

CLINICAL REPORT

Increased Antidepressant Drug Exposure in Psoriasis Patients: A Longitudinal Population-based Cohort Study

Emmilia A. DOWLATSHAHI¹, Marlies WAKKEE¹, Ronald M. C. HERINGS^{2,3}, Loes M. HOLLESTEIN¹ and Tamar NIJSTEN¹
Departments of ¹Dermatology and ³Health Policy and Management, Erasmus Medical Center, Rotterdam, and ²PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

Psoriasis has a major impact on health-related quality of life. The present cohort study investigated the use of antidepressant drugs in psoriasis patients and a reference cohort, using pharmacy and hospitalization data from 1998 to 2008 for more than 2.5 million Dutch residents. Multivariate Cox regression was used to compare the risk of first antidepressant use, and Poisson regression to compare the number of episodes of antidepressant use. A total of 25,691 psoriasis cases and 128,573 reference subjects were followed for more than 9 years. The incidence of first antidepressant use was 21 and 9 per 1,000 person years, respectively, and the adjusted hazard ratio (HR) was 1.55 (95% confidence interval (CI) 1.50–1.61). Within the psoriasis cohort, the HR of receiving an antidepressant was significantly higher after the first antipsoriatic treatment (HR 1.07, 95% CI 1.02–1.12). Psoriasis patients have a two-fold increase in antidepressant use, the period after antipsoriatic treatment being characterized by a further increase in antidepressant drug dispenses. Key words: psoriasis; cohort study; antidepressant use; comorbidity; pharmacoepidemiology.

Accepted Oct 15, 2012; Epub ahead of print Mar 25, 2013

Acta Derm Venereol 2013; 45: 544–550.

Tamar Nijsten, Department of Dermatology, Erasmus Medical Center, Burgemeester s'Jacobplein 51, NL-3015 CA Rotterdam, The Netherlands. E-mail: t.nijsten@erasmusmc.nl

In recent years much attention has been drawn to psychiatric disorders among patients with dermatological conditions, often referred to as “psychodermatology” (1). Reports of suicidal ideation among patients with skin diseases have led to increasing concerns (2, 3). In psoriasis, studies have demonstrated a significant impairment of health-related quality of life (HRQoL) and a higher likelihood of developing depression (4). Although the correlation between severity of psoriasis and impact on HRQoL is weak (5), the chance of psychiatric comorbidity seems to increase with the severity of psoriasis (6). Two large healthcare-database studies, focussing on major psychiatric disorders, have confirmed a significant and positive association with psoriasis (6, 7). Remarkably, the practical implications of actual antidepressant drug dis-

penses have received only limited attention. Two studies have investigated drug prescriptions in general, including antidepressants in psoriasis patients, during a restricted time-period: one cross-sectional study showed that, at the time of hospital admission, psoriasis patients had a 1.4-times higher risk of using an antidepressant drug compared with healthy individuals (8), while another case-control study focusing on the period 3 years before the date of psoriasis diagnosis observed no increased use of antidepressants (9). Furthermore, other studies investigated self-reported assessment of depressive symptoms, which can bias the outcome definition (4, 10–12), and had a cross-sectional study design, a limited sample size, or lacked a comparative control group.

The objective of the present study was to longitudinally compare antidepressant use and episodes in psoriasis patients from 1997 to 2008 with a non-psoriatic reference cohort from a large sample of the general population, focusing specifically on the time before, during and after treatment initiation for psoriasis.

MATERIALS AND METHODS

Data source

Data were retrieved from the Pharmo Record Linkage system, a large patient-centric data network linking multiple observational databases, including drug dispensing and hospitalization data for approximately 2.5 million residents in the Netherlands (13, 14). Information on each prescription includes product name, Anatomical Therapeutic Chemical (ATC) classification of the drug, date of dispensing, quantity dispensed, dosage and regimen.

Study population

Psoriasis patients were identified using a previously described algorithm based on dispensed drugs and hospitalizations for psoriasis and psoriatic arthropathy (15–17). The index date for psoriasis patients was the date of the first available active treatment for psoriasis, varying from topical corticosteroids to systemic antipsoriatic therapies. The reference population consisted of subjects without psoriasis, who were assigned a random index date. Five reference subjects were randomly selected for every psoriasis patient, using frequency matching for the index date.

