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ORIGINAL RESEARCH

Psoriasis is Associated with a High Comedication Burden: A Population Based Register Study

Albert Duvetorp · Ulrich Mrowietz · Mats Nilsson · Oliver Seifert

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ABSTRACT

Introduction: A large body of evidence supports the association between psoriasis and concomitant diseases. However, the study of comedication for these diseases in patients with psoriasis is limited. The current study aimed to investigate the prescription and drug dispensation for comorbidity associated with psoriasis.

Methods: We conducted a retrospective case-control study from 9 April 2008 until 1 January 2016 using an electronic medical records database covering the entire population of the County of Jönköping and the Swedish Prescribed Drug Register. ICD-10 and Anatomical Therapeutic Chemical codes were used to identify patients with psoriasis and dispensed pharmaceutical prescriptions. Individuals without psoriasis were selected as controls. Patients receiving systemic treatment for psoriasis were considered as having moderate-severe psoriasis. Odds ratios for being dispensed pharmaceutical prescriptions and differences in mean number of dispensed prescriptions were explored.

Results: A total of 4587 patients with psoriasis were identified in the medical records, and 268,949 individuals served as controls. Patients with psoriasis had a significantly higher number of different drug dispensations compared to controls. Only 1.3% of all patients with psoriasis were without any prescription (excluding medication for psoriasis) during the study period while the number in the general population was 9.3%. Sex- and age-adjusted odds ratios for dispensation of drug groups related to comorbid disease were significantly higher among patients with psoriasis including drug groups

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A. Duvetorp (✉)
Division of Dermatology, Skåne University Hospital, Malmö, Sweden
e-mail: albert.duvetorp@skane.se

A. Duvetorp · O. Seifert
Department of Clinical and Experimental Medicine, Faculty of Medicine and Health Sciences, Linköping University, Linköping, Sweden

U. Mrowietz
Psoriasis-Center at the Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Germany

M. Nilsson
Futurum-Academy for Health and Care, Region Jönköping County, Jönköping, Sweden

O. Seifert
Division of Dermatology and Venereology, Region Jönköping County, Jönköping, Sweden

such as anxiolytics and sedatives as well as drugs targeting COPD, migraine and erectile dysfunction. The most frequently dispensed comedications were oral antibiotics and analgesics including an increased risk for dispensation of opioids. Sex predisposed dispensation frequency for a variety of drug groups. Drugs targeting obesity, osteoporosis, psychiatric disease and anti-mycotics/-fungals were more frequent among women.

Conclusion: Patients with psoriasis have significantly increased numbers of different dispensed prescriptions than those without psoriasis. This underlines previous findings on increased comorbidity and health care costs for patients with psoriasis.

Keywords: Comorbidity; Drug therapy; Polypharmacy; Psoriasis; Psoriatic arthritis

Key Summary Points

Why carry out this study?

Although there is a vast amount of scientific evidence supporting high comorbidity among patients with psoriasis studies on comedication are sparse

There are currently no published comorbidity or comedication studies comparing individuals with psoriasis with the background population in Sweden

What was learned from the study?

Psoriasis patients have a significantly higher comedication burden. Patients with moderate-severe psoriasis are dispensed a higher number of different drugs suggesting that severe disease implies higher risk of comorbid diseases

Several comedication groups displayed uneven sex distribution. Drugs targeting osteoporosis, anti-migraine treatment, anti-mycotics/-fungals, anti-inflammatory opthalmologic agents, stomatologic preparations, anti-histamines, psychiatric drugs, topicals for joint and muscular pain and anti-obesity preparations were more commonly dispensed to women with psoriasis whereas drugs targeting sexual dysfunction were solely dispensed to men. Vasodilators used in cardiac disease and antiarrhythmic drugs are more commonly dispensed to men. Clinicians should be aware that results suggest that sex may affect comorbidity risk

INTRODUCTION

Psoriasis is a common inflammatory disease, which primarily engages the skin and has an estimated prevalence of 2–3% in Europe [1]. The pathogenesis of psoriasis is influenced by a combination of polygenic inheritance and multifactorial environmental activation [2]. Trigger factors such as stress, smoking, infections and drugs are known to influence disease onset and disease exacerbation.

Psoriasis is associated with an increased frequency of concomitant disorders including myocardial infarction [3], stroke [4], cardiovascular death [5] and metabolic syndrome [6–9]. Severe psoriasis may be an independent risk factor for atherosclerotic cardiovascular disease [3, 10], and patients with severe psoriasis die approximately 5 years earlier than patients without psoriasis [11]. Psoriasis is associated with anxiety, depression and sleep disturbance [12–15]. Furthermore, patients with psoriasis and psoriasis arthritis may suffer from chronic pain, have higher alcohol consumption and more nicotine addiction [16, 17]. The list of associated comorbid diseases can be made longer including conditions such as infections [18], osteoporosis [19], sexual dysfunction [20], uveitis [21], periodontitis [22], inflammatory bowel disease (IBD) [23] and migraine [24]. For

most comorbid conditions, common immunologic inflammatory pathomechanisms are proposed as a link between psoriasis and comorbidity; however, unknown residual confounding cannot be ruled out.

