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RESEARCH ARTICLE

Management of reticular oral lichen planus patients with burning mouth syndrome-like oral symptoms: a pilot study

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ABSTRACT

Objectives: We sought to determine the efficacy of psychotropic drug in the management of BMS-like oral symptoms in patients with reticular oral lichen planus (R-OLP) refractory to conventional therapies, and its impact on anxious and depressive symptoms.

Materials and methods: We enrolled 28 cases of symptomatic R-OLP. The Numeric Rating Scale (NRS), the Total Pain Rating Index (T-PRI), the Hamilton rating scales for Depression (HAM-D) and Anxiety (HAM-A) were performed at baseline (time 0), after 2 months of topical clonazepam (time 1) and after 6 months of benzodiazepine and antidepressant drugs (time 2).

Results: R-OLP patients showed a statistically significant improvement in the NRS and T-PRI scores from time 0 [median: 9.0 (IQR: 7.2–10.0) and 10.5 (IQR: 7.0–13.0), respectively] to time 2 [(median: 2.0 (IQR: 2.0-3.0) ($p < .001$) and 3.0 (IQR: 2.0–4.7) ($p < .001$), respectively]. Similarly, the HAM-A and HAM-D scores showed an improvement from time 0 [(median: 15.0 (IQR: 10.2–17.8) and 13.0 (IQR: 12.0–15.0), respectively] to time 2 [median: 6.0 (IQR: 4.0–7.0) ($p < .001$) and 5.5 (IQR: 4.25–6.0) ($p < .001$), respectively].

Conclusions: Psychotropic drugs turned out to be effective in the management of BMS-like oral symptoms in R-OLP patients refractory to conventional immunosuppressive therapy, although in a long-term period.

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Oral lichen planus; oral burning; oral discomfort; BMS; anxiety; depression

Introduction

Lichen planus (LP) is a chronic mucocutaneous, immune-mediated, inflammatory disease that frequently involves the oral mucosa (OLP), affecting from 0.5 to 3.0% of the general population (1,2).

OLP lesions are usually symmetrical and bilateral, rarely regress spontaneously and may present with different patterns: papular, reticular or plaque (keratotic forms), atrophic, erosive or bullous, or mixed, with the buccal mucosa, tongue, and gingival mucosa being the most commonly affected sites (3).

Indeed, some authors have observed that several patients have reported stressful life events before the onset of the disease (4). Others have found higher levels of anxiety and depression in patients with OLP and have reported that emotional state is relevant not only as a trigger but also as an aggravating factor, having a strong impact on the exacerbation of OLP (4,5). However, this hypothesis has not been universally supported (6,7).

Reticular OLP (R-OLP) is usually asymptomatic; however, a recent study has found that a subset of R-OLP patients reported unconventional oral symptoms, not related to clinical features, and very similar to those described in patients with Burning Mouth Syndrome (BMS), in association also with higher levels of anxious and depressive symptoms than in a control group (8).

In this study, we decided to evaluate the clinical response of this subset of R-OLP patients—previously treated in different centers with standard therapies for OLP (9) but turned out to be unresponsive—to a therapeutic regimen similar to that used in the management of oral symptoms in BMS and its impact on anxious and depressive symptoms.

Materials and methods

Study design

This was a longitudinal single-assessment open-label pilot study carried out at the Oral Medicine Unit of the 'Federico II University of Naples', involving patients with reticular oral lichen planus (R-OLP) presenting with oral symptoms mimicking BMS.

The study is in full accordance with the ethical principles of the World Medical Association Declaration of Helsinki and was approved by our Institutional Ethical Committee. All patients provided their written informed consent for the management of personal data before participating in the study. The nature of the drugs used for the treatment, the mechanisms of action, and the possible side effects were explained to all included patients.