The eligibility date represents the date of first registration in a pharmacy linked to the Pharmo system. Between 1997 and 2008 all subjects were followed from the eligibility date to the year of last available prescription, the date when registered subjects moved away, or the date of death, whichever came first.

Drug exposure

Antidepressants (ATC code N06A) were selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) or other antidepressants. The start of an episode of antidepressant use was defined as the date of dispensing of the first prescription for any antidepressant. The length was the number of days for which the prescribed quantity and prescribed dosage would suffice, and the end of an episode was defined as no new prescription within 4 months after the end date of the last antidepressant prescription. According to the American College of Neuropsychopharmacology and other guidelines, recovery from a major depressive episode can be ascribed after at least 4 months of remission have been ascertained (18, 19). An episode of antidepressant use is not equivalent to a major depressive episode, which is based on assessment of depressive symptoms; however according to the available recommendations, this seemed to be the most appropriate way to define an episode.

Covariates

The covariates gender and age at eligibility date included in the multivariate models were determined *a priori*. In order to adjust for comorbidities, we calculated the number of unique prescriptions at ATC second level (number of unique therapeutic main groups) during the 6 months before the index date. This method has been described previously (16). To avoid over-adjustment, we excluded antidepressants from this count.

Statistical analyses

Student's *t*-test was used to test for differences between continuous variables and χ^2 test for categorical variables. To quantify first antidepressant use we calculated incidence rates (IR) per 1,000 person years with 95% confidence interval (CI). Multivariable Cox proportional-hazards analyses compared hazards for the first antidepressant use between the 2 cohorts. We verified that the hazards for categorical variables were proportional using the log minus log function. Poisson regression model compared IRs of number of episodes of antidepressant use, where observation time from eligibility date until the end of follow-up was used as an offset. To investigate the pattern of antidepressant use, we calculated cumulative IRs and incidence rate ratios (IRR) of episodes of antidepressant use in both cohorts for the entire follow-up using time windows of 6

months, and plotted these rates with their respective 95% CI against time since diagnosis of psoriasis (± 10 years).

We conducted an internal comparison within the psoriasis cohort using psoriasis patients as their own controls and calculated the hazard ratio (HR) of antidepressant use before and after the index date using Cox proportional hazards model with robust standard errors (20). We report the mean number of episodes before and after the index date and the IRR using generalized estimating equations (GEE) for counts with unstructured correlation matrix, robust standard errors and exposure time as an offset (21).

Sensitivity analyses

We analysed antidepressant use 7 months before and after the index date (4 months is the maximum duration between 2 prescriptions in the same episode and 3 months is the usual maximum duration of a prescription in the Netherlands) and also in an analysis excluding the time around the index date.

The effect of disease severity was studied, whereby dispensing of topical antipsoriatic medication served as a proxy for mild disease and systemic psoriasis medication and hospitalization for psoriasis as a proxy for moderate to severe disease.

Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and SPSS version 17.0 (SPSS inc., Chicago, IL, USA).

The present study was conducted and reported according to the guidelines elaborated in the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) (22).

RESULTS

Study population

This study included 25,691 psoriasis patients and 128,573 reference subjects. Gender distribution was similar in the cohorts, while the mean age was 6 years higher in the psoriasis cohort (Table I). In both cohorts the mean follow-up time was approximately 9.5 years. Antidepressant use was more than twice as frequent in psoriasis subjects as in the reference population (17.8%

