 |
| -Oral pilocarpine | 365 | 7.4 |
| Monotherapy | 166 | 3.4 |
| Associated with topical therapy | 199 | 4.0 |
| -Lubricants and ocular humectants | 3906 | 79.0 |
| Hyaluronate | 1326 | 26.8 |
| Polyacrylic acid | 1002 | 20.3 |
| Carboxymethylcellulose + glycerin | 819 | 16.6 |
| Carboxymethylcellulose | 766 | 15.5 |
| Hyaluronate + chondroitin | 607 | 12.3 |
| Ciclosporin | 133 | 2.7 |
| Hydroxypropylmethylcellulose | 106 | 2.1 |
| Carboxymethylcellulose + glycerin + polysorbate | 14 | 0.3 |
| -Artificial saliva | 15 | 0.3 |
| **Treatment with disease-modifying antirheumatics** | 605 | 12.2 |
| -Conventional | 587 | 11.9 |
| Methotrexate | 229 | 4.6 |
| Chloroquine | 200 | 4.0 |
| Azathioprine | 103 | 2.1 |
| Sulfasalazine | 80 | 1.6 |
| Leflunomide | 75 | 1.5 |
| Hydroxychloroquine | 61 | 1.2 |
| -Biological | 62 | 1.3 |
| Rituximab | 15 | 0.3 |
| Etanercept | 10 | 0.2 |
| Golimumab | 8 | 0.2 |
| Others (8 different biotechnologies) | 29 | 0.6 |
| **Immunosuppressants** | 509 | 10.3 |
| -Systemic corticosteroids | 506 | 10.2 |
| Prednisolone | 281 | 5.7 |
| Dexamethasone | 141 | 2.9 |
| Deflazacort | 40 | 0.8 |
| Prednisone | 33 | 0.7 |
| Other (3 different corticosteroids) | 46 | 0.9 |
| -Other immunosuppressants (3 different) | 22 | 0.4 |

### 3.1. Interactions

Approximately 1629 (39.4%) patients receiving symptomatic pharmacological treatment for Sjögren's syndrome were prescribed medications with antimuscarinic properties; an anticholinergic burden ≥3 was present in 14.3% (n = 592). Of the patients (n = 811) who were not prescribed topical lubricants or oral pilocarpine, 37.4% (n = 303) were prescribed anticholinergic drugs, of which 14.4% (n = 109) had a burden ≥3 (Table 3).

**Table 2**
Anticholinergic drugs most prescribed to patients diagnosed with Sjögren's syndrome, Colombia.

| Drug | ADS | Frequency | % |
|---|---|---|---|
| Codeine | 1 | 321 | 6.5 |
| Prednisolone | 1 | 281 | 5.7 |
| Furosemide | 1 | 264 | 5.3 |
| Chlorpheniramine | 3 | 196 | 4.0 |
| Fluoxetine | 1 | 159 | 3.2 |
| Sertraline | 1 | 159 | 3.2 |
| Ranitidine | 2 | 148 | 3.0 |
| Dexamethasone | 1 | 145 | 2.9 |
| Tramadol | 1 | 142 | 2.9 |
| Nifedipine | 1 | 116 | 2.3 |
| Ketotifen | 1 | 108 | 2.2 |
| Azathioprine | 1 | 103 | 2.1 |
| Imipramine | 3 | 81 | 1.6 |
| Amitriptyline | 3 | 77 | 1.6 |
| Carbamazepine | 2 | 74 | 1.5 |

ADS: Anticholinergic Drug Scale.

### 3.2. Comorbidities and comedications

The most frequently identified comorbidities were hypertension (n = 2679, 54.2%), hypothyroidism (n = 1157, 23.4%), glaucoma (n = 992, 20.1%), diabetes mellitus (n = 738, 14.9%), dyslipidemia (n = 364, 7.4%), osteoarthritis (n = 316, 6.4%), rheumatoid arthritis (n = 280, 5.7%), chronic renal failure (n = 211, 4.3%), gastritis (n = 201, 4.1%), osteoporosis (n = 196, 4.0%), and fibromyalgia (n = 175, 3.5%). Comedication was found in 92.6% (n = 4580) of the patients, with the 10 most prescribed pharmacological groups being antihypertensives (n = 2432, 49.2%), lipid-lowering agents (n = 1847, 37.4%), non-steroidal analgesics/anti-inflammatory drugs (n = 1641, 33.2%), anti-ulcer drugs (n = 1635, 33.1%), antiglaucoma drugs (n = 1204, 24.3%), thyroid hormone supplement (n = 1157, 23.4%), platelet antiaggregants (n = 1091, 22.1%), diuretics (n = 887, 17.9%), normoglycemic agents (n = 738, 14.9%), and antidepressants (n = 689, 13.9%).

