Prevalence and Odds of Signs of Depression and Anxiety in Patients with Lichen Planus: Systematic Review and Meta-analyses

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The association between certain chronic inflammatory skin diseases and psychiatric disorders or conditions has been well documented. However, the exact magnitude of the association between lichen planus and depression/anxiety symptoms and disorders is unknown. A systematic review and pooled meta-analyses were performed to examine the prevalence and odds of depression and anxiety in patients with lichen planus. The meta-analyses showed a high prevalence of signs of depression (27% [19–36%]) and anxiety (28% [21–36%]). The geographical location of the study may be part in explaining these differences, but methodological differences could also be involved. Case-control studies showed a strong association between lichen planus and signs of depression (odds ratio 3.79, 95% confidence interval [2.35; 6.12]) or anxiety (odds ratio 2.54, 95% confidence interval [1.73; 3.72]). These results raise the necessity of screening for the presence of depressive and anxiety symptoms or disorders in patients with lichen planus, and of referring such patients for psychiatric evaluation and appropriate treatment, if necessary.

Key words: meta-analysis; lichen planus; depression; anxiety.

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Lichen planus (LP) is a chronic inflammatory mucocutaneous condition with a myriad of clinical manifestations (1). It most frequently involves the skin and oral mucosa, but other sites can also be affected, such as the genitals, oesophagus, conjunctiva and skin appendages/scalp, hair and nails. LP occurs in approximately 1–2% of the general adult population and commonly affects middle-aged women (2). Although the exact aetiology of LP is unknown, pathogenesis is widely thought to be immune-mediated.

The association between certain chronic inflammatory skin diseases and psychiatric disorders or conditions has been well documented (3–8). A recent systematic review found a link between psychological disorders and the development of oral LP (9). Previous studies have yielded divergent or conflicting results on the prevalence of depression and anxiety in patients with LP, but the exact magnitude of the association between LP and depression/anxiety is unknown.

The aim of this study was to provide a pooled estimate of the prevalence and odds of depression/anxiety in patients with LP.

SIGNIFICANCE

The exact prevalence and odds ratio of depression and anxiety in patients with lichen planus are unknown. In this systematic review and meta-analyses of 19 and 18 articles on depression and anxiety, respectively, the overall estimated pooled prevalence was 27% for signs of depression and 28% for signs of anxiety. This study showed a strong association between lichen planus and signs of depression (odds ratio 3.79) and anxiety (odds ratio 2.54). These results raise the necessity of screening for the presence of depressive and anxiety symptoms/disorders in patients with lichen planus.

MATERIALS AND METHODS

Literature search

A search and extraction of relevant literature from 5 medical databases (Cochrane Database, EMBASE, PubMed, PsychINFO, Science Direct) was conducted by 2 of the authors (IJ and FR) from inception to 3 October 2019 using the following search terms: (lichen planus) AND (depression OR anxiety OR generalized anxiety disorder OR phobia OR panic disorder OR panic OR obsessive compulsive disorder OR OCD). Studies had to be primary research. No limits were set regarding article language, year of publication, age of study participants or study size. All articles were independently screened according to title and abstract by 2 of the authors (IJ and FR). In addition, studies were searched by screening reference lists of previous key or review articles. Studies on all kind of lichen planus (LP) (with oral, genital or skin lesions) were included. Recommendations of the Preferred Items for the Reporting of Systematic Reviews and Meta-Analysis (PRISMA) were followed (10). In France, ethics approval is not required for this type of research.

Only articles with full-text access were retained; those with access only to an abstract were excluded. The full-text articles were independently assessed for inclusion by SA and FR. If several papers analysed data from the same cohort, the article with the most complete data was retained. Disagreements between the reviewers were adjudicated by consensus between 3 of the authors (FR, SA and IJ).

Data extraction

Two of the authors extracted, checked for accuracy and tabulated data (SA and FR). The data collected were sociodemographic, medical and methodological.
Risk of bias assessment
Three of the authors (FR, SA and IJ) assessed the risk of bias for all studies using the risk of bias tool (11), a specific instrument for assessing bias risk in studies measuring disease prevalence, which has high interrater agreement. Disagreements between the reviewers were adjudicated by consensus of 3 of the authors. All studies were included irrespective of their low, moderate or high risk of bias.

Lichen planus definition
Studies were classified according to the localization of the lesions (Table I). Studies involving patients with oral lesions (with or without genital and/or cutaneous lesions) were defined as oral LP. Studies mainly involving patients with cutaneous lesions (with a minority of patients with mucosal lesions or with patients with both cutaneous and oral lesions) were defined as cutaneous LP.

