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Evaluating the Suitability and Potential Efficiency of Cannabis sativa Oil for Patients with Primary Burning Mouth Syndrome: A Prospective, Open-Label, Single-Arm Pilot Study

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Abstract

Objective

To evaluate the use of a Cannabis sativa oil in the management of patients diagnosed with primary burning mouth syndrome (BMS).

Design

Prospective, open-label, single-arm pilot study.

Setting

University hospital.

Subjects

Seventeen patients with diagnosed BMS were included.

Methods

Subjects were treated for 4 weeks with a full cannabis plant extract, which was prepared from standardized plant material (cannabis flos) in specialized pharmacies by means of Romano-Hazekamp extraction and was diluted in oil (1 g of cannabis in 10 g of olive oil). The primary outcome was the change in pain intensity (assessed by the visual analog scale, Present Pain Intensity scale, McGill Pain Questionnaire, and Oral Health Impact Profiles) at the end of the protocol and during the succeeding 24 weeks; the neuropathic pain was also investigated with a specific interview questionnaire (DN4-interview [Douleur Neuropathique en 4 Questions]). Levels of anxiety and depression were considered as secondary outcomes, together with reported adverse events due to the specified treatment.

Results

Subjects showed a statistically significant improvement over time in terms of a clinical remission of the oral symptoms. Levels of anxiety and depression also changed statistically, displaying a favorable improvement. No serious reactions were detailed. None of the patients had to stop the treatment due to adverse events.

Conclusions

In this pilot evaluation, the C. sativa oil provided was effective and well tolerated in patients with primary BMS. Further bigger and properly defined randomized controlled trials, with different therapeutic approaches or placebo control, are needed, however.

Introduction

The International Headache Classification of Orofacial Pain has in 2020 defined the burning mouth syndrome (BMS) among the various form of idiopathic orofacial pain, as “an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions” [1].

The reported pain is described as moderate to severe, quite comparable to toothache in intensity, with a distinctive superficial and burning character, often accompanied by xerostomia and dysgeusia [2]. In the absence of clinically apparent mucosal alterations, the tip of the tongue is most habitually affected, but any part of the oral cavity may be involved. BMS occurs more commonly in middle-aged and older women [3]. Many patients with BMS

report less pain at night; the pain does not disturb sleep and is better in the morning, getting worse during the day [2]. By definition, clinical investigations and clinical sensory inspection, without quantitative psychophysical measures, should be normal [1].

Current evidence, covering neural pathways from the epithelial nerve fibers to the brain, indicates that typical BMS is in the majority of cases a chronic neuropathic pain condition, consisting of two main subgroups, peripheral and central [4].

In literature, BMS is commonly classified as either primary or secondary BMS, with the former being an idiopathic form, with no identifiable organic local or systemic causes, and the latter being instead triggered by local, systemic, or psychological factors [5]. BMS management should be directed to reduce symptoms and pain, but no therapy has been shown to be more effective than others; treatment of patients with primary BMS has been based on the avoidance of possible causes of oral irritation and the provision of psychological support [5, 6]. Recent evidence has shown that the use of antidepressants (e.g., clonazepam) and alpha-lipoic acid could provide favorable results [7, 8].

Cannabis (Cannabis sativa, or hemp) and its constituents (in particular the cannabinoids) have been the focus of extensive chemical and biological research since the discovery of the chemical structure of its major active constituent, Δ9-tetrahydrocannabinol (THC) [9]. The plant's behavioral and psychotropic properties are attributed primarily to THC, which is produced mainly in the leaves and flower buds of the plant. Besides THC, there are also non-psychoactive cannabinoids with several medicinal functions, such as cannabidiol (CBD), cannabichromene, cannabigerol, and many others [9].

In Italy, use of C. sativa for therapeutic purposes was first authorized in 2006. Suggestions for its use include reducing chronic pain, reducing nausea and vomiting associated with chemotherapy, stimulating appetite, inducing a hypotensive effect in glaucoma, and reducing uncontrolled body and facial movements [10]. Magistral formulations of C. sativa for therapeutic purposes are prepared by extraction from standardized products, which are obtained from dried and minced cannabis inflorescences (containing standardized THC and CBD concentrations) that are imported from the Dutch Office of Medicinal Cannabis [10]: Bedrocan® (9640 CA Veendam, Netherlands; mean concentrations of 22% for THC and <1% for CBD), Bedrobinol® (Hoftoren – Rijnstraat 50 – 2515 XP Den Haag, Netherlands; 13.5% for THC and <1% for CBD), Bediol® (Hoftoren – Rijnstraat 50 – 2515 XP Den Haag, Netherlands; 6.3% for THC and 8% for CBD), and Bedrolite® (Hoftoren – Rijnstraat 50 – 2515 XP Den Haag, Netherlands; 0.4% for THC and 9% for CBD) [11].