### 3.3. Comparison between age groups

The use of topical lubricants by patients with Sjögren's syndrome was not different among age groups, while the prescription of oral pilocarpine predominated in one-tenth of patients between 40 and 64 years. The anticholinergic burden increased progressively with age, in particular in almost half of the patients aged 75 years or older; likewise, the interactions between antimuscarinic drug-symptomatic treatment and between antimuscarinic-disease (Sjögren's syndrome) were more commonly found in this age group. Comorbidities and comedications were more frequently found in patient older than 65 years of age (Table 3).

### 3.4. Multivariate analysis

The multivariate analysis found that after 75 years of age, being female and having as comorbidities asthma, chronic obstructive pulmonary disease, depression, bipolar affective disorder, hypertension, diabetes mellitus, gastritis, systemic lupus erythematosus, peripheral neuropathy, osteoarthrosis and allergic rhinitis raised the probability of receiving drugs with anticholinergic burden scores of 1 and 2; living in the city of Bogotá reduced this risk. Additionally, residing in the city of Manizales and having as comorbidities headache, irritable bowel syndrome, depression, dyslipidemia, chronic pain, epilepsy, chronic obstructive pulmonary disease, atrial fibrillation, fibromyalgia, hypothyroidism, benign prostatic hyperplasia, hypertension, urinary incontinence, insomnia, peripheral neuropathy, urticaria, and vasculitis were associated with a statistically significant higher probability of receiving drugs with an anticholinergic burden ≥3, while living in the city of Bogotá and Monteria reduced this risk (Tables 4 and 5).

## 4. Discussion

This study allowed the identification of potentially inappropriate anticholinergic drug prescriptions for patients diagnosed with Sjögren's syndrome, which can be associated with an increased risk of local complications such as infections and ulcers, among others, in a group of patients enrolled in the Colombian Health System. These findings may be useful for caregivers, academics, and scientists in decision-making regarding the potential harmful interactions and adverse drug reactions that their patients face.

Patients diagnosed with Sjögren's syndrome had a mean age of 64.6 years, similar to that found in the United States (65.8 years) [1] but higher than what has been documented in several countries in Europe (51–55 years) [7,25–29], Asia (48.3–60.8 years) [30–32], and another report from Colombia (51.3 years) [33]. Sjögren's syndrome predominated in females (75.7%) but in a lower proportion than that described in the United States (96%) [30], Greece (95.2%) [26], Japan (94.2%) [32], Spain (93–95.1 years) [2,27,29], Iran (90.4%) [1], and France (89.9–93%) [7,25], as well as in local studies (82–97.3%) [5,33].

**Table 3**
Comparison of sociodemographic, clinical, and pharmacological variables by age group for patients diagnosed with Sjögren's syndrome, Colombia.