Statistical analysis
Statistical analysis was performed with Stata software (version 13, StataCorp, College Station, TX, USA). Study characteristics were summarized and reported as mean and 95% confidence interval (95% CI) for continuous parameters and percentage for categorical variables.

The meta-analysis took into account between- and within-study variability. To address the non-independence of data due to study effect, random-effects models (12) were preferred over the usual statistical tests to evaluate the prevalence of anxiety and depression. The same statistical approach was adopted for stratified analyses according to the area where the study take place. Results were expressed as prevalence and 95% confidence intervals (95% CI). For the comparison between cases and controls, random-effects models were also used. Results were expressed as odds ratios (OR) and 95% CI. Heterogeneity in the study results was assessed by examining forest plots and using I² statistic, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I² values range between 0% and 100% and are typically considered low for 25%, modest for 25–50%, and high for 50% (13). Publication bias was assessed by funnel plots and confidence intervals. When possible (sufficient sample size), meta-regressions were proposed to study the relationship between variations in prevalence and study characteristics, such as assessment method (interview, medical records with The International Classification of Diseases (ICD)/The Diagnostic and Statistical Manual of Mental Disorders (DSM) classification, unspecified medical records or self-administered questionnaire), risk of bias, sex, number and age of patients included, study design (prospective or retrospective), geographical area/region, and for case control studies only, type of controls, case-control ratio, and presence or absence of matching controls. Results were expressed as regression coefficients (estimated coefficient noted; EC) and 95% CI.

Finally, to verify the robustness of the results, sensitivity analyses were carried out that excluded studies that were not evenly distributed around the base of the funnel. A sensitivity analysis was also performed to study the prevalence estimate only in those studies for which a case-control comparison was possible, to ensure representativeness in terms of prevalence of this subsample.

RESULTS
A total of 828 and 683 articles on depression and anxiety, respectively, were identified. After screening of the titles and abstracts and removal of duplicates, 68 and 73 articles, respectively, remained and were submitted to full-text review. Of these articles, 49 on depression and 55 on anxiety were excluded. A total of 19 and 18 articles were included in the meta-analyses of depression and anxiety, respectively (Fig. 1). Among the 19 articles assessing depression, 4 involved cutaneous LP according to the main location of lesions. In the 18 articles assessing anxiety, 2 implied cutaneous LP. Others articles involved oral LP. In the studies involving cutaneous LP, 34–80% of patients had only cutaneous lesions. Other patients could have both cutaneous and mucosal lesions, or some of them only mucosal lesions (Table I).

Lichen planus and depression
The 19 studies selected for the meta-analysis of the prevalence of signs of depression are shown in Table II (14–32). In all, they involved only 921 patients, with more than 70% including fewer than 50 individuals. Patients had an mean age of 50.2 years (48.0–52.4 years) and 68% were female (61–74%). Fifteen of the studies included patients with oral LP. Only one study was retrospective and only one included child patients (mixed with adults). Most used self-administered questionnaires (n = 17; 89%) to assess signs of depression, mainly the Beck Depression Inventory (BDI) (33) and the Hos-
The current meta-analysis evidenced a high prevalence of signs of depression in patients with LP (27% (19–36%)) with very wide heterogeneity ($I^2=93.3\%$) (Fig. 2). The prevalence of signs of depression was similar between patients with oral LP (26% (15–36%)) and those with cutaneous LP (35% (9–60%)) (Fig. 2) as confirmed by the meta-regression ($EC=0.09 (–0.17; 0.34), p=0.483$).

By contrast, the location where the study took place affected the prevalence of signs of depression. Meta-regression showed that prevalence was significantly higher in studies performed in the Middle East than those performed in Europe ($EC=0.25 (–0.02; 0.52), p=0.048$) and tended to be higher in studies made in South America ($EC=0.25 (–0.02; 0.52), p=0.070$). The prevalence of signs of depression varied from 17% (9–25) in studies made in Asia to 23% (8–39) in Europe, 49% (40–59) in America.