Regular assessment of comedication is recommended in the management of psoriasis [25]. Specific comedication such as beta-blockers or angiotensin-converting enzymes (ACE) may influence and worsen psoriasis [26]. Comedication also serves as a proxy for comorbid diseases that can be used as a method of estimating the burden of patients' total morbidity.

Despite the awareness about comorbidity in psoriasis, data about the wider comorbidity comedication load are scarce. Gerdes et al. described that hospitalized patients with severe psoriasis received significantly more systemic drugs, and Dowlatshahi et al. found an overall increased drug utilization in patients with psoriasis in one of the few population-based studies [27, 28]. Published studies on psoriasis, comedication and comorbidity in a Swedish population context are nonexistent.

The present study was performed to analyze the presence of comedication of dispensed prescription drugs from ATC groups used to treat comorbidity associated with psoriasis in a Swedish population. We hypothesized that psoriasis patients would have increased comedication consolidating the perception that the comorbidity burden is high.

METHODS

A retrospective population based case-control study was carried out between 9 April 2008 and 1 January 2016. The target population was composed of all adult residents in the Jönköping Region in southern Sweden at 1 January 2016. Jönköping Region has both rural and urban areas and is demographically similar to Sweden as a whole (similar population income, educational level, percentage of population not born in Sweden) [29]. Since the clinical diagnosis of psoriasis may be challenging in children [30], we opted to include patients 18 years of age or older (n = 273,536).

Patients were identified via an electronic medical record (EMR) covering the entire population of Jönköping County, including inhabitants without contact with health care providers during the study period. EMR was introduced in the Jönköping region on 9 April 2008. Data on all primary care and specialized outpatient and inpatient care are continuously registered, including personal identification number, age, sex, health care provider, date of visits and diagnostic codes according to the World Health Organization (WHO) International Classification of Diseases (ICD-10-SE). Private and public care visits are registered in the same way.

All patients with ICD-10-SE codes marking psoriasis (L40.*) from 9 April 2008 until 1 January 2016 were identified in the EMR database. Patients were counted as cases with psoriasis if there was at least one visit to a dermatologist with the diagnostic codes L40.* and subcodes or at least two visits in primary care or any other clinic and concomitant topical (calcipotriol, calcipotriol and betamethasone, group III or IV steroids) or systemic treatment (methotrexate, acitretin, biologics, ciclosporine, apremilast, dimethylfumarate) for psoriasis. Prescription of systemic treatment served as a proxy to define patients with moderate-to-severe psoriasis. Individuals in the EMR not meeting the study definition of psoriasis served as controls.

The Swedish Prescribed Drug Register (PDR) covers data on all dispensed prescription pharmaceuticals in Sweden since July 2005, including drug identity registered using Anatomical Therapeutic Chemical (ATC) codes. PDR was used to identify prescription codes for prescription drugs of interest for individuals in the target population from 4 July 2007 until 31 December 2016. The proportion of invalid dispensation entries in the PDR is $< 2\%$ [31]. A systematic literature search aiming to identify all possible publications on psoriasis and comorbidity was performed. The ATC codes were selected on the basis of labeling drugs having a treatment indication for concomitant diseases associated with psoriasis. ATC codes used to search for individual dispensed prescriptions are provided as supplementary table (S1). Dispensed prescriptions of these

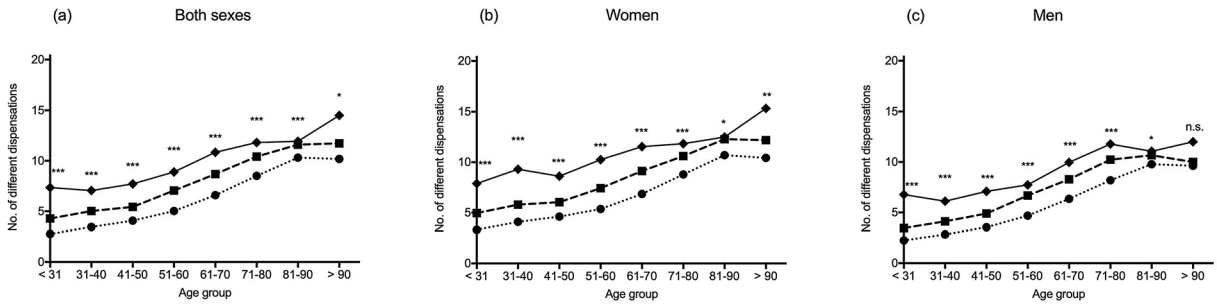

Fig. 1 Mean number of different dispensations during the study period (excluding psoriasis medication). Filled circle: control group; filled square: mild psoriasis; filled diamond: moderate-severe psoriasis. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ for Welch ANOVA test

medications during the study period were dichotomized into existing or non-existing for each individual in the target population.

