The Risk of Depression, Anxiety, and Suicidality in Patients With Psoriasis

A Population-Based Cohort Study

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Objective: To determine the incidence of depression, anxiety, and suicidality in patients with psoriasis compared with the general population.

Design: A population-based cohort study using data collected as part of patient’s electronic medical record from 1987 to 2002.

Setting: General Practice Research Database.

Patients: Analyses included 146,042 patients with mild psoriasis, 3,956 patients with severe psoriasis, and 766,950 patients without psoriasis. Five controls without psoriasis were selected from the same practices and similar cohort entry dates as patients with psoriasis.

Main Outcome Measure: Clinical diagnoses of depression, anxiety, and suicidality among patients.

Results: The adjusted hazard ratios (HRs) for receiving a diagnosis of depression, anxiety, and suicidality in patients with psoriasis compared with controls were 1.39 (95% confidence interval [CI], 1.37-1.41), 1.31 (95% CI, 1.29-1.34), and 1.44 (95% CI, 1.32-1.57), respectively. The adjusted HR of depression was higher in severe (HR, 1.72; 95% CI, 1.57-1.88) compared with mild psoriasis (HR, 1.38; 95% CI, 1.35-1.40). Younger patients with psoriasis had elevated HRs of outcomes compared with older patients with psoriasis.

Conclusions: Patients with psoriasis have an increased risk of depression, anxiety, and suicidality. We estimate that in the United Kingdom, in excess of 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality are attributable to psoriasis annually. It is important for clinicians to evaluate patients with psoriasis for these conditions to improve outcomes. Future investigation should determine the mechanisms by which psoriasis is associated with psychiatric outcomes as well as approaches for prevention.

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Psoriasis is a common chronic condition that affects 1% to 3% of the general population, and estimates suggest that 0.4% to 2.3% of the adult population have psoriasis but remain undiagnosed. Psoriasis is associated with impairments in health-related quality of life even in mild cases and is associated with excess cardiovascular risk and mortality in patients with more severe disease. Psoriasis is caused by a complex interaction of multiple genes and environmental factors and results in chronic T helper (Th)1 and Th17 inflammation in the skin, blood, and in some patients, joints.

Psoriasis has long been recognized to be associated with potentially adverse effects on mental health. In the 1960s, a popular ad campaign labeled the emotional burden of this skin disease as the “heartbreak of psoriasis.” However, there have been relatively few studies evaluating psychological outcomes in patients with psoriasis. Published studies have been primarily from tertiary care referral centers, are cross-sectional in nature, have suffered from small sample sizes, often lacked a control group, and have measured psychological symptomatology using a variety of research questionnaires rather than clinical diagnoses.

Quantifying the relationship between psoriasis and major psychological outcomes is important to identify to which mental health disorders patients with psoriasis may be particularly susceptible. We conducted a large, broadly representative, population-based cohort study to investigate the hypothesis that patients with psoriasis have an increased risk of clinical diagnoses of depression, anxiety, and suicidality (suicidal ideation, suicide attempt, or suicide) compared with the general population.
A population-based cohort study was conducted using data collected as part of patients’ electronic medical records between 1987 and 2002, maintained in the General Practice Research Database (GPRD). More than 1,500 practitioners in the United Kingdom (UK), who are unaware of research hypotheses to be tested, participate in the GPRD. The GPRD contains data on more than 8 million persons with more than 35 million years of follow-up time and is broadly representative of the UK population. General practitioners receive specific training and are subject to financial inducements and penalties to ensure data accuracy. The data are audited for completeness, and practices receive an up-to-standard (UTS) designation when at least 95% of relevant prescriptions and diagnoses are captured electronically. The ability of the GPRD to capture data from specialists and validly identify psoriasis has been demonstrated previously. The GPRD has been used extensively to study depression, anxiety, and suicidality.

EXPOSURES
Diseases are classified in the GPRD using Oxford Medical Information System (OXMIS) and Read codes. The data set was created by selecting all patients with a diagnostic code for psoriasis and 5 random controls who had at least 1 day of observation time. Controls were seen in the same practice and had a date of observation in the practice within 60 days of cohort entry for the corresponding patient with psoriasis. Control subjects did not have a diagnostic code for psoriasis at any time.

Severe psoriasis was defined by both a diagnostic code for psoriasis and a code indicating a systemic treatment modality. Systemic therapies include psoralen or phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, or mycophenolate. Patients with psoriasis who did not receive systemic therapy were classified as mild. This method for classification of psoriasis has been previously validated and used in several peer-reviewed publications.