| Variables | Total | | 18–39 years | | 40–64 years | | 65–74 years | | ≥75 years | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n = 4945 | % | n = 284 | % | n = 2123 | % | n = 1415 | % | n = 1123 | % |
| Woman | 3745 | 75.7 | 199 | 70.1 | 1686 | 79.4 | 1066 | 75.3 | 794 | 70.7 |
| **Symptomatic treatment** | 4134 | 83.6 | 237 | 83.5 | 1794 | 84.5 | 1170 | 82.7 | 933 | 83.1 |
| Oral pilocarpine | 365 | 7.4 | 18 | 6.3 | 214 | 10.1 | 96 | 6.8 | 37 | 3.3 |
| Lubricants and ocular humectants | 3966 | 80.2 | 232 | 81.7 | 1694 | 79.8 | 1122 | 79.3 | 918 | 81.7 |
| Artificial saliva | 15 | 0.3 | 0 | 0.0 | 7 | 0.3 | 4 | 0.3 | 4 | 0.3 |
| **Treatment with DMARD** | 605 | 12.2 | 41 | 14.4 | 357 | 16.8 | 150 | 10.6 | 57 | 5.1 |
| Convencional | 587 | 11.9 | 39 | 13.7 | 345 | 16.3 | 147 | 10.4 | 56 | 5.0 |
| Biological | 62 | 1.3 | 5 | 1.8 | 46 | 2.2 | 9 | 0.6 | 2 | 0.2 |
| **Anticholinergic load** | 1932 | 39.1 | 74 | 26.1 | 787 | 37.1 | 566 | 40.0 | 505 | 45.0 |
| ADS 1–2 points | 1231 | 24.9 | 49 | 17.3 | 484 | 22.8 | 366 | 25.9 | 332 | 29.6 |
| ADS ≥3 points | 701 | 14.2 | 25 | 8.8 | 303 | 14.3 | 200 | 14.1 | 173 | 15.4 |
| **Symptomatic treatment + ADS ≥1 points (n = 4134)** | 1629 | 39.4 | 63 | 26.6 | 666 | 37.1 | 477 | 40.8 | 423 | 45.3 |
| Symptomatic treatment + ADS 1–2 points | 1037 | 25.1 | 41 | 17.3 | 406 | 22.6 | 311 | 26.6 | 279 | 29.9 |
| Symptomatic treatment + ADS ≥3 points | 592 | 14.3 | 22 | 9.3 | 260 | 14.5 | 166 | 14.2 | 144 | 15.4 |
| **Without symptomatic treatment + ADS ≥1 points (n = 811)** | 303 | 37.4 | 11 | 23.4 | 121 | 36.8 | 89 | 36.3 | 82 | 43.2 |
| Without symptomatic treatment + ADS 1–2 points | 194 | 23.9 | 8 | 17.0 | 78 | 23.7 | 55 | 22.4 | 53 | 27.9 |
| Without symptomatic treatment + ADS ≥3 points | 109 | 13.4 | 3 | 6.4 | 43 | 13.1 | 34 | 13.9 | 29 | 15.3 |
| **Comorbidities** | 4372 | 88.4 | 194 | 68.3 | 1773 | 83.5 | 1322 | 93.4 | 1083 | 96.4 |

The most frequent comorbidity found was hypertension (54.2%), higher than what was described in the United States (25.4%) [1] and in Puerto Rico (39%) [34], with gastroesophageal reflux (45%) [1] and osteoarthrosis (43%) [34] predominating in those regions, respectively. The most common comedication was related to the most described comorbidity, with antihypertensives being found in 49.2% of the patients, which is consistent, although at a higher proportion, with the results of a study conducted in the United States (35.8%) [1].

In this study, pilocarpine was prescribed to 7.4% of patients, very similar to that found in Puerto Rico (8%) [34] but substantially less than what has been described in Japan (20–31.7%) [32,35]. Patients with residual function of the salivary and lacrimal glands can receive muscarinic agonists (pilocarpine) as a treatment of choice in the absence of contraindications [6,11,12]. Regarding topical treatment, the use of artificial saliva was only identified in 0.3% of patients, while in Japan, artificial saliva use was found in 19% of patients [35]. Artificial tears such as hyaluronate or carboxymethyl cellulose are the first-line treatment for improving xerophthalmia [6,11,12] and were prescribed to 79% of patients in our study, contrasting with what was found in Japan (52%) [35]. Cyclosporine was prescribed to only 2.7% of patients, while in Puerto Rico, this drug was prescribed to 26% of patients [34]. These differences are probably due to different physician prescription habits, diverse academic training of physicians, and availability of these drugs in the health systems of each country.

Sjögren's syndrome, in addition to presenting with symptoms related to mucocutaneous dryness, can lead to systemic complications in 30–40% of cases that will require treatment with corticosteroids, immunosuppressants or disease-modifying antirheumatic drugs (DMARD) type drugs [12]. In our study, the prescription of corticosteroids (10.2%) was similar to that described in the United States (14.6%) [1] and lower than what was documented in Japan (34.3%) [32], Spain (42%) [29], and France (79%) [7]. Methotrexate (4.6%) was the most prescribed DMARD in our study, whereas in Spain and France, hydroxychloroquine was the most prescribed DMARD (25% and 49%, respectively) [7,29]; notably, hydroxychloroquine has demonstrated beneficial effects in clinical trials [12].

bDMARDs were prescribed to 1.2% of patients with Sjögren's syndrome, similar to that described in Japan (3.1%) [32]. The most commonly prescribed bDMARD in our report was rituximab (0.3%), which was consistent with what was found in Spain, Puerto Rico, and France but where it was prescribed to a higher percentage of patients (3.1%, 4.0%, and 5.3%, respectively) [7,29,34]; in Japan, etanercept was the most prescribed bDMARD (0.95%) [32]. In the same way as the cDMARDs, few biological agents have been rigorously studied, and none have shown significant efficacy in multiple studies, with the exception of rituximab, which could have clinical benefits [12].