Introduced in 2007, Bediol® is the brand name for the cultivar C. sativa L. 'Elida'. C. sativa L. 'Elida' was one of the first cannabis cultivars to be developed specifically to have a higher

CBD content. The effects of CBD are distinctly different from those of THC. Bediol® has a balanced ratio of THC and CBD, and because it is easily tolerated, physicians often prescribe it for patients who previously have not used cannabis as a medicine.

We hypothesized that the use of a full cannabis plant extract, diluted in oil, could be useful in reducing primary BMS–related symptoms. We tested our hypothesis in a prospective, open-label study, by giving a galenic preparation of therapeutic C. sativa in a cohort of subjects with reported oral burning sensation and/or pain that was classified as BMS according the International Headache Society criteria. We decided to perform this preliminary evaluation to test logistics and gather information about sample size, exclusion criteria, and materials needed before a larger randomized controlled trial is conducted. Moreover, considering that cannabis oil may not appeal to all, we also sought to determine its acceptability.

Methods

Study Population

The study was approved by the board of CIR-Dental School, University of Turin, Turin, Italy (CIR-PO-2017/01), and was registered in the ISRCTN registry (#97009661).

Caucasian patients attending the Oral Medicine Section of the CIR-Dental School, Turin, Italy, for the first time from February 2017 through October 2019, were selected for the present study. The same expert oral physician (PGA) performed the baseline conventional intraoral examination.

At admission, the following information was recorded: age, gender, education level (in years), marital status, job status, social habits, oral reported symptoms, systemic disease, and daily medication taken.

The inclusion criteria were: 1) oral symptoms for at least 12 months; 2) age ≥18 years; 3) no detectable oral mucosal lesions; 4) no underlying local (e.g., candida) or systemic disease (e.g., endocrine disorder, nutritional deficiencies, medication-induced disorder), such as those potentially responsible for secondary BMS [5]; 5) ability to complete the present clinical trial; and 6) lack of response to any provided treatment in the previous 6 months, inclusive of a washout period (or a drug holiday) of at least one month, and yet suffering oral pain. Exclusion criteria were: 1) inability or unwillingness to provide informed consent; 2) noteworthy psychiatric or cognitive impairment; 3) existence of other diagnoses that could explain the neuropathic pain; 4) forms of hyposalivation due to any local or systemic causes that could appropriately justify the subjective complaint of xerostomia; 5) previous diagnosis of Sjögren syndrome on the basis of American-European Consensus Group criteria [12]; 6) previous head and neck radiotherapy; 7) hepatitis C infection; 8) current pregnancy or

breastfeeding; 9) current treatment with psychotropic drugs; and 10) history of alcohol or substance abuse.

Patch testing for dental allergens [13] and routine serological analyses were required, including quantification of different serum vitamins (B1, B6, and B12), folic acid, serum iron (Fe++), serum ferritin, transferrin, fasting blood glucose, zinc, and full blood count.

Different treatment options were discussed, and all patients submitted written, informed consent. Investigations were performed in full accordance with the ethical principles of the World Medical Association Declaration of Helsinki of 1975, as revised in 2000.

Valuation of Pain and Associated Variables

Different questionnaires were filled in by the same clinician (AG), as previously reported [14].

The subjective sensation of pain and its influence on oral health were assessed with the visual analog scale (VAS; consisting of a 100-mm vertical line, marked 0 [no pain] to 100 [most severe pain experienced]), the McGill Pain Questionnaire (MGP), the Present Pain Intensity (PPI) scale, and the Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49). The DN4 (Douleur Neuropathique en 4 Questions), a screening tool for neuropathic pain consisting of interview questions (DN4-interview), was also used.

Levels of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) and the Geriatric Depression Scale (GDS).