The inclusion criteria for R-OLP patients were: (i) either sex aged 18 or older; (ii) presence of bilateral clinical signs of symmetrical, reticular/papular patterned lesions; (iii) histological confirmation of the clinical diagnosis via incisional biopsy, revealing a well-defined band-like zone of cellular infiltration confined to the superficial part of the connective tissue, consisting mainly of lymphocytes, a sign of 'liquefaction degeneration', in the basal cell layer, and characterized by the absence of epithelial dysplasia, in agreement with the modified WHO criteria as proposed by Van der Meij and Van der Waal (10); (iv) presence of oral discomfort; and (v) lack of response to conventional therapies for OLP (9).

The exclusion criteria encompassed OLP patients with: (i) erosive, ulcerative, erythematous, atrophic and/or bullous lesions; (ii)

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epithelial dysplasia; (iii) present or past history of use of any psychotropic drugs, mainly benzodiazepines and antidepressants.

Data collection

Socio-demographic data, such as age, gender, educational level (in years), marital status, and job status, were recorded, as well as oral symptoms, oral clinical features, and oral localization of the lesions.

At admission, each R-OLP patient underwent a medical anamnesis (including past medical history, history of present illness, family history, surgical history, medication history, allergy history, and social habits), a general medical examination, an intra- and extra-oral examination, laboratory work-up, including immunologic profile, and a psychiatric evaluation along with *ad hoc* questionnaires.

R-OLP patients were assessed with the following battery scales: the Numeric Rating Scale (NRS) and the Total Pain Rating Index (T-PRI) from the short form of the McGill Pain Questionnaire (SF-MPQ) (11), and the Hamilton rating scale for anxiety (HAM-A) (12) and the Hamilton rating scale for depression (HAM-D) (13). All these scales were reviewed for completeness before collection and were administered in their Italian version (14–16).

The above-mentioned scales were administered at time 0 (before the use of psychotropic drugs), at time 1 (after 2 months of topical treatment with clonazepam), and at time 2 (after 6 months of systemic treatment with benzodiazepines and/or antidepressants, in addition to topical clonazepam).

Study intervention

The patient population was unsuccessfully treated with conventional therapies for OLP (9) in different centers and, then, reevaluated in our institution. As they presented with oral symptoms similar to those found in patients with BMS (8) and turned out be non-responders to previous conventional treatments, they were treated similarly to patients with BMS.

They were administered the above-mentioned scales (NRS, T-PRI, HAM-A, HAM-D) and prescribed clonazepam (oral solution 2.5 mg/ml) to be used topically as a mouthwash at baseline (time 0). Patients were asked to dilute 5 drops (1 drops = 0.1 mg) in 5 cc of water, hold the solution in the mouth for 5 min and spit it out, four times a day, and were reevaluated with all scales after 2 months of topical therapy (time 1).

At time 1, R-OLP patients who reported at least 75% reduction in the scores of NRS and/or TPR-I were considered responders to the treatment and asked to continue the same treatment without any additional medications. Conversely, those patients, who failed to reach 75% of reduction in the NRS and/or TPR-I score, were considered partly responders, and received a systemic treatment with psychotropic drugs in addition to Clonazepam. All patients were reevaluated after 6 months with all scales (time 2).

The psychotropic medications included either a Selective Serotonin Re-uptake Inhibitors (SSRI) (Paroxetine: 20 mg/daily; Sertraline: 50 mg/daily; Escitalopram: 10 mg/daily; Citalopram: 20 mg/daily), or a Serotonin and Norepinephrine Re-uptake Inhibitors (SNRI) (Duloxetine: 60 mg/daily).

Both responders and non-responders R-OLP patients, who reported high levels of insomnia, evaluated by a clinical visit with a psychiatrist and by the subscales present in the HAM-A and HAM-D, received an additional systemic medication, that could include an alpha-2 antagonist Noradrenaline and Specific Serotonergic agent (NaSSAs) (Mirtazapine: 30 mg/daily), or a Serotonin 2 Antagonist/Re-uptake Inhibitors (SARI) (Trazodone: 50 mg/daily), or a Tricyclic Anti-depressants (TCA) (Amitriptyline: 10 mg/daily), or a Benzodiazepine (Alprazolam: 0.5 mg/daily) or a Non-benzodiazepine hypnotics (Zolpidem: 10 mg/daily). Each R-OLP patient who received systemic benzodiazepines and/or antidepressants was checked every 2 months via blood work-up including the metabolic and endocrine panel, along with tests for cardiac functionality.