STUDY PERIOD, OUTCOMES, AND COVARIATES
Cohort entry was defined as the latest date of when the patient was registered in the practice, the practice was UTS, the patient first received a diagnostic code for psoriasis (patients with psoriasis only), and the date corresponding to the first code for systemic treatment (patients with severe psoriasis only). Follow-up time ended for both patients with psoriasis and controls at the earliest date of when the patient developed the outcome of interest, transferred out of the practice, or died or the practice was no longer UTS.

Patients were defined as having incident depression, anxiety, or suicidality by a corresponding diagnostic code occurring after the start of follow-up time. A database of Read and OXMIS diagnostic codes was queried to generate the coding algorithm used. Depression included all clinician diagnoses of depressive symptomology including bipolar disorder. Anxiety included clinician diagnosis of anxiety and related disorders in which anxiety symptoms are common. Suicidality was defined as diagnosis of suicidal ideation, suicide attempt, or suicide. This list included all diagnostic codes used in previously published GPRD studies of depression, anxiety, and suicidality.

Information on age, sex, and follow-up time was obtained as well as history of depression, anxiety, and suicidality (defined as a corresponding diagnostic code occurring prior to cohort entry).

STATISTICAL ANALYSIS
Calculations made prior to data analysis suggested that with a fixed sample size of 150,000 patients with psoriasis and approximately 765,000 controls we would have greater than 0.95 power to detect an effect size (hazard ratio [HR]) as small as 1.1, assuming baseline rates of 20, 15, and 5 per 1000 person-years for depression, anxiety, and suicidality, respectively.

Comparisons of age, sex, follow-up time, history of depression, anxiety, and suicidality and reason for censorship from the data set between groups were tested using the Fisher exact test for categorical variables and the paired t test for continuous variables. All P values reported are 2-sided, and P < .05 was considered statistically significant.

Incidence was calculated using the number of subjects who received a diagnostic code for the outcome, divided by the cumulative years of observation. Adjusted attributable risk was calculated using incidence rates in the exposed and unexposed groups, multiplied by HRs adjusted for age and sex. Number of cases of depression, anxiety, and suicidality each year in the UK attributable to psoriasis was calculated by multiplying the attributable risk by the estimated number of patients with psoriasis in the UK based on GPRD statistics.

Cox proportional hazard regression was used to determine the HR of receiving a clinical diagnosis of depression/anxiety/suicidality after cohort entry in patients with psoriasis compared with controls. The appropriateness of this model was tested using diagnostic log-log survival plots that demonstrated adequate proportionalality. The primary analysis incorporated adjustment for age and sex. Interaction terms for age and sex were tested a priori, and if significant, the analysis was stratified and presented accordingly. Numerous sensitivity analyses were conducted. Analysis excluding patients seen less than once per year on average was done to assess the impact of observation bias. Another excluded patients with a diagnosis of the outcome measured prior to or within 6 months of cohort entry to ensure capture of incident rather than prevalent psychiatric disease. An analysis was performed excluding patients treated with retinoids (etretinate and acitretin) because these therapies may be associated with depression or suicidality; another excluded patients with a diagnosis of psoriatic arthropathy to ensure the capture of severe skin phenotype. An analysis of only those patients treated with psoralen or phototherapy (treatments highly specific for psoriasis) and an analysis controlling for comorbid conditions such as diabetes, hypertension, hyperlipidemia, cancer, and body mass index were performed. All statistical analyses were performed using Intercooled Stata 10 (StataCorp, College Station, Texas).

This study was conducted in accordance with cohort study guidelines outlined in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (http://www.strobe-statement.org/) and with the Declaration of Helsinki. This study was approved by the independent scientific advisory committee for research involving the GPRD and was granted exempt status by the institutional review board at the University of Pennsylvania, Philadelphia.

A total of 146,042 patients with mild psoriasis, 3956 patients with severe psoriasis, and 766,950 patients without psoriasis were included in the analyses. Overall, patients with psoriasis were older, contributed greater person-years, and had higher rates of depression, anxiety, and suicidality occurring prior to cohort entry than patients without psoriasis (Table 1). Over half (57.74%) of the patients...
with severe psoriasis were treated with methotrexate (Table 2).

The unadjusted (crude) incidence of clinical diagnosis of depression, anxiety, and suicidality in patients with psoriasis was 25.9, 20.9, and 0.9 per 1000 person-years, respectively (data for mild and severe psoriasis groups are given separately in Table 1).