Treatment Provided

Medical cannabis consists of the dried, pulverized, and homogenized flowers of C. sativa, cultivated under standardized conditions in accordance with the requirements of good manufacturing practices [15]. A distinct pharmaceutical-grade cannabis preparation was used, obtained from Bedrocan International BV (Veendam, The Netherlands) and prepared by Proxy Laboratories BV (Leiden, The Netherlands). This preparation, Bediol®, contains 6.3% THC (63 mg/g) and 8% CBD (80 mg/g). The patients obtained the medical cannabis by submitting a prescription specifying the THC and CBD content. The full cannabis plant extract was prepared from standardized cannabis plant material (cannabis flos) in specialized pharmacies by means of Romano-Hazekamp extraction and was diluted in oil (1 g of cannabis in 10 g of olive oil) [16]. The prescription was provided as a nonrefillable receipt with an anonymous alpha-numeric code; specifics included exact nomenclature of the drug (Bediol®), pharmaceutical form (hereafter oil), dose required (10–40 drops), and motivation for prescription [10].

The pharmacy had to provide the patient with a certificate confirming an accurate analysis of the final product (in terms of respecting the THC and CBD concentrations). This analysis was carried out with a liquid chromatography–mass spectrometry system, as required by the current Italian legislation.

Before starting the protocol, patients were instructed on how to take the drug and were informed about its possible side effects. The dose prescribed ranged from 10 to 40 drops, as the ideal dosing schedule is currently unknown because no dose-finding studies have yet examined the optimal daily amount of specific molecular concentrations of THC and CBD [15, 17].

The schedule was prescribed as follows: 5 drops twice daily for 5 days, 10 drops twice daily for 5 days, 15 drops twice daily for 5 days, and 20 drops twice daily for 13 days.

Patients were also asked to abstain from using any herbal cannabis or cannabinoids other than the oil provided for the entire study duration.

Follow-Up Schedule

Follow-up visits were conducted at baseline (t1), at the end of the 4-week course of treatment (t2), and then 12 (t3) and 24 weeks (t4) after the end of treatment.

Outcome Measures

The primary outcome of the study was the change in spontaneous pain intensity (assessed through the VAS, PPI, MGP, and OHIPs) at t2, t3, and t4.

Levels of anxiety and depression were considered as secondary outcomes, as were reported adverse events due to the THC treatment. The patients were provided with a diary to record the treatment's unexpected effects (e.g., gastrointestinal disease, headache, dizziness, worsening of dry mouth, or anything else reported).

At every follow-up time (t1, t2, t3, t4), all the questionnaires were filled in, and every adverse effect was recorded.

Statistical Analysis

A descriptive analysis was performed, and continuous variables were expressed as medians and interquartile ranges (median [IQR]), whereas categorical variables were expressed as frequencies and percentages. The nonparametric Friedman test was used to assess whether there were any differences among the distributions of each score (HADS score, GDS score, MGP, PPI, OHIP-14 score, OHIP-49 score, DN4 score, and VAS) at four different times (t1, t2, t3, and t4). Five pairwise comparisons (t2 vs t1, t3 vs t1, t4 vs t1, t3 vs t2, and t4 vs t2) for each score were performed with the nonparametric Wilcoxon signed-rank test, and standard and adjusted (with the Bonferroni multiple testing correction method) P values were computed. All statistical analyses were carried out with R software (version 3.6.2). Statistical significance was defined at P values of <0.05.

Results

Figure 1 summarizes the main characteristics of the patient sample and the experimental design. Initially, 34 patients were selected; 2 of these were not included because of presenting exclusion criteria (diagnosis of Sjögren syndrome and treatment with psychotropic drugs). Fifteen patients refused to be part of this study.

Seventeen patients with primary BMS who fulfilled all the aforementioned inclusion criteria completed the treatment provided for 4 weeks. Of these 17 patients, 14 were women (82.4%). The mean age at presentation was 71 years.

Table 1 reports the sociodemographic characteristics, risk factors, and hematologic evaluation at baseline. Only one patient (5.9%) showed a positive patch test, specifically for nickel, but no dental allergen was detected in the oral cavity.

Subjects had been treated previously with different medications for the oral symptoms: 5 with clonazepam, 7 with antifungal and nonsteroidal anti-inflammatory drugs, 2 with salivary substitutes, and 3 with systemic steroids.

Evaluation of Subjective Sensation of Pain

The distribution of scores at different times is described in Table 4 and Figure 2. Over time, all subjects showed a statistically significant improvement in terms of a clinical remission of the oral symptoms. The VAS, OHIP-14, and OHIP-49 scores decreased from baseline (median [IQR] = 8.00 [5.00, 9.00], 27.00 [14.00, 33.00], and 88.00 [49.00, 108.00], respectively) to the end of the period of investigation (median [IQR] = 4.00 [2.00, 5.00], 8.00 [6.00, 12.00], and 32.00 [20.00, 45.00], respectively). Likewise, the MGP, PPI, and DN4 scores decreased from the beginning (median [IQR] = 20.00 [13.00, 28.00], 3.00 [3.00, 4.00], and 3.00 [2.00, 4.00], respectively) to the end of the follow-up period (median [IQR] = 3.00 [2.00, 8.00], 1.00 [1.00, 2.00], and 1.00 [1.00, 2.00], respectively).