### Table II. Description of selected studies

| Study | Psychiatry | Design | Continent | Patients, $n$ | Controls | Age category | Assessment method | Age, years, mean | Female (%) | Risk of bias |
|-------|------------|--------|-----------|--------------|----------|--------------|------------------|----------------|------------|-------------|
| 1964 Depaoli (35) | Anxiety | Retrospective | Europe | 150 | Children and adults | Anamnesis and clinical examination | 46 | High |
| 1995 McCartan (14) | Depression and anxiety | Prospective | Europe | 50 | Adults | Self-administered questionnaire | 50.5 | Moderate |
| 2002 Akay et al. (15) | Depression | Prospective | Middle East | 30 | Healthy Adults | Self-administered questionnaire | 46.9 | High |
| 2004 Soto Araya et al. (16) | Depression and anxiety | Prospective | South America | 9 | Healthy Adults | Self-administered questionnaire | 58.7 | High |
| 2006 Lundquist et al. (18) | Depression and anxiety | Prospective | Europe | 46 | Healthy Adults | Self-administered questionnaire | 48 | Moderate |
| 2009 Shah et al. (19) | Depression and anxiety | Prospective | Asia | 30 | Healthy Adults | Self-administered questionnaire | 40.0 | High |
| 2013 Hirota et al. (20) | Depression and anxiety | Prospective | South America | 91 | Other Adults | Self-administered questionnaire | 52.9 | Moderate |
| 2014 Gavic et al. (21) | Depression and anxiety | Prospective | Europe | 98 | Adults | Self-administered questionnaire | 49.0 | Low |
| 2014 Sandhu et al. (22) | Depression and anxiety | Prospective | Asia | 49 | Other Adults | Self-administered questionnaire | 56.2 | Moderate |
| 2015 Alves et al. (23) | Depression and anxiety | Prospective | South America | 48 | Other Adults | Self-administered questionnaire | 51.3 | Moderate |
| 2015 Barbosa et al. (36) | Anxiety | Prospective | South America | 37 | Adults | Self-administered questionnaire | 53.4 | Moderate |
| 2015 Kalkur et al. (24) | Depression and anxiety | Prospective | Asia | 25 | Other Adults | Self-administered questionnaire | 44.2 | High |
| 2015 Sawant et al. (25) | Depression | Prospective | Asia | 35 | Adults | Self-administered questionnaire | 44.2 | High |
| 2017 Gupta et al. (26) | Depression and anxiety | Prospective | Asia | 39 | Other Adults | Self-administered questionnaire | 44.2 | High |
| 2018 Di Stasio et al. (27) | Depression and anxiety | Prospective | Europe | 11 | Other Adults | Researcher-administered | 91 | High |
| 2018 Yang et al. (28) | Depression and anxiety | Prospective | Asia | 45 | Healthy Adults | Self-administered questionnaire | 47.2 | High |
| 2019 Kurmus et al. (29) | Depression | Prospective | Middle East | 40 | Healthy Adults | Self-administered questionnaire | 48.6 | High |
| 2019 Manczyk et al. (30) | Depression and anxiety | Prospective | Europe | 26 | Other Adults | Self-administered questionnaire | 63.1 | High |
| 2019 Vilar-Villanueva et al. (31) | Depression and anxiety | Prospective | Europe | 48 | Other Adults | Self-administered questionnaire | 59.7 | Moderate |
| 2019 Wang et al. (32) | Depression and anxiety | Prospective | Asia | 100 | Healthy Adults | Self-administered questionnaire | 47.8 | Moderate |

*aOther controls are other patients taking oral medicine.*
South America, and 54% (43–66) in the Middle East. It was not possible to perform meta-regressions for most of the other factors owing to the lack of data. However, the proportion of females included in the studies had no effect on the prevalence of signs of depression (EC 0.002 (–0.003; 0.008), p = 0.431).

Thirteen case-control studies, all prospective and using a self-administered questionnaire, were retained for analysis of an association between LP and signs of depression. They comprised 596 patients (85% of studies had fewer than 50 patients) and 896 controls (7 studies with patients taking oral medicine and 6 studies with healthy controls). Four studies, all with patients with oral LP, were excluded owing to funnel plot publication bias (Fig. S1†), which eliminated heterogeneity completely (I² 60% before these exclusions). The results showed a strong association between LP and signs of depression (OR 3.79, 95% CI [2.35;6.12], p < 0.001) (Fig. 3). The OR was similar in the 2 studies involving cutaneous LP (OR 3.68, 95% CI [1.69;7.98]) and in the remaining 7 studies on oral LP (OR 3.86, 95% CI [2.10;7.10]). None of the factors tested in the meta-regression showed any effect on the association between LP and signs of depression. Sensitivity analysis showed that the prevalence of signs of depression in patients from the case-control studies was similar to that observed in the current meta-analysis (26% (14–37%) after exclusion of the 4 studies).