Statistical Analysis

Data were processed into a Statistical Package for the Social Sciences (IBM SPSS version 24.0) data sheet for statistical analysis. Welch analysis of variance (ANOVA) test and post hoc Games-Howell test were used to explore differences in mean number of different dispensed prescriptions among controls, individuals with mild psoriasis and moderate-severe psoriasis groups after assessing for variance of homogeneity. Continuous data were described as mean ± SD. To estimate the relative risk of intake of medication the odds ratio (OR) presented with a 95% confidence interval (CI) was calculated using a binominal logistic regression and ORs were adjusted for age and sex and presented as such unless stated otherwise. Box-Tidwell procedures were applied to test for a linear relationship between the continuous independent variable age and the logit transformation of the dependent variable medication and revealed non-linearity; hence, the continuous variable age was categorized into eight age groups.

Compliance with Ethics Guidelines

The study was conducted according to the Declaration of Helsinki and approved by the Regional Ethical Review Board in Linköping, Sweden (2014/481-31, 2015/416-32). Data were anonymized prior to analysis.

RESULTS

Demographics of Patients and Controls

Of 4587 patients identified in the records with an established diagnosis of psoriasis (1.7% of the population), 2305 (50.3%) were female and 2282 (49.7%) were male. The age of the patients ranged from 18–103 years (57.4 ± 17.3) (S2); 268,949 individuals without psoriasis diagnosis served as controls (50% male and 50% female). The age of the controls ranged from 18–105 (49.7 ± 19.5) years.

One thousand one hundred eighty patients were classified as having moderate-severe psoriasis (0.4% of the population) by the intake of systemic psoriasis treatment; 605 (51.3%) of these patients were male, and 575 (48.7) were female. The most common dispensed systemic treatment for psoriasis was methotrexate (86.1%) followed by dimethylfumarate or acitretin (20.9%) and TNF inhibitors (19.9%) (S3).

Intake of Different Drugs During the Study Period

The mean number of different drugs (excluding systemic and topical anti-psoriatic medication) dispensed at least once during the study period by patients with mild psoriasis was 7.7 (± 4.6),

Table 1 Number, frequency and gender distribution of patients with psoriasis dispensed at least one prescription between 2008 and 2016 compared to controls