Table 5 shows the distribution of the scores' differences between the specified times and corresponding results. The MGP, PPI, OHIP-14, OHIP-49, DN4, and VAS statistically diminished at t2, t3, and t4 as compared with baseline (both unadjusted and Bonferroni adjusted). However, those improvements showed an immediate decrease after 4 weeks of treatment and remained substantially stable over the next 24 weeks. When data after 12 and 24 weeks were compared with data after 4 weeks of treatment, no statistical significances were detected (t3 vs t2 and t4 vs t3) (both unadjusted and Bonferroni adjusted).

Analysis of Anxiety and Depression

Levels of anxiety and depression changed statistically after treatment was provided, displaying a favorable lessening (Table 2 and Figure 1).

The HADS and GDS scores showed a decrease from baseline (median [IQR] = 20.00 [8.00, 25.00] and 9.00 [2.00, 11.00], respectively) to the end of the period of investigation (median [IQR] = 9.00 [8.00, 15.00] and 3.00 [1.00, 5.00] respectively).

When results obtained immediately after the end of therapy (t2) were compared with baseline (t1), the HADS and GDS scores did not show statistical differences if they were adjusted, whereas HADS alone showed a statistically significant reduction ($P < 0.05$) 24 weeks after the end of therapy as compared with baseline (Table 5). Similarly, for reported pain, when data after 12 and 24 weeks (after the end of the therapy) were compared with data after 4 weeks of treatment provided, no statistical significances were detected (t3 vs t2 and t4 vs t3) (similar whether unadjusted or if Bonferroni adjusted).

Side Effects

No serious reactions were reported with the oil administered. None of the patients had to stop the treatment due to adverse events.

Approximately one-third of the patients experienced adverse events, which did not cause any significant treatment modifications. The most frequent adverse event was dizziness, which occurred in 3 (17.6%) patients in the first week of treatment. Specifically, one patient complained of dizziness after 3 days, one after 5 days, and one after 6 days. Headache was described in 2 (11.8%) patients: one at day 5 and the other at day 15 of therapy. Finally, a complaint of constipation was reported in one (5.9%) case after 24 days of treatment. All reported effects were transient and disappeared within 2 weeks after the end of the therapy.

None of the patients reported a worsening in dry mouth, drowsiness, or weight gain.

Discussion

To date, the treatment of BMS remains a challenge and is considered to be of high urgency in oral medicine [18, 19]. Among the therapies used are hormone replacement therapy, anticonvulsants, antidepressants, capsaicin, benzodiazepines, analgesics, alpha-lipoic acid, and photobiomodulation with laser and cognitive therapies. Nevertheless, none of them appeared to be superior [20]. This wide-ranging diversity of treatments requires more detailed studies to assess which treatment should be the gold standard for this condition.

The actions of cannabinoids are due to selective binding to specific receptors. Among these, cannabinoid receptors types 1 and 2 (CBR1 and CBR2) are the main receptors, which are in the G protein–coupled receptor (GPCR) superfamily [21]. CBR1 is expressed predominantly in the central nervous system, particularly in the cerebral cortex, cerebellum, and hippocampus, and is activated by widespread signaling in the endocannabinoid system through endogenous cannabinoids such as anandamide and 2-arachidonyl glycerol [22], where it is involved in different pathways of neuronal plasticity, exerting the role of a neuromodulator rather than neurotransmitter. Specifically, CBR1 and CBR2 receptors are coupled directly to Gi/o proteins to downregulate adenylyl cyclase activity, which reduces intracellular levels of cyclic adenosine monophosphate (cAMP) [21], leading to inhibition of cAMP-dependent protein kinase (PKA) and subsequent reduction of the phosphorylation of $Ca2+$ and $K+$ channels. Thus, neurotransmitter release, such as that of glutamate and γ-aminobutyric acid (GABA) at the synaptic level, can be regulated [23] in cortical and medullar pathways of locomotion, memory, and pain [24]. However, CBR1 is also expressed in the gastrointestinal, urogenital, and cardiovascular systems, though its function is under scrutiny [25]. CBR2 is also expressed in immune systems, occurring also in neurons, glial cells, and endothelial cells of the substantia nigra, cerebral cortex, and hippocampus, with its activity and role still undefined as compared with CBR1 [24].