No other studies used quantification of anticholinergic burden through risk scales as a methodology; however, drugs with antimuscarinic properties are a heterogeneous group of drugs used for a large number of different pathologies. Smidt et al. in Denmark identified the risk of dry mouth (OR: 5.2; CI95%: 1.9–14.6) and eyes (OR: 4.4; CI95%: 1.6–12.3) was higher in medicated patients than in those who did not receive the medications, finding a statistically significant association with the risk of xerostomia with the use of cardiovascular, respiratory, neurological, and antineoplastic drugs and an increased risk of

**Table 4**
Multivariate analysis of variables associated with prescriptions with an anticholinergic burden of 1–2 for patients with Sjögren's syndrome, Colombia.

| Variables | Sig. | OR | CI 95% | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Woman | 0.004 | 1.279 | 1.083 | 1.511 |
| Age 18–39 years | 0.101 | Reference | Reference | Reference |
| Age 40–64 years | 0.187 | 1.266 | 0.892 | 1.797 |
| Age 65–74 years | 0.131 | 1.323 | 0.920 | 1.903 |
| Age ≥75 years | 0.030 | 1.511 | 1.042 | 2.191 |
| **Be treated in** | | | | |
| Bogota | <0,001 | 0.720 | 0.610 | 0.848 |
| Manizales | 0.694 | 1.048 | 0.828 | 1.327 |
| Bucaramanga | 0.151 | 1.296 | 0.910 | 1.844 |
| **Comorbidities** | | | | |
| Asthma | 0.006 | 1.945 | 1.214 | 3.115 |
| Ischemic heart disease | 0.191 | 1.287 | 0.882 | 1.877 |
| Dementia | 0.205 | 1.411 | 0.828 | 2.402 |
| Depressive disorders | <0,001 | 2.230 | 1.590 | 3.127 |
| Diabetes mellitus | 0.001 | 1.351 | 1.128 | 1.619 |
| Chronic pain | 0.136 | 1.336 | 0.913 | 1.955 |
| Parkinson's disease | 0.106 | 1.930 | 0.869 | 4.288 |
| Chronic obstructive pulmonary disease | 0.035 | 1.479 | 1.027 | 2.129 |
| Fibromyalgia | 0.306 | 0.827 | 0.574 | 1.190 |
| Gastritis | 0.007 | 1.548 | 1.128 | 2.124 |
| Hypothyroidism | 0.352 | 1.079 | 0.919 | 1.267 |
| Arterial hypertension | <0,001 | 1.545 | 1.334 | 1.790 |
| Insomnia | 0.237 | 1.432 | 0.790 | 2.597 |
| Systemic lupus erythematosus | <0,001 | 5.213 | 3.159 | 8.603 |
| Peripheral neuropathy | 0.042 | 1.390 | 1.011 | 1.911 |
| Osteoarthrosis | <0,001 | 1.970 | 1.540 | 2.520 |
| Allergic rhinitis | 0.023 | 1.841 | 1.086 | 3.122 |
| Bipolar affective disorder | <0,001 | 2.536 | 1.550 | 4.150 |

Sig: Statistical significance; OR: Odds Rattio; CI: Confidence Interval.