Comedication	ATC-code	Dispensed to patients with psoriasis (N = 4587) N (%)	Sex distribution (%)		Odds ratio (95% CI)	Adjusted odds ratio[b] (95% CI)	Significance level
			M (N = 2282)	F (N = 2305)			
Anti-infectives/oral antibiotics	J01	3754 (81.8)	47.3	52.7	2.09 (1.95–2.26)	1.95 (1.81–2.11)	***
Non-steroidal anti-inflammatory and anti-rheumatic drugs (NSAID)	M01A	3042 (66.3)	47.9	52.1	2.08 (1.96–2.21)	1.91 (1.79–2.04)	***
Other analgesics	N02B	2730 (59.5)	44.9	54.1	2.29 (2.16–2.43)	1.90 (1.79–2.04)	***
Opioids	N02A	2107 (45.9)	45.8	54.2	1.94 (1.83–2.05)	1.64 (1.55–1.75)	***
Topical anti-fungals	D01A	1984 (43.3)	48.5	51.5	4.89 (4.61–5.19)	4.50 (4.24–4.78)	***
Anxiolytics and sedatives	N05B	1896 (41.3)	40.1	59.9	1.88 (1.77–1.99)	1.63 (1.54–1.74)	***
	N05C						
Systemic corticosteroids	H02A	1675 (36.5)	45.1	54.9	2.31 (2.18–2.46)	2.07 (1.95–2.20)	***
Agents acting on the renin-angiotensin system	C09	1643 (35.8)	53.2	46.8	2.19 (2.06–2.33)	1.69 (1.57–1.81)	***
Beta-blocking agents	C07	1426 (31.1)	49.4	50.6	1.98 (1.86–2.11)	1.50 (1.40–1.61)	***
Antithrombotic agents	B01	1403 (30.6)	51.5	48.5	2.05 (1.93–2.19)	1.56 (1.45–1.68)	***
Antidepressants	N06A	1383 (30.2)	37.6	62.4	1.59 (1.49–1.70)	1.48 (1.39–1.58)	***
Antihistamines	R06	1381 (30.1)	40.8	59.2	1.47 (1.38–1.57)	1.56 (1.46–1.66)	***
Lipid-modifying agents	C10	1361 (29.7)	54.1	45.9	2.23 (2.09–2.38)	1.75 (1.63–1.88)	***
Diuretics	C03	1154 (25.2)	43.5	56.5	2.11 (1.97–2.26)	1.65 (1.52–1.78)	***
Drugs for obstructive airway disease	R03	1095 (23.9)	41.5	58.5	1.56 (1.46–1.68)	1.48 (1.38–1.58)	***
Calcium channel blockers	C08	1010 (22.0)	51.5	48.5	2.09 (1.95–2.25)	1.63 (1.50–1.76)	***
Anti-inflammatory opthalmologic agents	S01B	910 (19.8)	37.7	62.3	1.88 (1.75–2.03)	1.48 (1.37–1.59)	***
Corticosteroids and anti-infectives, combinations for ear and eye diseases	S03CA	899 (19.6)	43.0	57.0	1.82 (1.69–1.96)	1.68 (1.56–1.80)	***
Stomatologic preparations	A01A	782 (17.0)	37.0	63.0	1.85 (1.71–2.00)	1.58 (1.46–1.71)	***
Calcium, including combinations with vitamin D	A12A	713 (15.5)	28.5	71.5	2.16 (1.99–2.35)	1.78 (1.63–1.94)	***
Drugs used in diabetes	A10	618 (13.5)	51.3	48.7	2.23 (2.05–2.43)	1.79 (1.64–1.96)	***
Topicals for joint and muscular pain	M02	563 (12.3)	40.1	59.9	2.13 (1.94–2.32)	1.77 (1.62–1.94)	***
Vasodilators used in cardiac disease	C01D	548 (11.9)	58.8	41.2	1.96 (1.79–2.15)	1.51 (1.37–1.66)	***
Antimycotics/antifungals for systemic use	J02	498 (10.9)	32.9	67.1	1.79 (1.63–1.97)	1.86 (1.69–2.05)	***
	D01B						
Vasoprotectives (hemorrhoid and thrombophlebitis treatment)	C05	484 (10.6)	46.7	53.3	1.44 (1.31–1.58)	1.27 (1.15–1.39)	***
Drugs used in erectile dysfunction	G04BE	344 (7.5)	100	0	1.73 (1.54–1.93)	1.39 (1.24–1.58)	***
Drugs affecting bone structure and mineralization	M05B	317 (6.9)	22.1	77.9	2.08 (1.85–2.33)	1.67 (1.48–1.89)	***

Table 1 continued

Comedication	ATC-code	Dispensed to patients with psoriasis (*N* = 4587) *N* (%)	Sex distribution (%)		Odds ratio (95% CI)	Adjusted odds ratio[b] (95% CI)	Significance level
			M (*N* = 2282)	F (*N* = 2305)			
Nicotine and alcohol dependence drugs	N07BA	304 (6.6)	47.4	52.6	2.39 (2.13–2.70)	2.20 (1.96–2.48)	***
	N07BB						
Intestinal anti-inflammatory agents	A07E	237 (5.2)	49.7	50.3	3.91 (3.42–4.48)	3.79 (3.32–4.35)	***
Antipsychotics/neuroleptics	N05A	235 (5.1)	40.0	60.0	1.44 (1.26–1.64)	1.33 (1.16–1.52)	***
Antimigraine preparations	N02C	204 (4.4)	27.9	72.1	1.24 (1.08–1.43)	1.36 (1.18–1.57)	***
Vitamin A, D and analogs	A11C	186 (4.1)	31.2	68.8	1.27 (1.09–1.48)	1.19 (1.02–1.38)	*
Vitamin B1, B6 or 12	A11D	150 (3.3)	46.7	53.3	1.59 (1.32–1.83)	1.23 (1.04–1.45)	*
	A11E						
Immunosuppressive agents[a]	L04AA	35 (0.8)	49.7	50.3	1.22 (0.87–1.71)	1.20 (0.86–1.68)	ns
	L04AX						
Corticosteroids for otologic use	S02B	118 (2.6)	37.3	62.7	2.13 (1.77–2.57)	2.02 (1.68–2.44)	***
Anti-obesity preparations	A08A	93 (2.0)	32.3	67.7	2.23 (1.81–2.75)	2.14 (1.73–2.64)	***
Cardiac glycosides	C01A	60 (1.3)	55.0	45.0	1.49 (1.16–1.93)	1.16 (0.89–1.51)	ns
Antiarrhythmic drugs	C01B	49 (1.1)	63.3	36.7	1.82 (1.37–2.42)	1.39 (1.05–1.86)	*
Mineralocorticoids	H02AA	5 (0.1)	40.0	60.0	2.02 (0.83–4.94)	1.77 (0.73–4.34)	ns

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns $p > 0.05$

[a] Excluding apremilast, leflunomide, methotrexate and dimethylfumarate

[b] Odds ratio adjusted for age group and sex

Table 2 Number, frequency and gender distribution of patients with moderate-severe psoriasis dispensed at least one prescription during the study period compared to patients with mild psoriasis