Table I. Baseline characteristics of the reference and psoriasis cohorts

	Reference cohort	Psoriasis cohort	<i>p</i> -value
Total number of subjects (<i>n</i> =154,264), <i>n</i> (%)	128,573 (83.3)	25,691 (16.7)	
Gender, male, <i>n</i> (%)	62,141 (48.3)	12,494 (48.6)	0.38
Age at eligibility date, years, median (interquartile range)	33.0 (18.0; 50.0)	42.0 (28.0; 56.0)	<0.001
Years of follow-up ^a , mean	9.38	9.46	
Antidepressant use			
Any antidepressant, <i>n</i> (%)	10,137 (7.88)	4,576 (17.81)	<0.001
Selective serotonin reuptake inhibitor, <i>n</i> (%) ^b	6,630 (5.16)	3,014 (11.73)	<0.001
Tricyclic antidepressant, <i>n</i> (%) ^b	3,336 (2.59)	1,650 (6.42)	<0.001
Other antidepressants, <i>n</i> (%) ^b	2,784 (2.16)	1,359 (5.29)	<0.001
Episodes of antidepressant use, <i>n</i> (%)			
1	6,326 (4.92)	2,593 (10.09)	<0.001
2	2,020 (1.57)	959 (3.73)	
3	803 (0.62)	471 (1.83)	
4	435 (0.34)	239 (0.93)	
5	234 (0.18)	127 (0.49)	
≥6	300 (0.23)	167 (0.65)	

^aYears of follow-up from eligibility date to the end of follow-up in Pharmo database.

^bValues do not add up to sum of all antidepressants because patients could have more than one type of antidepressant.

Table II. First antidepressant use in reference and psoriasis cohorts

	Reference cohort	Psoriasis cohort
First antidepressant use	10,137	4,576
Person years ^a	1,148,051	215,562
IR/1,000 person years (95% CI)	8.83 (8.66–9.00)	21.23 (20.61–21.84)
Crude hazard ratio (95% CI)	1	2.37 (2.29–2.45)
Adjusted hazard ratio ^{b,c}	1	1.55 (1.50–1.61)

^aSum of number of person years from eligibility date to date of first prescription for an antidepressant or to the end of follow-up in Pharmo database.

^bAdjusted for age, gender and number unique prescriptions 6 months before index date.

^cCOX regression.

IR: Incidence rate; CI: confidence interval.

vs. 7.9%, $p < 0.001$). In particular, SSRIs were the most commonly prescribed antidepressants in both populations (Table I). Multiple episodes of antidepressant use were observed in 7.6% of the psoriasis and 2.9% of the reference population ($p < 0.001$).

Antidepressant use in the psoriasis cohort compared with the reference population

First antidepressant use. The unadjusted incidence rate (IR) of antidepressant use per 1,000 person years was significantly increased in psoriasis patients (21.2, 95% CI 20.6–21.8) compared with the reference population (8.8, 95% CI 8.7–9.0). The crude HR was 2.37 (95% CI 2.29–2.45), demonstrating that psoriasis patients were approximately 2.4 times more likely to use antidepressant drugs without adjusting for factors that may confound this association (Table II).

Adjusting for age and gender had only a limited effect on the HR (adjusted HR 2.19, 95% CI 2.11–2.27), while adjusting for unique prescriptions dispensed 6 months before index date had a remarkable effect, since the HR decreased to 1.55 (95% CI 1.50–1.61), but remained significant.

Episodes of antidepressant use. Psoriasis patients had more than twice as many episodes of antidepressant use than the reference population, 37 vs. 15 per 1,000 person years (IRR 2.54, 95% CI 2.48–2.61) (Table III). After Poisson regression, the adjusted HR of 1.47 (95%

Table III. Episodes of antidepressant use in reference and psoriasis cohorts

	Reference cohort	Psoriasis cohort
Episodes of antidepressant use, <i>n</i>	18,070	8,961
Person years ^a	1,206,416	242,934
IR/1,000 person years, 95% CI	14.98 (14.76–15.20)	36.89 (36.12–37.65)
Crude IRR, 95% CI	1	2.54 (2.48–2.61)
Adjusted IRR ^{b,c} , 95% CI	1	1.47 (1.43–1.51)

^aSum of number of person years from eligibility date to the end of follow-up in Pharmo database.

^bAdjusted for age, gender and number unique prescriptions 6 months before index date.

^cPoisson regression using entire follow-up time of each patient as offset.

IR: Incidence rate; IRR: Incidence rate ratio; ICI: confidence interval.

