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

Isabelle JALENQUES¹, Sophie LAURON², Sebastien ALMON², Bruno PEREIRA³, Michel D'INCAN⁴ and Fabien RONDEPIERRE² ¹Adult Psychiatry and Medical Psychology Department and ⁴Dermatology Department, CHU Clermont-Ferrand, Clermont Auvergne University, ²Adult Psychiatry and Medical Psychology Department, and ³Department of Clinical Research and Innovation, CHU Clermont-Ferrand, Clermont-Ferrand, France

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 partly explain these variations, 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.

Accepted Oct 7, 2020; Epub ahead of print Oct 13, 2020

Acta Derm Venereol 2020; 100: adv00330.

Corr: Isabelle Jalenques, Adult Psychiatry and Medical Psychology Department, CHU Clermont-Ferrand, 58 rue Montalembert, FR-63003 Clermont-Ferrand, France. E-mail: ijalenques@chu-clermontferrand.fr

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

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.

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.

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 between 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

Table I. Description of lichen planus (LP) lesions

	Locali	ization of	lesions (%	6)		
Study	Oral	Mucosa	l Genital	Cutaneous	Oral and mucosal	- I Type of LP
1964 Depaoli (35)	13	5 ^a	1	34	48	Cutaneous
1995 McCartan (14)	100				?	Oral
2002 Akay et al. (15)				100	?	Cutaneous
2004 Soto Araya et al. (16) 2004 Gimenez-Garcia &) 100			h	?	Oral
Pérez-Castrillón (17)		_		36 ⁰	?	Cutaneous
2006 Lundquist et al. (18)	15	78 ^a	7		0	Oral
2009 Shah et al. (19)	80				20	Oral
2013 Hirota et al. (20)	100				?	Oral
2014 Gavic et al. (21)	100				?	Oral
2014 Sandhu et al. (22)	100				?	Oral
2015 Alves et al. (23)	100				0	Oral
2015 Barbosa et al. (36)	81				19	Oral
2015 Kalkur et al. (24)	100				?	Oral
2015 Sawant et al. (25)		20 ^a		80		Cutaneous
2017 Gupta et al. (26)	100				?	Oral
2018 Di Stasio et al. (27)	100				?	Oral
2018 Yang et al. (28)	100				0	Oral
2019 Kurmus et al. (29)				65	35	Cutaneous
2019 Manczyk et al. (30)	100				?	Oral
2019 Vilar-Villanueva et al. (31)	100				?	Oral
2019 Wang et al. (32)	100				?	Oral

^aPercentage of patients with oral and genital lesions (mucosal). ^bAccurate distribution of lesions in each patients not documented. Study included 101 patients with 236 lesion locations described. Among these, 53 were oral lesions and 12 were genital; hence a maximum of 65 patients had mucosal lesions (existence of both lesions are not documented) and a minimum of 36 patients had cutaneous lesions only.

?: Presence of cutaneous lesions in patients with oral LP or presence of oral lesions in cutaneous LP not documented.

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-



Fig. 1. Flow diagram of article selection for the meta-analysis of the prevalence of depression and anxiety in lichen planus (LP) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA 2009). The numbers (n) on the left represent the number of articles on depression and those on the right the number of articles on anxiety (Depression/Anxiety).

Table II. Description of selected studies

pital Anxiety and Depression Scale (HADS) (34). One study used a researcher-administered questionnaire and one was based on medical records. No study included a clinical interview. Ten studies were classified as having a high risk of bias, 8 a moderate risk, and only one a low risk. The studies were conducted mainly in Europe and Asia (Table II).

The current meta-analysis evidenced a high prevalence of signs of depression in patients with LP (27% (19-36%)) with very wide heterogeneity (I²=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. Metaregression showed that prevalence was significantly higher in studies performed in the Middle East than those performed in Europe (EC 0.31 (0.00; 0.62), 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