Comedication	ATC code	Dispensed to patients with moderate-to-severe psoriasis (N = 1180) N (%)	Sex distribution (%)		Odds ratio (95% CI)	Adjusted odds ratio[b] (95% CI)	Significance level
			M (N = 605)	F (N = 575)			
Intestinal anti-inflammatory agents	A07E	164 (13.9)	50	50	7.37 (5.55–9.79)	7.49 (5.62–9.96)	***
Immunosuppressive agents[a]	L04AA L04AX	20 (1.7)	65	35	3.89 (1.99–7.64)	3.87 (1.97–7.58)	***
Systemic corticosteroids	H02A	683 (57.9)	48.5	51.5	3.35 (2.92–3.84)	3.49 (3.03–4.01)	***
Calcium, including combinations with vitamin D	A12A	313 (26.5)	33.2	66.8	2.71 (2.29–3.20)	3.16 (2.65–3.77)	***
Other analgesics	N02B	898 (76.1)	47.4	52.6	2.74 (2.36–3.18)	3.07 (2.62–3.59)	***
Topical for joints and muscular pains	M02	249 (21.1)	45.0	55.0	2.64 (2.19–3.16)	2.76 (2.29–3.32)	***
Non-steroidal anti-inflammatory and anti-rheumatic drugs (NSAID)	M01A	941 (79.7)	49.7	50.3	2.44 (2.09–2.87)	2.47 (2.11–2.89)	***
Drugs affecting bone structure and mineralization	M05B	123 (10.4)	78.0	22.0	1.92 (1.52–2.44)	2.41 (1.87–3.11)	***
Opioids	N02A	659 (55.8)	47.5	52.5	1.71 (1.49–1.96)	1.78 (1.55–2.04)	***
Anti-infectives/oral antibiotics	J01	1017 (86.2)	49.4	50.6	1.53 (1.27–1.84)	1.56 (1.29–1.88)	***
Diuretics	C03	325 (27.5)	37.2	62.8	1.18 (1.02–1.37)	1.43 (1.21–1.69)	***
Stomatologic preparations	A01A	236 (20.0)	35.2	64.8	1.31 (1.11–1.55)	1.37 (1.16–1.64)	***
Drugs for obstructive airway disease	R03	323 (27.4)	39.0	61.0	1.29 (1.11–1.49)	1.31 (1.12–1.52)	**
Agents acting on the renin-angiotensin system	C09	444 (37.6)	50.0	50.0	1.11 (0.96–1.27)	1.26 (1.08–1.47)	**
Antidepressants	N06A	397 (33.6)	38.5	61.5	1.25 (1.08–1.43)	1.27 (1.10–1.47)	**
Anxiolytics and sedatives	N05B N05C	530 (44.9)	41.7	58.3	1.22 (1.07–1.39)	1.26 (1.09–1.44)	**
Antihistamines	R06	390 (33.1)	57.9	42.1	1.20 (1.04–1.39)	1.22 (1.06–1.41)	**
Anti-inflammatory opthalmologic agents	S01B	248 (21.0)	36.7	63.3	1.10 (0.94–1.30)	1.21 (1.02–1.44)	*
Beta-blocking agents	C07	380 (32.2)	55.8	44.2	1.07 (0.93–1.24)	1.19 (1.02–1.39)	*
Nicotine and alcohol dependence drugs	N07BA N07BB	92 (7.8)	43.5	56.5	1.27 (0.99–1.64)	1.28 (0.99–1.65)	ns
Topical anti-fungals	D01A	536 (45.4)	48.7	51.3	1.13 (0.99–1.29)	1.13 (0.99–1.29)	ns
Anti-obesity preparations	A08A	31 (2.6)	32.3	67.7	1.46 (0.94–2.25)	1.48 (0.96–2.29)	ns
Corticosteroids for otologic use	S02B	29 (2.5)	31.0	69.0	0.94 (0.61–1.44)	0.95 (0.62–1.45)	ns