CI 1.43–1.51) was comparable to the adjusted HR of the analysis on first antidepressant use.

We compared IRs of episodes of antidepressant use in the psoriasis cohort with those of the reference population during 10 years before and after first treatment for psoriasis (index date) (Fig. 1) and plotted the cumulative IRRs (Fig. 2). The IRRs gradually increased from 2.17 10 years before to 2.48 1.5 years before first antipsoriatic treatment. The IRRs were highest within the first 6 months after psoriasis treatment, namely 2.79, and slowly decreased in the 5 years thereafter to reach a plateau at an IRR of approximately 2.64 until the end of follow-up after 10 years. Looking at the entire period before and after the index date and excluding the year around the index date, the IRR for episodes of antidepressant use is higher in the years after the index date than in the years before. If we adjusted these crude rates for age, gender and comorbidity, the risk of dispensing an antidepressant was reduced, but still remained 50% higher in the psoriasis cohort. The adjusted risk of antidepressant use followed the pattern of the crude data, by peaking around the index date (adjusted HR 7 months before index date 1.54, 95% CI 1.39–1.71, adjusted HR 7 months after index date 1.89, 95% CI 1.70–2.09) and when excluding the 7 months before and after index date, the adjusted HR were higher in the years after (adjusted HR 1.73, 95% CI 1.65–1.81) than before the index date (adjusted HR 1.33, 95% CI 1.25–1.42).

Internal comparison of antidepressant use within the psoriasis cohort

When restricting the analysis to the psoriasis cohort and comparing antidepressant use before and after the index date, psoriasis patients were approximately 7% more likely to receive antidepressant drugs after the index date, when controlling for within-patient variation using the GEE model (HR 1.07, 95% CI 1.02–1.12) (Table IV). However, there was no significant difference in the mean number of episodes before and after the index date, 0.035 and 0.037, respectively (IRR 1.03, 95% CI 0.98–1.09, $p = 0.26$).

Effect of psoriasis severity on antidepressant drug use

Patients with mild psoriasis had a 2.3-times higher risk (95% CI 2.23–2.40) of using antidepressant drugs compared with reference subjects. In a multivariate COX regression model, the age, gender and comorbidity adjusted HR for antidepressant use remained significant (adjusted HR 1.55, 95% CI 1.49–1.61) in this subgroup of patients. Patients with more severe psoriasis had a crude HR of 2.81 (95% CI 2.59–3.04) and an adjusted HR of 1.57 (95% CI 1.44–1.70) compared with the non-psoriasis cohort. Psoriasis patients with severe disease were at a higher risk of having a

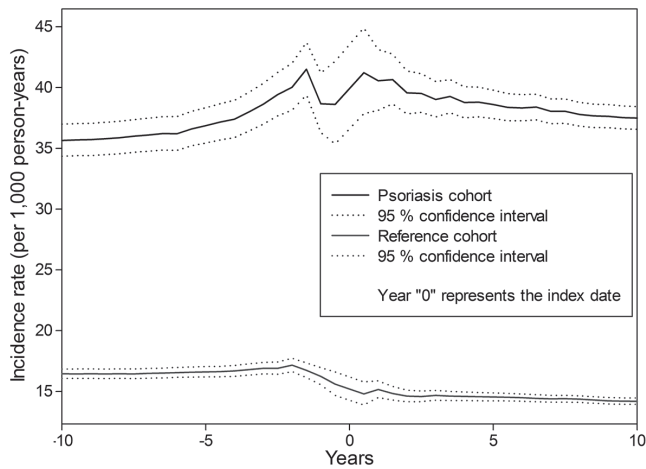


Fig. 1. Incidence rates of antidepressant use in psoriasis and reference cohorts.