**Lichen planus and anxiety**

The 18 studies selected for meta-analysis of the prevalence of signs of anxiety are listed in Table II (14, 16, 18–24, 26–32, 35, 36). They involved a total of 942 patients with a mean age of 51.4 years (48.9; 53.8), of whom 70% were female (63; 77). Seventeen studies were prospective, included only adults, and were based on self-administered questionnaires. The remaining study was retrospective and included both children and adults. Ten studies were classified as having a high risk of bias, 7 a moderate risk, and only one a low risk. Most of the studies were the same as those selected for the prevalence of signs of depression (Table II).

The meta-analysis evidenced a high prevalence of signs of anxiety in patients with LP (28% (21–36%)) with very wide heterogeneity (I² 87.0%) (Fig. 4). One study was excluded from the meta-analysis because, as shown by the funnel plot, all patients had signs of anxiety (27). Only 2 studies were based on cutaneous LP. Their pooled prevalence of signs of anxiety was 31% (24–37%), whereas the prevalence in oral LP studies was 27% (19–35%) (Fig. 4). Meta-regression confirmed that oral and cutaneous LP had similar prevalences of signs of anxiety (EC 3.22 (–0.90; 7.34), p = 0.109), but evidenced a lower prevalence of signs of anxiety in studies made in Asia (EC −0.17 (–0.33;−0.01), p = 0.044).

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The search for an association between signs of anxiety and LP was performed with 12 case-control studies, all of which used a self-administered questionnaire, and included 566 patients and 856 controls. The results of the funnel plot (Fig. S2) led us to remove the 2 most distant studies from the analysis. The meta-analysis showed an association between signs of anxiety symptoms and LP (OR 2.54, 95% CI [1.73; 3.72], p < 0.001) with lower heterogeneity (I² = 18.2%) (Fig. 5). Only one study involved patients with cutaneous LP: surprisingly, the association was stronger than in oral LP (OR 6.26, 95% CI [1.58; 24.78] and 2.35, 95% CI [1.62; 3.41] respectively). Sensitivity analysis showed that the prevalence of signs of anxiety in patients from the case-control studies was close to that observed in the current meta-analysis (34% (24–43%). None of the factors tested in the meta-regression showed any effect on the association between LP and signs of anxiety.

**DISCUSSION**

This study evidences high prevalence rates of signs of depression (27%) and anxiety (28%) and a positive and significant association between LP and signs of depression and anxiety. In addition, it shows that, for both signs of depression and anxiety, prevalence varies according to geographical area, and not according to the location of the lesions. To the best of our knowledge, this is the first systematic review and meta-analysis assessing the prevalence rates and OR of signs of depression and anxiety in LP.

This study observed a higher overall prevalence of current signs of depression among patients with LP (27%) than in the general population, as estimated by studies using a similar method of self-administered questionnaires (37). This overall prevalence of signs of depression is higher than that in patients with alopecia areata (5). Prevalence rates of signs of depression in patients with LP are close to those in patients with chronic urticaria (7) and those with psoriasis or hidradenitis suppurativa in studies using self-administered questionnaires (3, 8, 38). The association between LP and signs of depression (OR 3.79) is much stronger than that seen in meta-analyses of signs of depression in hidradenitis suppurativa, alopecia areata and atopic dermatitis (5, 6, 8, 38, 39).

This study observed a higher overall prevalence of current signs of anxiety among patients with LP (28%) than in the general population, as estimated by studies using a similar method of self-administered questionnaires (40). This overall prevalence of signs of anxiety among patients with LP is close to that found in meta-analyses of signs of anxiety in adults with AA (5) and chronic urticaria (7). Prevalence studies of patients with psoriasis using a self-administered questionnaire reported rates ranging from 20% to 50%, which makes comparisons difficult (4). The association between LP and signs of anxiety is close to that found in meta-analyses of signs of anxiety among patients with alopecia areata (5, 39) and greater than that observed in meta-analyses of signs of anxiety among...
Variations were observed in prevalence rates of signs of depression or anxiety that could be attributed partly to geographical factors. The prevalence of signs of anxiety is lower among patients with LP in Asia; an observation that should be seen in the light of variations in the prevalence of signs of anxiety across population subgroups (40). The prevalence of signs of depression among patients with LP is higher in South America and in the Middle East. This regional difference is consistent with variations across continents in the prevalence of signs of depression in the general population reported in the meta-analysis of Lim et al. (37).