Table 2 continued

Comedication	ATC code	Dispensed to patients with moderate-to-severe psoriasis (N = 1180) N (%)	Sex distribution (%)		Odds ratio (95% CI)	Adjusted odds ratio[b] (95% CI)	Significance level
			M (N = 605)	F (N = 575)			
Antiarrhythmic drugs	C01B	15 (1.3)	66.7	33.3	1.27 (0.69–2.35)	1.42 (0.77–2.64)	ns
Antimycotics/antifungals for systemic use	J02 D01B	129 (10.9)	51.3	48.7	1.01 (0.82–1.25)	1.03 (0.83–1.27)	ns
Drugs used in diabetes	A10	156 (13.2)	47.4	52.6	0.97 (0.79–1.18)	1.03 (0.85–1.26)	ns
Lipid-modifying agents	C10	355 (30.1)	51.3	48.7	1.03 (0.89–1.19)	1.15 (0.98–1.35)	ns
Corticosteroids and anti-infectives, combinations for ear and eye disease	S03C	252 (21.4)	41.3	58.7	1.16 (0.98–1.36)	1.17 (0.99–1.38)	ns
Calcium channel blockers	C08	265 (22.5)	50.9	49.1	1.04 (0.88–1.21)	1.16 (0.98–1.38)	ns
Anti-thrombotic agents	B01	352 (29.8)	51.3	48.7	0.95 (0.83–1.10)	1.11 (0.94–1.30)	ns
Vasodilators used in cardiac disease	C01D	141 (11.9)	56.7	43.3	1.00 (0.82–1.23)	1.21 (0.97–1.50)	ns
Drugs used in erectile dysfunction	G04BE	86 (7.3)	100	0	0.96 (0.75–1.24)	1.03 (0.79–1.35)	ns
Anti-migraine preparations	N02C	60 (5.1)	28.3	71.7	1.21 (0.89–1.65)	1.29 (0.94–1.76)	ns
Anti-psychotics/neuroleptics	N05A	59 (5.0)	39.0	61.0	0.96 (0.71–1.31)	0.98 (0.72–1.32)	ns
Vasoprotectives (hemorrhoids and thrombophlebitis treatment)	C05	127 (10.8)	47.2	52.8	1.03 (0.83–1.28)	1.05 (0.85–1.30)	ns
Vitamin B1, B6 or 12	A11D A11E	27 (2.3)	59.3	40.7	0.63 (0.41–0.95)	0.66 (0.43–1.00)	ns
Vitamin A, D and analogs	A11C	56 (4.7)	33.9	66.1	1.26 (0.91–1.73)	1.28 (0.93–1.77)	ns
Cardiac glycosides	C01A	12 (1.0)	66.7	33.3	0.72 (0.38–1.36)	0.92 (0.48–1.77)	ns
Mineralocorticoids	H02AA	1 (0.1)	100.0	0.0	0.77 (0.08–6.46)	0.74 (0.08–6.66)	ns

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns $p > 0.05$

[a] Excluding apremilast, leflunomide, methotrexate and dimethylfumarate

[b] Odds ratio adjusted for age groups and sex

in all patients with psoriasis 8.2 (± 4.7) and in moderate-severe psoriasis 9.5 (± 4.7). In the control population the number was 5.1 (± 4.2). There were significant differences when comparing mean different dispensed prescriptions between controls, mild and moderate-severe psoriasis stratified by age groups and sex (with exemption for males > 91 years of age) (Fig. 1). Post hoc Games-Howell tests showed significant differences between controls and mild psoriasis, controls and moderate-severe psoriasis, and mild psoriasis and moderate-severe psoriasis for all age groups < 81 years.

Of the 268,949 control individuals 9.3% never received any prescribed medication from the pharmacy during the study period. Among these, 12.1% were male and 6.4% female. In all patients with psoriasis, 1.3% had not been dispensed a prescription drug during the study period (1.8% male and 0.8% female); 0.6% patients classified as having moderate-severe psoriasis were never dispensed any prescription from the studied ATC groups (1.0% male and 0.2% female).

Dispensations in Patients with Psoriasis vs. Controls

The three most common dispensed drug types were anti-infectives/oral antibiotics (81.8%), non-steroidal anti-inflammatory and anti-rheumatic drugs (NSAID) (66.3%) and other analgesics (59.5%) (Table 1). All three showing a fairly even sex distribution.

Individuals with psoriasis had an increased risk of having dispensed drug prescription for all ATC groups studied except for immunosuppressive agents, cardiac glycosides and oral mineralocorticoids (Table 1). The comedications with the highest odds ratio were topical anti-fungal agents OR of 4.50 (95% CI 4.24–4.78) followed by intestinal anti-inflammatory agents 3.79 (95% CI 3.32–4.35), drugs used against alcohol and nicotine addiction 2.20 (95% CI 1.96–2.48), anti-obesity treatment 2.14 (95% CI 1.73–2.64) and systemic corticosteroids 2.07 (95% CI 1.95–2.20).

Dispensations in Mild vs. Moderate-Severe Psoriasis

The most common dispensed drug types for patients with moderate-severe psoriasis were anti-infectives/oral antibiotics (86.2%), NSAIDs (79.7%) and other analgesics (76.1); 55.8% of patients with moderate-severe psoriasis received a prescription of opioids at least once during the study period. Intestinal anti-inflammatory agents (OR 7.49, 5.62–9.96), immunosuppressive agents (OR 3.87, 1.97–7.58) and systemic corticosteroids (OR 3.49, (3.03–4.01) were medications showing the largest difference in dispensation between patients with mild vs. moderate-severe disease (Table 2).