The choice of the above-mentioned medications was mainly based on the safety profile of each single drug, considering that there is no universal standardized protocol for treating anxious and depressive symptoms with or without insomnia (17,18). In general, we considered the following parameters when we prescribed systemic medications: age, body mass index (BMI), potential side effects, and underlying medical comorbidities or other somatic symptoms.

Study outcomes

The primary outcome variable was the change in NRS and TPR-I score measured at visits from baseline (Time 0) to month 2 (Time 1) and 6 (time 2), whereas the secondary outcome variable was the change in HAM-A and HAM-D score from Time 0 to Time 1 and 2.

Assessment of oral discomfort and the level of anxious and depressive symptoms

The Numeric Rating Scale (NRS-11) was used for the evaluation of oral symptoms. The T-PRI of the SF-MPQ of Melzack is a validated test for the measurement of the intensity and quality of pain. The HAM-A and HAM-D are a rating scales developed to measure the intensity and severity of anxious and depressive symptoms, respectively. The structure of all these scales have been previously described in detail by Adamo et al. (8).

Statistical analysis

Descriptive statistics, including means, standard deviations, medians, and interquartile ranges were used for socio-demographic and clinical characteristics. Frequencies and percentages were calculated for all categorical variables. The difference between medians of anxiety, depression and oral discomfort at time 0, time 1, and time 2 were evaluated with the Friedman Test. Multiple comparisons between medians of anxiety, depression and oral discomfort at different times, i.e. time 0 versus time 1, time 0 versus time 2, and time 1 versus time 2, were evaluated with the Wilcoxon test. The statistical significance was established as a p values $< .05$. However, for multiple comparisons at different times, the Bonferroni correction was established at a value of 0.003.

Results

Socio-demographic data and medical history

Between January and September 2013, 96 patients with R-OLP were screened in our institution: 35 out of 96 patients (36.5%) were referred by other centers because their oral symptoms were not responders to conventional therapies for OLP (9), but only 28 patients (29.2%) met the inclusion criteria of this study.

Of the 28 OLP patients, 21 were females (75%) and 7 male (25%) with a median age of 65.3 ± 11.5 years and an average educational level of 7.9 ± 3.8 years. More than half of the patients

Table 1. Socio-demographic characteristics in a sample of 28 symptomatic reticular oral lichen planus patients.

Demographic variables	Mean ± SD
Age	65.3 ± 11.5
Education level (in years)	7.9 ± 3.8
	Frequency (%)
Gender	
Male	7 (25.0)
Female	21 (75.0)
Job status	
Employed	16 (57.1)
Unemployed	12 (42.9)
Marital status	
Single	1 (3.6)
Married	23 (82.1)
Divorced	0 (0)
Widowed	4 (14.3)

SD: standard deviation.

were employed (57.1%) and the majority was married (82.1%) (Table 1).

Clinical characteristics of oral symptoms, medical history and treatment

All R-OLP patients were affected by oral burning: 23 patients (82.1%) showed a diffuse oral burning, while 5 (17.9%), a localized oral burning on the tongue. None of the patients with localized oral burning showed reticular lesions on the tongue. In addition to the oral burning, R-OLP patient presented with other oral symptoms, such as taste disturbance in 16 patients (57%), xerostomia in 13 patients (46%), oral itching in 7 patients (25%), sialorrhea in 4 patients (14.3%), and globus in 5 patients (17.9%).

The most frequent oral site involved by OLP was the buccal mucosa in 23 patients (82.1%), upper and/or lower gingival mucosa in 12 patients (42.9%), tongue in three patients (10.7%), and palate in just one patient (3.3%) (Table 2).

The majority of R-OLP patients presented with hypertension (35.7%), followed by hypercholesterolemia and hypothyroidism (14.3%), and was taking angiotensin-converting enzyme inhibitors (ACEIs) and anti-platelets (25%), followed by thyroid hormone (14.3%) (Tables 2 and 3).