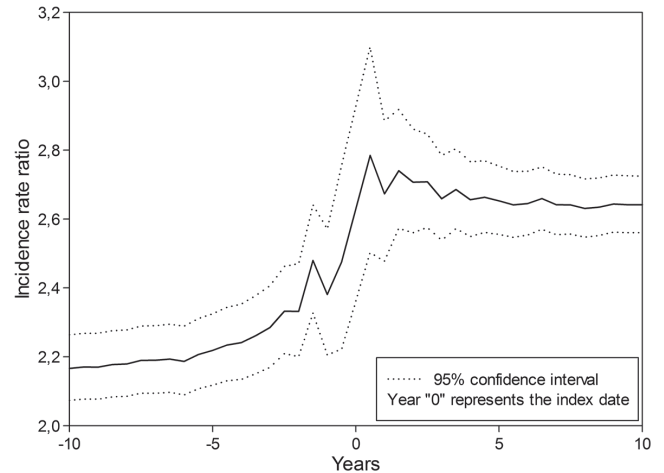


Fig. 2. Incidence rate ratio of antidepressant use in the psoriasis cohort compared with the reference population.

first antidepressant than patients with mild disease, with an overall p -value < 0.001 .

DISCUSSION

This study shows that dispensing of antidepressants is two-fold higher in psoriasis patients and that they have twice as many episodes of antidepressant use than the reference population. The longitudinal study design enabled us to demonstrate that antidepressant use is already increased before psoriasis patients seek medical treatment for their skin and that it peaks around the time of treatment initiation, but also remains increased thereafter.

Our outcomes are in line with prescription data from German hospitalized psoriasis patients, showing a 1.4-times higher risk of using an antidepressant (8) and are also comparable to the 1.4–1.5-times higher risk of major psychiatric disorders in psoriasis observed in the General Practice Database from the UK and

an interdisciplinary administrative outpatient database from Germany (6, 7).

Adjusting for unique number of prescription drugs 6 months prior to the index date, as a proxy for the general healthcare consumption pattern, resulted in a considerable decrease in the risk of using an antidepressant. This effect could be explained by detection bias, i.e. patients with psoriasis visit their physician more often, which equally increases their risk of diagnosis and treatment of other diseases, including depression (23). This effect was also confirmed by other studies, showing that the likelihood of being diagnosed with depression increases with the number of physician visits due to psoriasis (6) and that, on average, psoriasis patients with severe disease receive more different systemic drugs than the general population (8).

The increased risk of antidepressant use after adjustment may be explained by the effect of psoriasis on the HRQoL, leading to stigmatization, shame, difficulties in daily activities and coping problems (11, 24–26), which

Table IV. Analysis of antidepressant use within the psoriasis cohort before and after index date (n = 25,691)

	Before index date	After index date
First antidepressant use in psoriasis patients		
Antidepressant users, <i>n</i>	1,977	3,480
Person years ^a , <i>n</i>	74,369	148,241
IR/1,000 person years, 95% CI	26.58 (25.41–27.76)	23.48 (22.70–24.26)
Hazard ratio ^b (95% CI)	1	1.07 (1.02–1.12)
Episodes of antidepressant use in psoriasis patients		
Episodes of antidepressant use, <i>n</i>	2,810	6,151
Person years ^c , <i>n</i>	78,871	164,064
IR/1,000 person years, 95% CI	35.63 (34.31–36.95)	37.49 (36.55–38.43)
Mean number of episodes, 95% CI	0.035 (0.033–0.037)	0.037 (0.033–0.041)
IR ratio ^d , 95% CI	1	1.032 (0.977–1.090)

^aSum of number of person years from eligibility date to date of first antidepressant or to index date (for analysis before the index date) and from index date to first antidepressant after index date or to the end of follow-up in Pharmo database (for analysis after the index date).

^bCox proportional hazard model with robust standard errors.

^cSum of number of person years from eligibility date to index date (for analysis before the index date) and from index date to the end of follow up in Pharmo database (for analysis after the index date).

^dPoisson regression model using generalized estimating equations with unstructured correlation matrix and robust standard errors.