Sex and Comedication

Several comedication groups displayed uneven sex distribution. Drugs targeting osteoporosis (calcium, including combinations with vitamin D and drugs affecting bone structure and mineralization), anti-migraine treatment, anti-mycotics/-fungals, anti-inflammatory opthalmologic agents, stomatologic preparations, anti-histamines, psychiatric drugs (anxiolytics and sedatives, antidepressants, antipsychotics/neuroleptics), topicals for joint and muscular pain and anti-obesity preparations were more commonly dispensed to women with psoriasis whereas drugs targeting sexual dysfunction were solely dispensed to men. Vasodilators used in cardiac disease and antiarrhythmic drugs are more commonly dispensed to men (Table 1).

DISCUSSION

The present study represents a large population-based analysis to evaluate comedication in patients with psoriasis. The prescription data are unique compared to other studies in this field, since these are medications that are actually dispensed from the pharmacy to the patients. All comedications were obtained by the Swedish Prescribed Drug Register (PDR), which covers reliable and valid data on all

dispensed pharmaceuticals in Sweden since July 2005, hence giving a precise record of patients' medication [31]. Strict criteria were applied to define psoriasis diagnosis. The positive predictive value (PPV) of diagnostic codes in a similar electronic medical databases in Sweden has been shown to be 81–100% [32], and in the current study criteria for the definition of psoriasis was even more rigorous. Selection bias was minimized as data were collected from an entire population.

People with psoriasis had more different dispensed drug types during the study period compared to the control population. This difference was enhanced among individuals with moderate-severe psoriasis, suggesting that severe disease implies greater risk for high comorbidity. Differences in dispensed drugs were present in all age groups, but diminished in age groups > 80 years of age, being non-significant in male patients > 90 years of age. This could be attributable to the lower number of individuals in older age groups or to increased mortality in psoriasis patients with high comorbidity as suggested by Abuabara et al. [11]. Psoriasis patients had higher odds of receiving medication against IBD, addiction, components of the metabolic syndrome, osteoporosis, heart disease (except for cardiac glycosides), depression, anxiety, pain, prurigo, migraine, erectile dysfunction, obstructive lung disease and mouth and teeth disease. It is remarkable that only 1.3% of all patients with psoriasis in our study were without any prescription during the study period while the number in the general population is 9.3% (excluding systemic and topical anti-psoriatic medication). Our results reinforce the picture that comorbidity with need for treatment is common among individuals with psoriasis and that a multidisciplinary approach to patient care as suggested in the WHO global report on psoriasis is highly relevant [33].

Our results are generally in line with Gerdes et al. and Dowlatshahi et al. [27, 28] although differences exist such as the significantly increased prescription of anti-obesity preparations, drugs used in erectile dysfunction, opioids, drugs affecting bone structure and mineralization and drugs for nicotine and alcohol dependence in the current study. We also describe sex differences in comedication. Some are expected, such as the increased prescription of anti-migraine medication, depression and osteoporotic treatment among women with psoriasis due to the general heterogeneous sex distribution of these diseases. Other differences such as the increased use of systemic antimycotics/-fungals among women with psoriasis are noteworthy, especially since mucosal fungal infections may be facilitated by psoriasis IL-17 inhibition treatment. In light of the current results, IL-23 inhibitors could be preferable over IL-17 inhibitors when treating women with second-generation biologics. Anti-inflammatory opthalmologic agents and stomatologic preparations were more often dispensed to women with psoriasis and vasodilators used in cardiac disease, and antiarrhythmic drugs were more commonly dispensed to men with psoriasis, suggesting that sex can influence psoriasis comorbidity distribution.

It is noteworthy that in absolute terms the most common dispensed comedication among psoriasis patients was oral antibiotics, which is in concordance with the findings of Dowlatshahi et al. [28]. Bacterial infection is a common reason to contact the healthcare system and a possible trigger or aggravator of psoriasis. Patients with moderate-severe psoriasis were more likely to take oral antibiotics compared to patients with mild disease, suggesting that systemic anti-psoriatic treatment could make patients more sensitive to infections. A Danish nationwide cohort study published in 2015 showed that patients with IBD have a higher risk of invasive pneumococcal disease even before IBD diagnosis, which the authors speculate could be caused by an underlying impaired immune response [34]. Many studies on psoriasis have suggested that psoriasis patients' immune response may also be divergent, psoriasis susceptibility loci commonly carry immune related genes and psoriasis patients have fewer skin infections but more bacteremia [8, 34, 35]. Screening for streptococcal throat infections in patients with psoriasis may in part be an explanation for the increased prescription of oral antibiotics. However, our results suggest a need for further studies on infections, antibiotics and psoriasis.