All patients received topical clonazepam as mouthwash, but only four were fully responders and did not receive any systemic medication. The remaining 24 R-OLP were treated with different systemic psychotropic drugs: 21 patients (87.5%) were treated with one medication, while only three patients (12.5%) were treated with two. The majority of patients were prescribed an SSRI: six patients (25%) received sertraline and six patients (25%) paroxetine (Tables 2 and 4).

Twelve (50%) out of 24 R-OLP patients demonstrated a high level of insomnia and were prescribed specific systemic medication accordingly, in addition to topical clonazepam: nine patients were treated with just one medication for insomnia [3 (10.7%) with mirtazapine, 2 (7.1%) with Alprazolam, 2 (7.1%) with Zolpidem, 1 (3.6%) with Trazodone, and 1 (3.9%) with Amitriptyline], whereas three patients received a combination of a drug for insomnia (Trazodone or Mirtazapine or Alprazolam) with an SSRI (Paroxetine or Sertraline) (Tables 2 and 4).

Treatment outcomes

At baseline (Time 0), all 28 R-OLP patients showed a high level of oral discomfort [NRS: median, 9.0 (IQR: 7.2–10.0) and T-PRI: median, 10.5 (IQR: 7.0–13.0)], as well as a mild-moderate level of anxious and depressive symptoms [HAM-A: median, 14.5 (IQR: 10.0–16.8); HAM-D: median, 13.0 (IQR 10.3–14.8) (Table 5).

At time 1, 2 months after topical therapy with clonazepam, only four patients (14.3%) reported a reduction of at least 75% in the scores of all scales, and, indeed, the median score of all scales calculated on all patients were not found to be statistically significantly different between time 0 and time 1 ($p > .001$). Therefore, those 4 patients were advised to continue using only topical clonazepam until the end of the study (time 2), whereas the remaining 24 patients (85.7), who reported a partial improvement, in addition to topical clonazepam, were prescribed systemic psychotropic drugs.

At time 2, 6 months after topical and systemic therapy, the median score of all scales in all 28 R-OLP patients significantly improved ($p < .001$): the NRS and T-PRI median score dropped to 2.0 (IQR: 2.0–3.0) and 3.0 (IQR: 2.0–4.7), respectively, and the HAM-D and the HAM-A median score dropped to 5.5 (IQR: 4.25–6.0) and 6.0 (IQR: 4.0–7.0), respectively (Table 5). All the difference in the score of all scales between time 0 and time 2 and between time 1 and time 2 were found statistically significant ($p < .001$) (Table 5), highlighting the improvement of both oral discomfort and anxious/depressive symptoms.

Side effects

Only 4 (16.6%) out of 24 R-OLP patients reported side effects: three patients reported transient side effects and one long-term side effect. Transient side effects started 10 days after the beginning of the therapy and disappeared after 40 days. Those were nausea and constipation, reported by two patients treated with paroxetine, and dizziness reported by one patient treated with duloxetine. The long-term side effect was increase in appetite and weight gain in one patient treated with a combination of paroxetine and mirtazapine and controlled by a diet regimen (Table 2).

Discussion

In our study, we recruited a group of R-OLP patients, whose oral symtoms were not responders to conventional therapies for OLP (9) and whose oral symptomatology mimicked that of patients with BMS, as previously reported (8), along with mild depressive and anxious symptoms associated with insomnia.

Therefore, we decided to use the same therapeutic protocol that is commonly used for treating patients with BMS. We initially prescribed topical clonazepam, which seems to be more effective in controlling pain than other benzodiazepines (19), that previously demonstrated to be effective in controlling oral symptoms in OLP (20).

Interestingly, four patients in our study reported a complete remission of oral discomfort just with the topical use of clonazepam as well as a good response rate on their mood. In the remaining 24 patients, partially responsive to topical clonazepam, we prescribed systemic psychotropic drugs.