Study	Psychiatry	Design	Continent	Patients, <i>n</i>	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 observation		46	High
1995 McCartan (14)	Depression and anxiety	Prospective	Europe	50		Adults	Self-administered questionnaire	50.5	74	Moderate
2002 Akay et al. (15)	Depression	Prospective	Middle East	30	Healthy	Adults	Self-administered questionnaire	46.9	40	High
2004 Soto Araya et al. (16)	Depression and anxiety	Prospective	South America	9	Healthy	Adults	Self-administered questionnaire	58.7	89	High
2004 Gimenez-Garcia & Pérez- Castrillón (17)	Depression	Retrospective	Europe	101		Children and adults	Medical records	48	56	Moderate
2006 Lundquist et al. (18)	Depression and anxiety	Prospective	Europe	46	Healthy	Adults	Self-administered questionnaire		80	Moderate
2009 Shah et al. (19)	Depression and anxiety	Prospective	Asia	30	Healthy	Adults	Self-administered questionnaire	40.0	56	High
2013 Hirota et al. (20)	Depression and Anxiety	Prospective	South America	91	Other ^a	Adults	Self-administered questionnaire	52.9	78	Moderate
2014 Gavic et al. (21)	Depression and anxiety	Prospective	Europe	98		Adults	Self-administered questionnaire	49.0	63	Low
2014 Sandhu et al. (22)	Depression and anxiety	Prospective	Asia	49	Other ^a	Adults	Self-administered questionnaire	56.2	53	Moderate
2015 Alves et al. (23)	Depression and anxiety	Prospective	South America	48	Other ^a	Adults	Self-administered questionnaire	51.3	88	Moderate
2015 Barbosa et al. (36)	Anxiety	Prospective	South America	37		Adults	Self-administered questionnaire	53.4	76	Moderate
2015 Kalkur et al. (24)	Depression and anxiety	Prospective	Asia	25	Other ^a	Adults	Self-administered questionnaire			High
2015 Sawant et al. (25)	Depression	Prospective	Asia	35		Adults	Self-administered questionnaire	44.2	43	High
2017 Gupta et al. (26)	Depression and anxiety	Prospective	Asia	39	Other ^a	Adults	Self-administered questionnaire		64	High
2018 Di Stasio et al. (27)	Depression and anxiety	Prospective	Europe	11	Other ^a	Adults	Researcher-administered questionnaire Self-administered questionnaire	66.6	91	High
2018 Yang et al. (28)	Depression and anxiety	Prospective	Asia	45	Healthy	Adults	Self-administered questionnaire	47.2	62	High
2019 Kurmus et al. (29)	Depression and anxiety	Prospective	Middle East	40	Healthy	Adults	Self-administered questionnaire	48.6	55	High
2019 Manczyk et al. (30)	Depression and anxiety	Prospective	Europe	26	Other ^a	Adults	Self-administered questionnaire	63.1	69	High
2019 Vilar-Villanueva et al. (31) Depression and anxiety	Prospective	Europe	48	Other ^a	Adults	Self-administered questionnaire	59.7	85	Moderate
2019 Wang et al. (32)	Depression and anxiety	Prospective	Asia	100	Healthy	Adults	Self-administered questionnaire	47.8	63	Moderate

^aOther controls are other patients taking oral medicine.

ActaDV

Acta Dermato-Venereologica

ActaDV

				%
Study			ES (95% CI)	Weigh
Oral Lichen Pla	anus	1		
2018 Yang (28	3)		0.16 (0.08, 0.29)	5.49
2015 Alves (23	3)		0.42 (0.29, 0.56)	5.20
2006 Lundquis	t (18) 🗕		0.07 (0.02, 0.18)	5.73
1995 McCartar	n (14) 🗕 💻		0.06 (0.02, 0.16)	5.76
2014 Gavic (2	1)		- 0.54 (0.44, 0.64)	5.55
2018 Di Stasio	(27)		0.09 (0.02, 0.38)	4.90
2019 Manczyk	(30)	<u> </u>	0.15 (0.06, 0.34)	5.20
2019 Vilar-Villa	nueva (31)		0.65 (0.50, 0.77)	5.24
2014 Sandhu	(22)		0.04 (0.01, 0.14)	5.82
2015 Kalkur (24)	<u> </u>	0.12 (0.04, 0.30)	5.31
2017 Gupta (2	6)	<u> </u>	0.13 (0.06, 0.27)	5.50
2019 Wang (3)	2) -		0.25 (0.18, 0.34)	5.65
2003 Soto Ara	va (16) -		0.44 (0.19, 0.73)	3.34
2013 Hirota (2	0)		- 0.55 (0.45, 0.65)	5.52
2009 Shah (19) —		0.30 (0.17, 0.48)	4.96
Subtotal (I^2 =	93.48%, p = 0.00)		0.26 (0.15, 0.36)	79.16
Cutaneous Lic	hen Planus			
2004 Gimenez	-Garcia (17) 🛛 💻		0.08 (0.04, 0.15)	5.83
2015 Sawant	(25)		0.26 (0.14, 0.42)	5.15
2002 Akay (15)		0.53 (0.36, 0.70)	4.81
2019 Kurmus	(29)		0.55 (0.40, 0.69)	5.06
Subtotal (I^2 =	94.24%, p = 0.00) ===		0.35 (0.09, 0.60)	20.84
Heterogeneity	between groups: p = 0.523	3		
Overall (I ^A 2 =	93.27%, p = 0.00);	\Leftrightarrow	0.27 (0.19, 0.36)	100.0
	1		1	
	U	.4	.8	