IR: Incidence rate; CI: confidence interval.

may result in depressive symptoms (27). An alternative explanation may be reverse causality; depression may lead to self-neglecting behaviour, isolation and therefore induces lifestyle changes, such as smoking, alcoholism and obesity, which in turn can lead to increased inflammation and eventually to psoriasis. However, since the effects of generalized inflammation mostly become apparent after a long induction period, the association between depression, lifestyle changes and psoriasis would take years to manifest itself (28, 29). Genetics could play a role in the association between psoriasis and depression. Genome-wide association studies on psoriasis susceptibility loci (30–34) and on genes for major depressive disorder (35) showed no common genes. However, a recent study on inflammation-related genes in depression identified that the gene PSMB4, critical for T-cell function, was associated with susceptibility to major depressive disorder (36). Susceptibility to psoriasis has also been associated with the area of chromosome 1q21 (PSORS4) that encodes for the PSMB4 gene (34).

The pattern of antidepressant use in this study shows 3 discernable periods (Fig. 2): first, during the years before the index date, antidepressant use gradually increases and reaches a maximum in the proximity of the index date. Thereafter, antidepressant use does not decline to its level from before the index date, but remains constantly high and reaches a plateau until the end of follow-up. The use of antidepressant drugs remained increased after the index date, also when adjusting for confounders. Assuming that the index date represents the date of first diagnosis of psoriasis, the period of more than one year before the index date would represent a period without active psoriasis or where psoriatic disease has not yet manifested itself. The risk difference of antidepressant use between the 2 cohorts in this first period may, therefore, be explained by intrinsic factors at work, such as unhealthy lifestyle factors, different healthcare consumption attitudes and genetic factors, leading to higher use of antidepressants than in subjects who do not develop psoriasis. Interestingly, other studies have shown that psoriasis patients are already more obese before the manifestation of psoriatic disease (28), which may also lead to depression (37). We then observed a deviation of antidepressant use starting 1.5 years prior to the first dispensing of antipsoriatic medication until 1.5 years thereafter in the psoriasis cohort and in the analyses comparing the psoriasis cohort with the reference population. This increase in antidepressant use may not merely be explained by increased healthcare consumption in psoriasis patients. Antidepressant use attains a maximum around the index date, whereupon the patient seeks medical care due to psoriasis *de novo* or exacerbation of disease, and thus the severity of disease in this acute phase may have a more pronounced impact on the psychological condition of the patient.

If there is a causal relationship between psoriasis and depression, then this may be reflected in the risk difference of 0.5 comparing the period before and after the index date (Fig. 2) where the IRR of antidepressant use increases from 2.2 to 2.7. The observation that, beyond the index date, the risk of antidepressant use does not return to the level prior to the index date suggests that it remains difficult to control psoriasis in the long-term, and that disease severity remains relatively stable in time (38). Therefore, the significant increase in risk of antidepressant dispensing beyond the index date could be attributed to the impact of chronic skin disease on patients' HRQoL. On the other hand, a study comparing QoL scores in an 11-year period demonstrated a significant decrease of approximately 25% in the overall psychosocial impact of psoriasis on patients' HRQoL, suggesting that this group of patients accommodate to the impact of their disease over time (39).

Strengths and limitations

The present study is the largest population-based longitudinal study comparing antidepressant prescriptions during an almost 10-year observation period in psoriasis patients to a reference cohort. It is based on prescription data from 2.5 million Dutch residents, and is therefore well representative of the Dutch population. The longitudinal study design enabled us to focus in detail on drug prescriptions around the time of initiation of psoriasis therapy. Besides analyzing unique prescriptions, we also investigated multiple episodes of antidepressant use, which resulted in comparable outcomes. The obtained risk estimates confirm the estimates found in studies on the association between psoriasis and major psychiatric disorders (6, 7), also strengthening our definition of depressive episodes based on antidepressant prescription data. We are aware that antidepressant drug use does not imply the diagnosis of depression, but may also represent other psychiatric morbidities. In the Dutch general practice, 45% of antidepressant users had depression, 17% had anxiety and panic disorders, and 9% had sleeping disorders (40).

