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.

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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 \( \chi^2 \) 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%...
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% 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 IRs gradually increased from 2.17 10 years before to 2.48 1.5 years before first antipsoriatic treatment. The IRs 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 IR 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 IR 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
Antidepressant use in psoriasis patients

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>
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<th>Table IV. Analysis of antidepressant use within the psoriasis cohort before and after index date (n = 25,691)</th>
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<td>Mean number of episodes, 95% CI</td>
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*a*Sum 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).

*b*Cox proportional hazard model with robust standard errors.

*c*Sum 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).

*d*Poisson 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. The 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.

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