Fig. 2. Meta-analysis of the prevalence of signs of depression in lichen planus. CI: confidence interval; ES: Effect Size (prevalence).

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. S1¹), 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 metaanalysis (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).

¹https://doi.org/10.2340/00015555-3660



Fig. 4. Meta-analysis of the prevalence of signs of anxiety in lichen planus. CI: confidence interval. ES: Effect Size (prevalence).

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. S2¹) led us to remove the 2 most distant studies from the analysis. The meta-analysis showed an 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%



Fig. 5. Odds ratio (OR) meta-analysis of the association between signs of anxiety and lichen planus. CI: confidence interval.

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

ActaDV

patients with atopic dermatitis (6) or hidradenitis suppurativa (38).

Comparing the prevalence of signs of depression and anxiety in patients with cutaneous lesions with those with oral/mucosal LP presents some difficulties. There are few studies of the prevalence of signs of depression or anxiety in patients with cutaneous LP. These studies realized in dermatology allowed the inclusion of patients with oral/mucosal lesions; but they do not provide sufficient details about the cases. Only 3 studies (25, 29, 35), including patients with cutaneous LP, indicate the respective percentages of patients with only cutaneous or oral/mucosal lesions or with oral and cutaneous lesions. One study (15), including patients all dealing with cutaneous LP, does not state whether some patients also had oral lesions. However, most of these studies showed high prevalence rates of signs of depression or anxiety in patients with cutaneous LP and a positive and significant association with signs of depression or anxiety regardless of the proportion of patients with only cutaneous lesions. It therefore seemed justified to include them in our meta-analysis. The meta-regression confirmed that the prevalence of signs of depression and the prevalence of signs of anxiety was similar between patients with cutaneous LP and those with oral/mucosal LP. The current study also showed a similar association between cutaneous or oral/mucosal LP and signs of depression.

Further research is needed to explore the increased association between cutaneous LP and signs of depression/anxiety in specific studies including only patients dealing with cutaneous LP. To date, the results prompt us to look for other explanatory factors for the variations in prevalence, using all the data from studies that included patients with oral/mucosal or cutaneous LP.

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 remain-

ing 2 studies used medical records and a researcheradministered 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 vielded 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 the that 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 vield 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 metaanalysis, 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 metaanalysis 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.

ACKNOWLEDGEMENTS

The authors thank J. Watts for advice on the English version of the manuscript.

The authors have no conflicts of interest to declare.