We decided to use this non-conventional therapeutic modality with benzodiazepine and antidepressants, not only because their symptoms were similar to BMS and patients were not responders to conventional therapies for OLP, but also because of the complex relationship between mood and sleep disturbance and chronic pain (21). Recently, it has been hypothesized that neuroinflammation could play an important pathogenetic role in OLP and could, after several years, cause oral burning (20). Therefore, the use of systemic benzodiazepines can be justified as they modulate neuroinflammation through central and peripheral action (20).

Table 2. Clinical features, medical history and management of study group.

Pt	Sex	Age	Oral sites	Systemic diseases	Medications	Oral symptoms	BMI	Prescribed Psychotropic drugs	Side effects of prescribed medications
1	F	50	BM Gingivae	Hypothyroidism	L-Thyroxin	LBT Xerostomia Globus	>30	TC Zolpidem	None
2	M	75	BM	Hypertension	Beta-Blockers	DOB Taste disturbance	<30	TC	None
3	M	79	BM Gingivae	Congestive heart failure	Anti-platelets	DOB Xerostomia	<30	TC Sertraline	None
4	F	49	Gingivae	None	None	DOB Xerostomia Taste disturbance	<30	TC Paroxetine	Nausea and Constipation
5	M	63	BM	Hypercholesterolemia	Statins	LBT Xerostomia	>30	TC	None
6	M	64	Gingivae	Hypertension Hypercholesterolemia	ACEIs	LBT Taste disturbance Oral Itching	>30	TC Alprazolam	None
7	F	54	Gingivae	Hypothyroidism	L-Thyroxin	DOB Taste disturbance	<30	TC Duloxetine	Dizziness
8	F	63	BM	None	None	DOB Xerostomia Oral Itching	<30	TC	None
9	F	70	BM Tongue	None	None	DOB Xerostomia Taste disturbance Oral Itching Globus	<30	TC Paroxetine Trazodone	None
10	F	70	BM	Hypertension Congestive heart failure	Anti-platelets Diuretics	DOB Taste disturbance	>30	TC Sertraline	None
11	F	53	BM	Mitral valve replacement	Anti-platelets Diuretics ACEIs Amiodarone	DOB Xerostomia Taste disturbance Itching	>30	TC Sertraline Alprazolam	None
12	M	62	BM Gingivae Tongue	Hypercholesterolemia	Statin	DOB Oral Itching Sialorrhea	>30	TC Citalopram	None
13	F	49	BM	Hypertension	ACEIs	DOB Taste disturbance Oral Itching Globus	<30	TC Paroxetine	Nausea and Constipation
14	F	70	BM Tongue	Transient ischemic attack	Anti-platelets	DOB Xerostomia	<30	TC	None
15	F	56	Gingivae	Type II diabetes mellitus Hepatitis C virus infection	Metformin	DOB Taste disturbance	>30	TC Sertraline	None
16	F	81	BM	Hypertension	Calcium antagonist	LBT Xerostomia	<30	TC Mirtazapine	None
17	F	56	Gingivae	None	None	DOB Globus	<30	TC Mirtazapine	None
18	F	84	BM	Hypertension	ACEIs	DOB Xerostomia	<30	TC Sertraline	None
19	F	82	BM	None	Anti-platelets	DOB Taste disturbance	>30	TC Trazodone	None
20	F	47	BM Gingivae	None	None	DOB Taste disturbance	<30	TC Paroxetine	None
21	F	74	BM	Hypertension	Beta-blocker	LBT Xerostomia Taste disturbance	>30	TC Sertraline	None
22	F	65	BM Gingivae	Hypothyroidism	L-Thyroxin	DOB Taste disturbance	>30	TC Alprazolam	None
23	M	60	BM	Hypertension Hypercholesterolemia	Calcium antagonist, and ACEIs	DOB Sialorrhea	<30	TC Paroxetine	None
24	F	49	BM Gingivae	Hypothyroidism	L-Thyroxin	DOB Xerostomia Taste disturbance	<30	TC Mirtazapine	None
25	F	76	BM	Hypertension	ACEIs	DOB Oral Itching Sialorrhea Globus	<30	TC Paroxetine Mirtazapine	Increase in appetite
26	F	77	BM Gingivae	Congestive heart failure	Anti-platelets	DOB Xerostomia Taste disturbance	>30	TC Escitalopram	None
27	M	73	BM Palate	Hypertension	ACEIs	DOB Taste disturbance	>30	TC Zolpidem	None
28	F	69	BM	Breast Cancer	Anti-platelets	DOB Sialorrhea	>30	TC Amitriptyline	None