The HRs for receiving a clinical diagnosis of depression, anxiety, and suicidality after cohort entry in patients with psoriasis compared with controls, after adjusting for age and sex, were 1.39 (95% confidence interval [CI], 1.37-1.41), 1.31 (95% CI, 1.29-1.34), and 1.44 (95% CI, 1.32-1.57), respectively. The adjusted HR of diagnosis of depression was higher in patients with severe psoriasis (HR, 1.72; 95% CI, 1.57-1.88) than mild psoriasis (HR, 1.38; 95% CI, 1.35-1.40) (Table 3). The adjusted HR of anxiety was similar in both mild and severe psoriasis groups compared with controls (Table 3). The adjusted HR of suicidality was higher in patients with severe psoriasis (HR, 1.51; 95% CI, 0.92-2.49) than mild psoriasis (HR, 1.44; 95% CI, 1.32-1.57); the 95% CI for the severe psoriasis group, however, spanned an HR of 1.0 (Table 3).

A statistically significant interaction between psoriasis and sex was found only for depression when comparing patients with severe psoriasis with controls (interaction term HR, 1.21; 95% CI, 1.00-1.46) (Table 3). These results suggest that the HR of receiving a clinical diagnosis of depression is significantly higher in men compared with women with severe psoriasis. An interaction of psoriasis and age was seen in mild and severe psoriasis groups for all 3 outcomes with the exception of suicidality in the severe psoriasis cohort, suggesting that the HR of these outcomes is greatest in younger patients.

The absolute risk of diagnosis of depression, anxiety, and suicidality attributable to psoriasis (adjusted for age and sex) was 11.8, 8.1, and 0.4 per 1000 person-years, respectively (Table 4). Attributable risks for these outcomes were similar between mild and severe psoriasis except for depression (11.5 and 25.5 per 1000 person-years, respectively). Stated another way, the excess risk attributable to psoriasis is 1 case of depression for every 39 patients with severe psoriasis per year (or per 87 patients with mild psoriasis per year). The excess risks associated with psoriasis for anxiety and suicidality correspond to 1 case per 123 and 2500 patients with psoriasis per year, respectively.

Sensitivity analyses were conducted to ensure capture of incident rather than prevalent depression, anxiety, and suicidality, as well as to test for several types of observation and misclassification. The HRs for the risk of incident depression, anxiety, and suicidality remained robust to these sensitivity analyses with the exception of suicidality in the severe psoriasis cohort when patients with a history of suicidality were excluded from the analysis; these data are included in eTable 1 and eTable 2 (http://www.archdermatol.com).

Our results suggest that patients with psoriasis are at increased risk for the development of depression, anxiety, and suicidality. On the basis of these data and the prevalence of psoriasis in the UK,22 we estimate that in the UK there

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### Table 1. Summary of Baseline Variable, Follow-up Time, and Incident Outcomes by Psoriasis Severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild Psoriasis</th>
<th>Severe Psoriasis</th>
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<tbody>
<tr>
<td><strong>Controls</strong> (n=746 930; 81.44%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Patients With Mild Psoriasis</strong></td>
<td>(n=146 042; 15.94%)</td>
<td></td>
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<tr>
<td><strong>P Value</strong></td>
<td></td>
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</tr>
<tr>
<td>Male sex, %</td>
<td>356 669 (47.82)</td>
<td>69 231 (47.40)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>33 (18-53)</td>
<td>40 (26-57)</td>
</tr>
<tr>
<td>History of depression, %</td>
<td>31 984 (4.29)</td>
<td>14 327 (9.81)</td>
</tr>
<tr>
<td>History of anxiety, %</td>
<td>24 152 (3.24)</td>
<td>10 890 (7.46)</td>
</tr>
<tr>
<td>History of suicidality, %</td>
<td>2946 (0.39)</td>
<td>1041 (0.71)</td>
</tr>
<tr>
<td>Person-years, median (IQR)</td>
<td>5.24 (2.8-9.12)</td>
<td>6.18 (2.9-7.7-5.5)</td>
</tr>
<tr>
<td>Reason for censorship, %</td>
<td>39 206 (5.26)</td>
<td>7324 (5.02)</td>
</tr>
<tr>
<td>Death</td>
<td>493 810 (66.20)</td>
<td>108 377 (74.21)</td>
</tr>
<tr>
<td>Practice no longer UTS</td>
<td>212 914 (28.54)</td>
<td>30 331 (20.77)</td>
</tr>
<tr>
<td>Transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted incidence rate per 1000 person-years (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>17.4 (17.3-17.6)</td>
<td>25.7 (25.3-26.1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>14.7 (14.6-14.9)</td>
<td>20.9 (20.6-21.3)</td>
</tr>
<tr>
<td>Suicidality</td>
<td>0.86 (0.8-0.68)</td>
<td>0.93 (0.85-1.00)</td>
</tr>
</tbody>
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### Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; UTS, up-to-standard.