REFERENCES

- Mauskar M. Erosive lichen planus. Obstet Gynecol Clin North Am 2017; 44: 407–420.
- Li C, Tang X, Zheng X, Ge S, Wen H, Lin X, et al. Global prevalence and incidence estimates of oral lichen planus: a systematic review and meta-analysis. JAMA Dermatol 2020; 156: 172–181.
- Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. J Invest Dermatol 2014; 134: 1542–1551.
- Fleming P, Bai JW, Pratt M, Sibbald C, Lynde C, Gulliver WP. The prevalence of anxiety in patients with psoriasis: a systematic review of observational studies and clinical trials. J Eur Acad Dermatol Venereol 2017; 31: 798–807.
- Lee S, Lee H, Lee CH, Lee W-S. Comorbidities in alopecia areata: a systematic review and meta-analysis. J Am Acad Dermatol 2019; 80: 466–477.e16.
- Rønnstad ATM, Halling-Overgaard A-S, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. J Am Acad Dermatol 2018; 79: 448–456.e30.
- Konstantinou GN, Konstantinou GN. Psychiatric comorbidity in chronic urticaria patients: a systematic review and metaanalysis. Clin Transl Allergy 2019; 9: 42.
- Machado MO, Stergiopoulos V, Maes M, Kurdyak PA, Lin P-Y, Wang L-J, et al. Depression and anxiety in adults with hidradenitis suppurativa: a systematic review and meta-analysis. JAMA Dermatol 2019; 155: 939–945.
- Cerqueira JDM, Moura JR, Arsati F, Lima-Arsati YB de O, Bittencourt RA, Freitas VS. Psychological disorders and oral lichen planus: a systematic review. J Investig Clin Dent 2018; 9: e12363.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
- Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012; 65: 934–939.
- DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139–145.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560.
- McCartan BE. Psychological factors associated with oral lichen planus. J Oral Pathol Med 1995; 24: 273–275.
- Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. J Eur Acad Dermatol Venereol 2002; 16: 347–352.
- Soto Araya M, Rojas Alcayaga G, Esguep A. Association between psychological disorders and the presence of oral lichen planus, burning mouth syndrome and recurrent aphthous stomatitis. Med Oral 2004; 9: 1–7.
- Giménez-García R, Pérez-Castrillón JL. Liquen plano y enfermedades asociadas: estudio clinicoepidemiológico. Actas Dermo-Sifiliográficas 2004; 95: 154–160.
- Lundqvist E, Wahlin Y, Bergdahl M, Bergdahl J. Psychological health in patients with genital and oral erosive lichen planus. J Eur Acad Dermatol Venereol 2006; 20: 661–666.
- 19. Shah B, Ashok L, Sujatha GP. Evaluation of salivary cortisol

and psychological factors in patients with oral lichen planus. Indian J Dent Res 2009; 20: 288–292.

- Hirota SK, Moreno RA, Dos Santos CHR, Seo J, Migliari DA. Psychological profile (anxiety and depression) in patients with oral lichen planus: a controlled study. Minerva Stomatol 2013; 62: 51–56.
- 21. Gavic L, Cigic L, Biocina Lukenda D, Gruden V, Gruden Pokupec JS. The role of anxiety, depression, and psychological stress on the clinical status of recurrent aphthous stomatitis and oral lichen planus. J Oral Pathol Med 2014; 43: 410–417.
- Sandhu SV, Sandhu JS, Bansal H, Dua V. Oral lichen planus and stress: an appraisal. Contemp Clin Dent 2014; 5: 352–356.
- Alves MGO, do Carmo Carvalho BF, Balducci I, Cabral LAG, Nicodemo D, Almeida JD. Emotional assessment of patients with oral lichen planus. Int J Dermatol 2015; 54: 29–32.
- Kalkur C, Sattur A, Guttal K. Role of depression, anxiety and stress in patients with oral lichen planus: a pilot study. Indian J Dermatol 2015; 60: 445.
- Sawant NS, Vanjari NA, Khopkar U, Adulkar S. A study of depression and quality of life in patients of lichen planus. Sci World J 2015; 2015: 817481.
- Gupta A, Mohan RPS, Gupta S, Malik SS, Goel S, Kamarthi N. Roles of serum uric acid, prolactin levels, and psychosocial factors in oral lichen planus. J Oral Sci 2017; 59: 139–146.
- Di Stasio D, Lauritano D, Gritti P, Migliozzi R, Maio C, Minervini G, et al. Psychiatric disorders in oral lichen planus: a preliminary case control study. J Biol Regul Homeost Agents 2018; 32: 97–100.
- Yang C, Liu L, Shi H, Zhang Y. Psychological problems and quality of life of patients with oral mucosal diseases: a preliminary study in Chinese population. BMC Oral Health 2018; 18: 226.
- Kurmuş GI, Gönül M, Canpolat F, Yılmazer D, Cankurtaran EŞ. Serotonin expression in lichen planus lesions and its relationship with depression/anxiety. Ann Dermatol 2019; 31: 146.
- Manczyk B, Gołda J, Biniak A, Reszelewska K, Mazur B, Zając K, et al. Evaluation of depression, anxiety and stress levels in patients with oral lichen planus. J Oral Sci 2019; 61: 391–397.
- Vilar-Villanueva M, Gándara-Vila P, Blanco-Aguilera E, Otero-Rey EM, Rodríguez-Lado L, García-García A, et al. Psychological disorders and quality of life in oral lichen planus patients and a control group. Oral Dis 2019; 25: 1645–1651.
- Wang C, Li S, Shen C, Shan J, Fan Y. Expression and significance of phosphodiesterase 4B gene in peripheral blood of patients with oral lichen planus. Int J Dermatol 2019; 58: 302–310.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–571.
- 34. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361–370.
- 35. Depaoli M. Clinico-statistical data on lichen ruber planus. Minerva Dermatol 1964; 39: 166–171 (in Italian).
- 36. Barbosa NG, Silveira ÉJD, Lima EN de A, Oliveira PT, Soares MSM, de Medeiros AMC. Factors associated with clinical characteristics and symptoms in a case series of oral lichen planus. Int J Dermatol 2015; 54: e1–6.
- Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep 2018; 8: 2861.
- Jalenques I, Ciortianu L, Pereira B, D'Incan M, Lauron S, Rondepierre F. The prevalence and odds of anxiety and de-