ACEIs: angiotensin-converting enzyme inhibitors; BM: buccal mucosa; BMI: body mass index; DOB: diffuse oral burning; LBT: localized burning on the tongue; TC: topical clonazepam.

Table 3. Frequency of systemic diseases and drug consumption in 28 reticular oral lichen planus patients.

	Frequency (%)
Systemic diseases	
Hypertension	10 (35.7)
Hypercholesterolemia	4 (14.3)
Hypothyroidism	4 (14.3)
Congestive heart failure	3 (10.7)
Type II diabetes mellitus	1 (3.6)
Hepatitis C virus infection	1 (3.6)
Breast cancer	1 (3.6)
Others (mitral valve replacement, transient ischemic attack)	2 (7.1)
None	6 (21.4)
Hypertension and hypercholesterolemia	2 (7.1)
Hypertension and congestive heart failure	1 (3.6)
Hepatitis C virus infection and Type II diabetes mellitus	1 (3.6)
Medications	
Angiotensin-converting enzyme inhibitors	7 (25.0)
Beta-adrenergic receptor blockers	2 (7.1)
Calcium antagonists	2 (7.1)
Diuretics	2 (7.1)
Statins	2 (7.1)
Anti-platelets	7 (25.0)
L-Thyroxin	4 (14.3)
Metformin	1 (3.6)
Amiodarone	1 (3.6)
None	5 (17.9)
Anti-platelets	1 (3.6)
Angiotensin-converting enzyme inhibitors and Calcium antagonists	1 (3.6)
Anti-platelets, diuretics, angiotensin-converting enzyme inhibitors	1 (3.6%)

Table 4. Frequency of systemic psychotropic drugs in addition to topical clonazepam in the treatment of 24 R-OLP patients.

Psychotropic drug	Frequency (%)
Paroxetine	4 (14.3)
Sertraline	5 (17.8)
Alprazolam	2 (7.1)
Mirtazapine	3 (10.7)
Zolpidem	2 (7.1)
Amitriptyline	1 (3.6)
Citalopram	1 (3.6)
Duloxetine	1 (3.6)
Escitalopram	1 (3.6)
Trazodone	1 (3.6)
Paroxetine and trazodone	1 (3.6)
Paroxetine and mirtazapine	1 (3.6)
Sertraline and alprazolam	1 (3.6)

In our study, half of patients' population did not show insomnia but moderate level of anxious and depressive symptoms (HAM-A and HAM-D scores higher than 13) and were treated with SSRIs, due to their more efficacious and safer profile than tricyclics, as a first-line treatment of anxiety and depression (22). However, those medications were wisely chosen based on their safety profile: paroxetine and mirtazapine were avoided in obese patients (23,24), as well as paroxetine, and citalopram in patients with preexisting cardiovascular diseases (17,18).

We prescribed an SSRI drug for 12 patients: paroxetine for four patients who did not report any cardiovascular diseases or present obesity, sertraline for five patients with a cardiovascular illness, and citalopram and escitalopram for two older patients.

As the neurochemical pathways involved in mood disorders, sleep disturbances, and the transmission and processing of pain have multiple neurotransmitters in common, it is not surprising that some medications used to treat depression have been used to treat chronic pain (25).