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### Table 2. Systemic Psoriasis Therapy

<table>
<thead>
<tr>
<th>Systemic Psoriasis Therapy</th>
<th>Patients With Severe Psoriasis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>2284 (57.74)</td>
</tr>
<tr>
<td>Psoralen or phototherapy</td>
<td>680 (17.19)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>625 (16.48)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>412 (10.14)</td>
</tr>
<tr>
<td>Etretinate or acitretin</td>
<td>351 (8.87)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>222 (5.61)</td>
</tr>
<tr>
<td>Mycophenolate motofit</td>
<td>12 (0.30)</td>
</tr>
</tbody>
</table>

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*Percentages may not add to 100 because some subjects received multiple treatments.*
are over 10,400 diagnoses of depression, 7,100 diagnoses of anxiety, and 350 diagnoses of suicidality attributable to psoriasis each year. The HR of these psychiatric outcomes is particularly elevated in younger patients with psoriasis, with depression having the highest HR in patients with severe psoriasis (especially if young and male).

To our knowledge, a higher HR of depression in men has not been previously described, and this novel finding warrants attention. Interestingly, excess alcohol consumption in male patients with psoriasis has been demonstrated by several studies, suggesting the possibility of self-medication with alcohol for depression and other psychological problems in men with psoriasis.

This study significantly advances the literature of psoriasis and psychiatric outcomes in that it examines the incidence of clinical diagnosis of depression, anxiety, and suicidality in patients with psoriasis. Particular strengths of this study include its population-based design, which minimizes bias while maximizing generalizability of the results. Furthermore, the results remained robust to multiple sensitivity analyses, further ensuring the validity of the findings. The large sample size also allowed for the identification of subpopulations of patients with psoriasis who are particularly susceptible to these psychiatric disorders as well as the study of rarer outcomes such as suicidality.

As with all epidemiological studies, there are important limitations to consider. By using systemic psoriasis treatment as a construct to measure severe psoriasis, it is likely that there is misclassification with regard to psoriasis severity. Although patients with mild psoriasis are unlikely to receive systemic therapies, patients with severe psoriasis may not receive systemic treatment and therefore may be misclassified into the mild psoriasis cohort. In addition, there may be confounding by indication in the severe psoriasis cohort whereby the systemic treatment, rather than severe psoriasis itself, is associated with the outcome. Oral retinoids (etretinate and acitretin) have been associated with depression and suicidality, although sensitivity analyses excluding subjects treated with retinoids showed consistent results. The majority of patients with severe psoriasis were treated with methotrexate, and the authors are unaware of any evidence that shows methotrexate can cause depression, anxiety, or suicidality. In database studies, it is possible that there may be miscoding of the outcome leading to misclassification. As the data were
collected by general practitioners unaware of hypotheses to be tested, it is unlikely that misclassification would occur preferentially in either the psoriasis or control cohorts, and therefore such misclassification will bias findings toward the null. It is also possible that the relationship between psoriasis and these psychiatric outcomes could be indirect (eg, due to confounding by unmeasured factors) and not a direct consequence of having psoriasis. Finally, the outcomes measured are general practitioner clinical diagnosis of depression, anxiety, and suicidality. Formal validation of these codes with psychiatrist diagnosis using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria has not been conducted. It is important to recognize that clinical diagnosis may not predictably correlate with the gold standard of diagnosis (ie, DSM criteria applied by a psychiatrist or psychologist). Moreover, based on study design, we cannot comment on the degree of severity nor the duration of outcomes measured.

In conclusion, patients with psoriasis are at increased risk for depression, anxiety, and suicidality compared with the general population. It is important to identify these psychiatric disorders because they represent substantial morbidity that can be improved with a variety of pharmacological and nonpharmacological approaches. Recent data suggest that psychiatric comorbidity may negatively affect response to certain psoriasis treatments (eg, photochemotherapy), while other studies suggest that control of psoriasis is associated with improvements in psychological symptoms. Future studies are necessary to determine the mechanisms by which psoriasis is associated with depression, anxiety, and suicidality as well as approaches to prevent such adverse outcomes in patients with psoriasis.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kurd, Crits-Christoph, and Gelfand. Acquisition of data: Kurd and Gelfand. Analysis and interpretation of data: Kurd, Troxel, Crits-Christoph, and Gelfand. Drafting of the manuscript: Kurd and Gelfand. Critical revision of the manuscript for important intellectual content: Kurd, Troxel, Crits-Christoph, and Gelfand. Statistical analysis: Kurd, Troxel, Crits-Christoph, and Gelfand. Obtained funding: Kurd and Gelfand. Administrative, technical, and material support: Kurd. Study supervision: Kurd, Crits-Christoph, and Gelfand.

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REFERENCES