Our definition of psoriasis was based on a drug and hospitalization algorithm; nevertheless it had a 98.2% sensitivity and a 80.2% specificity (16). This could result in non-differential misclassification of psoriasis cases, which might lead to underestimation of the effect of psoriasis on antidepressant use. As is also the case in other secondary database studies, residual confounding was likely because data on potential confounders, such as weight, smoking, alcohol consumption, physical activity or socioeconomic status, were not available. However, the risk estimates were stable across the different analyses including the within patient analysis, in which the effect from unmeasured confounding factors

between psoriasis cases and reference subjects was attenuated. We calculated the exposure to antidepressants from dispensed pharmacy prescriptions assuming good drug compliance. However, the rate of non-adherence to antidepressant treatment can vary from 40% to 75% (41), especially among long-term users, which was not the objective of this study. Although the mean follow-up was almost a decade, it is possible that patients had depression before they were registered in the database, resulting in non-differential misclassification. To minimize the impact of this bias, prevalent antidepressant users ($n = 143$) who had changed pharmacists and who had an antidepressant drug dispensed in the first pharmacy where they were registered, were excluded from the analysis.

Conclusion

Psoriasis patients use more antidepressant medication than the general population, especially at the time when they seek medical care for their psoriasis and thereafter. Physicians should be aware that patients who seek care for chronic dermatological conditions such as psoriasis may have an increased risk of experiencing psychological or psychiatric disorders.

ACKNOWLEDGEMENTS

The authors would like to thank M. Molas, from the Department of Biostatistics of the Erasmus Medical Centre, for his help in programming macros for SAS and advice on the statistical methods.

Funding source: This study was sponsored by an unrestricted grant from Abbott.

Conflicts of interest: E. A. Dowlatshahi, M. Wakkee and L. M. Hollestein have no conflicts of interest to declare. T. Nijsten served as speaker and consultant for Abbott, Celgene, Leo Pharma, Schering Plough (Merck) and Wyeth (Pfizer). As an employee of the PHARMO Institute dr. R.M.C. Herings is not allowed to have any personal profit from contacts with clients, i.e. pharmaceutical industry or others. The absence of personal financial rewards for dr. R.M.C. Herings is true for all studies and all activities he is involved in. He does not own shares, does not get any income for any patent, does not profit from any profit-sharing arrangement, does not receive royalties, nor does he receive any form of personal financial benefit.

REFERENCES

- Gupta MA, Gupta AK. Psychodermatology: an update. *J Am Acad Dermatol* 1996; 34: 1030–1046.
- Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; 139: 846–850.
- Picardi A, Mazzotti E, Pasquini P. Prevalence and correlates of suicidal ideation among patients with skin disease. *J Am Acad Dermatol* 2006; 54: 420–426.
- Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. *Dermatology* 2006; 212: 123–127.
- Sampogna F, Sera F, Abeni D, Investigators IDIMPRoVE. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. *J Invest Dermatol* 2004; 122: 602–607.
- Schmitt J, Ford DE. Psoriasis is independently associated with psychiatric morbidity and adverse cardiovascular risk factors, but not with cardiovascular events in a population-based sample. *J Eur Acad Dermatol Venereol* 2010; 24: 885–892.
- Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010; 146: 891–895.
- Gerdes S, Zahl VA, Knopf H, Weichenthal M, Mrowietz U. Comedication related to comorbidities: a study in 1203 hospitalized patients with severe psoriasis. *Br J Dermatol* 2008; 159: 1116–1123.
- Naldi L, Chatenoud L, Belloni A, Peserico A, Balato N, Virgili AR, et al. Medical history, drug exposure and the risk of psoriasis: evidence from an Italian case-control study. *Dermatology* 2008; 216: 125–130.
- Leibovici V, Canetti L, Yahalomi S, Cooper-Kazaz R, Bonne O, Ingber A, et al. Well being, psychopathology and coping strategies in psoriasis compared with atopic dermatitis: a controlled study. *J Eur Acad Dermatol Venereol* 2010; 24: 897–903.
- Sampogna F, Chren MM, Melchi CF, Pasquini P, Tabolli S, Abeni D, et al. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *Br J Dermatol* 2006; 154: 325–331.
- Devrimci-Ozguven H, Kundakci TN, Kumbasar H, Boyvat A. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. *J Eur Acad Dermatol Venereol* 2000; 14: 267–271.
- PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands. Available from: <http://www.pharmo.nl/>.
- Herings RMC. Pharmo, a record linkage system for post marketing surveillance of prescription drugs in the Netherlands. In: Thesis Department of Pharmacoepidemiology and Pharmacotherapy Utrecht. The Netherlands: Utrecht University, 1993.
- Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. *J Am Acad Dermatol* 2011; 65: 1135–1134.
- Wakkee M, Meijer W, Neumann HA, Herings RM, Nijsten T. Psoriasis may not be an independent predictor for the use of cardiovascular and anti-diabetic drugs: a 5-year prevalence study. *Acta Derm Venereol* 2009; 89: 476–483.
- Wakkee M, Herings RM, Nijsten T. Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based Dutch cohort. *J Invest Dermatol* 2010; 130: 962–967.
- Prien RF, Kupfer DJ. Continuation drug therapy for major depressive episodes: how long should it be maintained? *Am J Psychiatry* 1986; 143: 18–23.
- Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 2006; 31: 1841–1853.
- Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. *J Amer Stat Assoc* 1989; 84: 1074–1078.
- Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988; 44: 1049–1060.
- Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC,

- Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; 18: 805–835.
23. Nijsten T, Wakkee M. Complexity of the association between psoriasis and comorbidities. *J Invest Dermatol* 2009; 129: 1601–1603.
 24. Ginsburg IH, Link BG. Feelings of stigmatization in patients with psoriasis. *J Am Acad Dermatol* 1989; 20: 53–63.
 25. Hrehorow E, Salomon J, Matusiak L, Reich A, Szepletowski JC. Patients with psoriasis feel stigmatized. *Acta Derm Venereol* 2012; 92: 67–72.
 26. Sampogna F, Tabolli S, Abeni D, investigators IDIM-PRoVE. Living with psoriasis: prevalence of shame, anger, worry, and problems in daily activities and social life. *Acta Derm Venereol* 2012; 92: 299–303.
 27. Kotrulja L, Tadinac M, Joki-Begi NA, Gregurek R. A multivariate analysis of clinical severity, psychological distress and psychopathological traits in psoriatic patients. *Acta Derm Venereol* 2010; 90: 251–256.
 28. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Arch Intern Med* 2007; 167: 1670–1675.
 29. Wolk K, Mallbris L, Larsson P, Rosenblad A, Vingard E, Stahle M. Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis. *Acta Derm Venereol* 2009; 89: 492–497.
 30. Feng BJ, Sun LD, Soltani-Arabshahi R, Bowcock AM, Nair RP, Stuart P, et al. Multiple Loci within the major histocompatibility complex confer risk of psoriasis. *PLoS Genet* 2009; 5: e1000606.
 31. Elder JT. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. *Genes Immun* 2009; 10: 201–209.
 32. Stuart PE, Nair RP, Ellinghaus E, Ding J, Tejasvi T, Gudjonsson JE, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. *Nat Genet* 2010; 42: 1000–1004.
 33. Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. *Nat Genet* 2010; 42: 991–995.
 34. Zhang XJ, Huang W, Yang S, Sun LD, Zhang FY, Zhu QX, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet* 2009; 41: 205–210.
 35. Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Mol Psychiatry* 2011; 16: 516–532.
 36. Wong ML, Dong C, Maestre-Mesa J, Licinio J. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. *Mol Psychiatry* 2008; 13: 800–812.
 37. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010; 67: 220–229.
 38. Nijsten T, Looman CW, Stern RS. Clinical severity of psoriasis in last 20 years of PUVA study. *Arch Dermatol* 2007; 143: 1113–1121.
 39. Unaeze J, Nijsten T, Murphy A, Ravichandran C, Stern RS. Impact of psoriasis on health-related quality of life decreases over time: an 11-year prospective study. *J Invest Dermatol* 2006; 126: 1480–1489.
 40. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007; 98: 109–115.
 41. Bambauer KZ, Adams AS, Zhang F, Minkoff N, Grande A, Weisblatt R, et al. Physician alerts to increase antidepressant adherence: fax or fiction? *Arch Intern Med* 2006; 166: 498–504.