Apart from oral antibiotics, analgesics, NSAIDs and opioids were the most common dispensed comedications in psoriasis patients in this study. Concomitant psoriatic arthritis could in part explain this result but the dispensation of pain medication (79.6%) is more common than in previous published reports on psoriatic arthritis occurrence [36]. It is suggested that psoriasis skin lesions often are perceived as painful and that drugs can be a way to alleviate this symptom [16, 37]. Furthermore, imaging studies have shown that clinically asymptomatic patients with psoriasis often exhibit subclinical enthesitis [36], suggesting that PsA is more common than previously recorded. The methodology of the current study cannot clarify whether psoriasis arthritis/enthesitis caused pain and subsequent dispensation. It is likely that other painful conditions may have occurred during the study period. Nevertheless, our data suggest that pain could be a symptom overlooked when treating patients with psoriasis and that this may be a topic for further research. The increased risk of opioid dispensation among patients with psoriasis is important since it could contribute to addiction apart from being a sign of PsoA under treatment.

Neurologic and psychiatric disorders are associated with psoriasis. Stroke, migraine and multiple sclerosis (MS) are the reported neurologic diseases, while depression, bipolar mood disorder, anxiety, psychosis, sexual disorders and sleep disturbance are psychiatric presentations in patients with psoriasis [38]. In the present study significantly increased dispensation of medication such as anticoagulant drugs, migraine treatment, neuroleptics, benzodiazepines, sedatives and antidepressants were found. Moderate-to-severe disease increased the odds for dispensation of drugs targeting anxiety and depression compared to mild disease.

Hypertension is a common comorbidity and is even associated with an increase in psoriasis incidence [39, 40]. Several studies have shown that psoriasis and psoriasis severity are associated with a lack of hypertensive control [41, 42]. This implies that psoriasis patients with hypertension could require parallel treatment with several antihypertensive drugs. In the current study, psoriasis was associated with higher risks of having ACE inhibitors and angiotensin II receptor antagonists, diuretics, calcium-channel blockers and beta-blockers with patients with severe disease having higher ORs compared to those with mild disease for all ATC groups but calcium channel blockers.

There are some limitations to our study. Prescriptions were limited to a number of ATC codes associated to known psoriasis comorbidity, and a complete prescription analysis including all ATC codes would have been desirable to draw conclusions on the total amount of comedication. We cannot be entirely sure about validation of the psoriasis diagnosis despite the strict criteria aiming to enhance PPV. The prevalence of psoriasis in the Jönköping region according to the present data is 1.7% and is near the expected prevalence between 2 and 3%. A Swedish medical records-based study from 2014 with a similar methodology reported a prevalence of 1.23% [1, 32]. Psoriasis patients with no or few health care visits or visits without psoriasis diagnosis being recorded will have been included in the control group, leading to an underestimation of the prevalence. It is possible that such cases would mainly have mild disease or psoriasis in total remission. However, in our study 25.7% of individuals were classified as having moderate-to-severe disease on the basis of having systemic treatment; this is exactly the same figure as found in the NORPAPP study on psoriasis from Nordic countries with a self-reported methodology [43].

The stratification of psoriasis severity using systemic treatment risks misclassification in cases where patients have comorbid conditions treated with the same drug types, i.e., a patient with mild psoriasis and adalimumab-treated IBD, would be classified as having severe psoriasis. Considering this, it is noteworthy that the most common immunosuppressive agent being dispensed to psoriasis patients is azathioprine (66% of cases). Azathioprine has an IBD indication, and misclassification as described could increase the OR of moderate-severe psoriasis patients being dispensed immunosuppressive drugs. Our methodology does not address psoriasis disease onset. We can assume that a majority of individuals classified as having

psoriasis in the study would have acquired the disease before the study period. However, in the cases where disease onset occurs within the study period, any medication dispensed before this event will also have been accounted for as belonging to the psoriasis group.

CONCLUSIONS

The level of comedication found in the present study reinforces the evidence of the high comorbidity load associated with psoriasis. Painkillers and antibiotics are the most commonly dispensed comedications, suggesting that clinicians should be vigilant when it comes to undertreated PsA and infections in general. Results also show that sex in part influences comedication risk, suggesting that not all comorbid diseases have an even sex distribution. Comorbidity highly influences the total morbidity, healthcare costs and socioeconomic burden of psoriasis. It has been estimated that a third of productivity losses in psoriasis patients are attributed to psoriasis while comorbidity accounts for the rest [44]. We suggest that addressing comorbidities early and working with prevention are beneficial not only for patients but also a valuable investment for the society as a whole.

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Compliance with Ethic Guidelines. This study was conducted according to the Declaration of Helsinki and approved by the Regional Ethical Review Board in Linköping, Sweden (2014/481-31, 2015/416-32).DATA. Data were anonymized prior to analysis.

Data Availability. The datasets generated during the current study are available from the corresponding author on reasonable request.

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