Methodological factors could also partly account for the high heterogeneity in studies. Variations in prevalence rates for both signs of depression and anxiety can be explained in part by the diagnostic tools used. However, the current study was unable to assess the influence of this factor owing to the small number of studies using different methods: 89% of the studies of the prevalence of signs of depression were based on self-administered questionnaires, mainly HADS or BDI, while the remaining 2 studies used medical records and a researcher-administered questionnaire that yielded lower prevalence rates than the pooled results in the current study (17, 27). Similarly, 94% of studies of anxiety prevalence used self-administered questionnaires, mainly STAI or HADS. The single exception (35) was based on case histories and clinical observation and yielded prevalence rates similar to the current pooled results. The almost exclusive use of self-administered questionnaires does not guarantee satisfactory heterogeneity. Studies performed in Europe and Asia used the same questionnaires with the same threshold, whereas those made in South America and the Middle East generally used different questionnaires or lower thresholds to assess signs of depression and anxiety, which would clearly have an effect on prevalence rates.

Recently, some authors have recommended the use of a multimodal assessment approach of depression, including self-reporting and a diagnostic interview (37). To the best of our knowledge, no study of LP has so far assessed the prevalence of anxiety or depressive disorders in patients with LP based on a (semi-)structured clinical interview; an approach that would, however, have the advantage of differentiating between the prevalence of depressive and anxiety symptoms and disorders (41).

Self-administered questionnaires were used in all the case-control studies. As the controls were assessed by the same method as the patients, questionnaire-related heterogeneity had a lesser effect. This would explain the lack of heterogeneity of the OR for signs of depression and the low level of heterogeneity of the OR for anxiety. In contrast, even when controls are assessed by the same self-administered questionnaires as patients, the possibility cannot be ruled out that the signs of depression and anxiety are over-reported by patients owing to the effect of the symptoms of LP. This would increase the OR and is consistent with previous research on depression and anxiety, which showed that self-report measures tend to yield a substantially higher frequency of cases, compared with the frequencies obtained by clinical diagnosis in the general population (37, 42, 43) and in some studies of patients with skin diseases (3, 8, 38). All these findings are in line with the results of the current study, which show higher OR of signs of depression or anxiety than other meta-analyses of inflammatory skin disorders, in which there was a smaller proportion of studies based on self-administered questionnaires (5, 6, 8, 38).

There are several possible explanations of the increased association between oral LP, which is strongly represented in the studies included in the current meta-analysis, and signs of depression or anxiety. Discomfort or pain, impact on quality of life, and fear of a malignant transformation are commonly cited factors (28, 31, 44). In addition, LP has been associated with hepatitis C virus (HCV) infection (45, 46), which, in itself, can be associated with depression and anxiety symptoms (47–52).
Lastly, there is some evidence that inflammation could be a contributor to signs of depression/anxiety in oral LP (53–55).

Study limitations
A meta-analysis is influenced by the limitations of the studies that it includes. The sample size of this meta-analysis was smaller than 1,000 individuals, and 75% of the studies analysed involved fewer than 50 patients. The term LP covers a myriad of clinical mucocutaneous manifestations. While the validity of the diagnosis of oral LP is guaranteed by histology in the majority of studies, most studies do not provide sufficient details about the cases. For example, only 4 studies among those dealing with oral LP state whether the patients had lesions elsewhere. On the other hand, all studies realized in dermatology allowed the inclusion of patients with oral/mucosal lesions. We note that most of the studies included patients with different types of oral LP (e.g. erosive, reticular, atrophic) without specification about anxiety or signs of depression prevalence in each type of LP. Thus, we cannot specify the prevalence of signs of depression or anxiety according to the type of oral LP. In addition, owing to lack of information in most of the included studies, we were unable to take into account psychological or pharmacological treatments that can modify mood or anxiety. Finally, only one study had a low risk of bias, as assessed by the validated tool used, which made it impossible to gauge the effect of risk of bias on the prevalence rates of signs of depression and anxiety. Given these substantial limitations in the literature, research efforts should be made to resolve them.

Conclusion
This study evidenced a high prevalence of current signs of depression and anxiety among patients with LP and a positive and significant association between LP and signs of depression and anxiety.

Prospective studies with large population-based samples using a structured or semi-structured clinical psychiatric interview with a precise description of patients’ dermatological data would make it possible to assess the specific prevalence of depression and anxiety disorders such as generalized anxiety, social anxiety, panic disorder and agoraphobia stating the prevalence period studied. Studies including only patients dealing with cutaneous LP would make it possible to assess the specific prevalence of depression and anxiety in patients with cutaneous LP and the strength of the association. However, these results raise the necessity of starting to screen patients immediately for the presence of clinically significant depressive or anxious symptoms or disorders, and to refer them for psychiatric evaluation and appropriate treatment.

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