We considered the poor quality of sleep with great attention, because previous studies found that sleep disturbance, specifically insomnia, is a common problem in R-OLP, and might be considered as a prodromal symptom of mood disorders (26). We initially decided to treat 9 (37.5%) out of 24 of non-responders to topical clonazepam just for insomnia because they demonstrated moderate level of insomnia with low level of anxious and depressive symptoms at baseline at both psychiatric interview and questionnaires (HAM-A and HAM-D scores between 10 and 13). Interestingly enough, these nine patients treated systemically just for insomnia—and with topical clonazepam—showed a remarkable improvement in their oral discomfort, confirming previous investigations on the relationship between sleep disturbance and pain (27,28). The other three patients with insomnia showed higher levels of anxious and depressive and were treated also in combination with an SSRI (Table 5).

Each medication for insomnia was accurately chosen based on its safety profile in agreement with a psychiatrist: for instance, Mirtazapine was prescribed in patients who did not report any systemic diseases or obesity, or Alprazolam in patients who had already used this drug in the past and reported a good efficacy and safety. Therefore, safety of use, ease of availability, cost-effectiveness, and non-invasiveness of this non-conventional management of oral symptoms in patients with R-OLP might make this type of treatment a valid alterative.

The main limitations of this study are represented by the small sample size and the absence of a control group, as this is a pilot study, and of a specific questionnaire to assess sleep disturbances.

Table 5. Anxiety, depression and pain variations from time 0 (at baseline) to time 2 (6 months after treatment).

Clinical parameters	Time 0 median; [IQR]	Time 1 Median; [IQR]	Time 2 Median; [IQR]	*p*-value
NRS	9.0; [7.2–10.0]	9.0; [7.0–9.8]	2.0; [2.0–3.0]	<.001**
T-PRI	10.5; [7.0–13.0]	8.0; [6.3–12.8]	3.0; [2.0–4.7]	<.001**
HAM-A	15.0; [10.2–17.8]	14.5; [10.0–16.8]	6.0; [4.0–7.0]	<.001**
HAM-D	13.0; [12.0–15.0]	13.0; [10.3–14.8]	5.5; [4.25–6.0]	<.001**

Multiple comparisons of anxiety, depression, and pain medians among time 0, time 1 and time 2

	p-value		
Clinical parameters	Time 0 versus Time 1	Time 0 versus Time 2	Time 1 versus Time 2
NRS	.059	<.001**	<.001**
T-PRI	.066	<.001**	<.001**
HAM-A	.068	<.001**	<.001**
HAM-D	.066	<.001**	<.001**

The significance difference among three medians was measured by the Freedman's test. The significance of multiple comparisons between two medians was measured by the Wilcoxon test. HAM-A: the Hamilton rating scale for anxiety; HAM-D: the Hamilton rating scale for depression; NRS: the Numeric Rating Scale; T-PRI: the Total Pain Rating Index.
Significance level has been chosen through Bonferroni correction. Significance $.01 < p \leq .05$, **Significance $p \leq .01$. **Significant $p \leq .003$.

Our study confirms that a subset of R-OLP patients with oral symptoms similar to those ones seen in patients with BMS and non-responders to conventional therapy for OLP may be treated with the use of antidepressants and benzodiazepines, underlying also the importance of screening this type of patients' population for mood disorders and sleep disturbances.

It is still unclear as to why our symptomatic R-OLP patients responded to our non-conventional therapeutic approach. One explanation may reside in the fact that oral discomfort may be induced by a peripheral neuropathy caused by a chronic inflammation in OLP (29)—thereby justifying the effectiveness of topical clonazepam—and amplified/modulated by anxiety/depression (30), thereby justifying the effectiveness of antidepressants.

On the other hand, considering that oral symptoms in our R-OLP patients were very similar to those found in BMS patients, as previously described (8), as well as their pharmacological management, as shown in this current investigation, we are wondering whether it would be possible to have a subset of patients who, despite the presence oral lesions, such as R-OLP for instance, may develop BMS. If this second hypothesis should prove to be valid through multicentric studies involving a larger sample of patients with a long period of follow-up, it could mean that we would face a new era in which current classification and current diagnostic criteria of BMS should be revised and modified.

Disclosure statement

No potential conflict of interest was reported by the authors.

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