pression in children and adults with hidradenitis suppurativa: systematic review and meta-analyses. J Am Acad Dermatol 2020; 83: 542–553.

- Okhovat J-P, Marks DH, Manatis-Lornell A, Hagigeorges D, Locascio JJ, Senna MM. Association between alopecia areata, anxiety, and depression: a systematic review and meta-analysis. J Am Acad Dermatol 2019: S0190-9622(19)30890-4.
- 40. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav 2016; 6: e00497.
- Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, et al. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. J Neurol Sci 2017; 372: 331–341.
- Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med 2013; 43: 897–910.
- Bonsaksen T, Heir T, Ekeberg Ø, Grimholt TK, Lerdal A, Skogstad L, et al. Self-evaluated anxiety in the Norwegian population: prevalence and associated factors. Arch Public Health 2019; 77: 10.
- 44. González-Moles MÁ, Ruiz-Ávila I, González-Ruiz L, Ayén Á, Gil-Montoya JA, Ramos-García P. Malignant transformation risk of oral lichen planus: a systematic review and comprehensive meta-analysis. Oral Oncol 2019; 96: 121–130.
- Shengyuan L, Songpo Y, Wen W, Wenjing T, Haitao Z, Binyou W. Hepatitis C virus and lichen planus: a reciprocal association determined by a meta-analysis. Arch Dermatol 2009; 145: 1040–1047.
- Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. Oral Dis 2010; 16: 601–612.
- 47. Fialho R, Pereira M, Rusted J, Whale R. Depression in HIV and HCV co-infected patients: a systematic review and meta-analysis. Psychol Health Med 2017; 22: 1089–1104.
- Adinolfi LE. Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. World J Gastroenterol 2015; 21: 2269–2280.
- 49. Rivelli SK, Shirey KG. Prevalence of psychiatric symptoms/ syndromes in medical settings. In: Summergrad P, Kathol RG, eds. Integrated care in psychiatry: redefining the role of mental health professionals in the medical setting. New York, NY: Springer; 2014.
- Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 2008; 31: 2383–2390.
- Wells KB, Golding JM, Burnam MA. Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. Gen Hosp Psychiatry 1989; 11: 320–327.
- Weyerer S, Hewer W, Pfeifer-Kurda M, Dilling H. Psychiatric disorders and diabetes – results from a community study. J Psychosomatic Res 1989; 33: 633–640.
- DeAngelis LM, Cirillo N, McCullough MJ. The immunopathogenesis of oral lichen planus – is there a role for mucosal associated invariant T cells? J Oral Pathol Med 2019; 48: 552–559.
- 54. Toben C, Baune BT. An act of balance between adaptive and maladaptive immunity in depression: a role for T lymphocytes. J Neuroimmune Pharmacol 2015; 10: 595–609.
- 55. Miyajima M, Zhang B, Sugiura Y, Sonomura K, Guerrini MM, Tsutsui Y, et al. Metabolic shift induced by systemic activation of T cells in PD-1-deficient mice perturbs brain monoamines and emotional behavior. Nature Immunol 2017; 18: 1342–1352.

Cta