**Table 5**
Multivariate analysis of the variables associated with having prescriptions with anticholinergic burden ≥3 for patients with Sjögren's syndrome, Colombia.

| Variables | Sig. | OR | CI 95% | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Woman | 0.054 | 1.255 | 0.996 | 1.581 |
| Age 18–39 years | 0.828 | Reference | Reference | Reference |
| Age 40–64 years | 0.359 | 1.240 | 0.784 | 1.962 |
| Age 65–74 years | 0.465 | 1.194 | 0.742 | 1.920 |
| Age ≥75 years | 0.450 | 1.206 | 0.742 | 1.961 |
| **Be treated in** | | | | |
| Bogota | 0.001 | 0.700 | 0.565 | 0.867 |
| Manizales | 0.007 | 1.444 | 1.104 | 1.889 |
| Monteria | 0.044 | 0.557 | 0.315 | 0.984 |
| **Comorbidities** | | | | |
| Asthma | 0.054 | 1.742 | 0.990 | 3.064 |
| Headache | <0,001 | 3.074 | 2.152 | 4.393 |
| Irritable bowel syndrome | 0.001 | 2.078 | 1.350 | 3.199 |
| Depressive disorders | 0.004 | 1.753 | 1.191 | 2.580 |
| Dyslipidemia | 0.019 | 1.425 | 1.059 | 1.917 |
| Chronic pain | 0.001 | 2.014 | 1.339 | 3.029 |
| Epilepsy | <0,001 | 3.526 | 1.960 | 6.343 |
| Chronic obstructive pulmonary disease | <0,001 | 2.311 | 1.544 | 3.459 |
| Atrial fibrillation | 0.010 | 2.039 | 1.184 | 3.512 |
| Fibromyalgia | <0,001 | 3.691 | 2.593 | 5.253 |
| Gastritis | 0.062 | 1.436 | 0.982 | 2.100 |
| Hypothyroidism | 0.008 | 1.305 | 1.071 | 1.591 |
| Benign prostatic hyperplasia | 0.006 | 1.902 | 1.204 | 3.004 |
| Arterial hypertension | <0,001 | 1.473 | 1.220 | 1.779 |
| Urinary incontinence | <0,001 | 4.227 | 2.733 | 6.538 |
| Insomnia | 0.001 | 2.839 | 1.510 | 5.338 |
| Peripheral neuropathy | <0,001 | 1.926 | 1.356 | 2.735 |
| Osteoarthrosis | 0.395 | 1.146 | 0.837 | 1.571 |
| Allergic rhinitis | 0.054 | 1.835 | 0.990 | 3.403 |
| Bipolar affective disorder | 0.571 | 1.181 | 0.664 | 2.103 |
| Urticaria | <0,001 | 5.177 | 2.120 | 12.642 |
| Vasculitis | <0,001 | 3.322 | 1.763 | 6.259 |

Sig: Statistical significance; OR: Odds Rattio; CI: Confidence Interval.

xerophthalmia with the use of antihypertensives, neurological drugs, and analgesics [14].

Rudolph et al., from a list of drugs with anticholinergic properties, identified that patients with a high anticholinergic burden had a 90% increased risk (OR: 1.9; 95% CI: 1.5–2.5) of having peripheral adverse effects (xerostomia, xerophthalmia and constipation) [21]. In our report, 39.1% of patients were prescribed at least one drug with anticholinergic properties, and their risk of being prescribed other medication increased due to a large number of comorbidities, especially urticaria, urinary incontinence, fibromyalgia, epilepsy, and vasculitis. These prescriptions could increase the risk of having dryness symptoms or aggravate existing symptoms and may generate multiple local complications [3,6,10].

Some limitations should be recognized when interpreting certain results. Clinical histories were not assessed to determine non-pharmacological management of symptoms by patients, time of evolution of Sjögren's syndrome, classification into primary or secondary Sjögren's syndrome, and possible complications. In addition, the diagnosis of dry syndrome (Sjögren) found in the ICD-10 could be used in patients with symptoms secondary to chemotherapy/radiotherapy or as an adverse reaction to medications. Only the potential risk of triggering local ophthalmic or oral complications could be considered due to the association between antimuscarinic drugs and the development of xerostomia/xerophthalmia; therefore, it is necessary to develop studies that can identify this possible causality.

## 5. Conclusions

With the above findings, it can be concluded that a high proportion of patients with Sjögren's syndrome identified in a population database were prescribed topical lubricants, mainly hyaluronate, and more than a third were prescribed some medication with an anticholinergic burden that may worsen symptoms, mainly in those older than 40 years of age. These results should be useful for promoting and strengthening educational and pharmacovigilance strategies that improve the prescription habits of physicians involved in the care of these patients.

## Conflict of interest statement

The authors declare no conflicts of interest.

## Funding sources

The present study did not receive funding.

## Acknowledgments

To Soffy Claritza López for her work in obtaining the database.

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