Of the components of cannabis, THC is the most abundant compound and is responsible for the most intense psychoactive properties [26]. THC has ability to bind to both CBR1 and CBR2, in contrast to CBD, which is considered an isomer of THC deprived of its psychoactive activity, with an overall lower affinity than THC for both CBR1 and CBR2 and a preference for CBR2 rather than CBR1 [27]. THC has been known largely for its psychoactive effects, and it is an approved treatment for chemotherapy-induced nausea and vomiting and as an appetite stimulant in cachectic patients [26]. On the other hand, CBD has been reported to bear analgesic, anti-inflammatory, and neuroprotective properties. CBD has been deployed with encouraging outcomes in the management of anxiety and post-traumatic stress disorder [28, 29] and has been approved by the US Food and Drug Administration as an antiepileptic for rare disorders [30].

The main strength of the present study is the novelty of the intervention. This is, to the best of our knowledge, the first study analyzing the role of cannabinoids in the management of unresponsive BMS. Our hypothesis is derived from previous assessments of the potentialities of THC/CBD formulations in the management of other neuropathic disorders [15, 31].

With regard to the route of administration, oral and inhaled formulations have been approved by Italian Ministry of Health [32], with decoction being the preferential pharmaceutical form, whereas the inhaler route should be considered in those cases where the oral form would not be able to provide its therapeutic properties. As reported in the present work, the oil extract form is also allowed. Despite inhalation being more often studied in literature and considered more effective [33], for the present pilot study we considered oral drops to be more patient friendly and to provide a better control of the daily dosage among the elderly. Furthermore, literature has shown that the oral formulation could provide a lower peak plasma concentration of THC and CBD, as well as a more prolonged delay to reach this peak [33]. Therefore, it seemed more appropriate to use such a preparation among patients with BMS, who are known to require pain relief over an extended period of time [34]. Furthermore, such a formulation was preferred to facilitate reproducibility, given that inhaled formulations are not allowed in some countries [26] and that the use of vaporizers or similar devices could encourage, if not reinforce, the habit of smoking in some patients.

The Bediol® formulation, despite its relatively high concentration of THC (6.3%), which has well-known psychoactive effects [35], did not lead to serious adverse effects in the present study. On the other hand, the composition of Bediol® is well balanced in terms of similar concentrations of CBD (8%) and THC (6.3%), and it appeared to provide an immediate effect on pain relief, with VAS, PPI, MGP, OHIP-14, and OHIP-49 significantly decreased ($P < 0.05$ in each scale) right after end of treatment (t2), as well as 6 months after end of treatment (t4). The sole exception was a minimal increase in OHIP-49, from t3 (average 29.00) to t4 (average 32.00), which was still insufficient to jeopardize the scale of reduction of OHIP-49 from t4 to t1, where the starting average of OHIP-49 was 88.00. On the other hand, despite what has been reported in the literature with regard to the ability of THC/CBD to facilitate the management of anxiety or depression [28, 29], Bediol® did not provide any immediate antidepressant or anxiolytic effect, as revealed statistically by $P > 0.05$ for HADS and GDS at t2 vs HADS and GDS at t1 (Table 5). However, a late anxiolytic outcome emerged when HADS values at 6 months after the end of treatment were compared with baseline values (t4 vs t1; $P < 0.05$). The latter might be arguably an indirect consequence of the steady reduction of pain experienced by the patients in each of the evaluation steps. This association between pain amelioration and reduction of anxiety is suggested by the most recent etiopathogenetic theories of BMS, which contemplate an intertwined psychological and neuropathic pathway [36].

Despite the relatively high concentration of THC, no serious adverse effects were experienced. However, this might be a consequence of the smallness of the present sample

and the relatively brief duration of treatment. The small sample size was a consequence of the strict aforementioned eligibility criteria. On the other hand, the short-term therapy was decided on due to the novelty of the product and the absence of empirical evidence in literature on its application in oral medicine. In this sense, future research should compare Bediol® with a different formulation, such as Bedrolite®, to assess whether similar or even more encouraging results can be obtained with an even lower concentration of THC and a slightly higher concentration of CBD.

To date, no studies have provided evidence of a reliable and safe treatment for long-term management of BMS both in terms of symptom relief and quality of life [37]. Even clonazepam, which is considered effective for symptom remission in patients with BMS, as shown in a recent meta-analysis [38], is associated with important repercussions, especially in the form of potential addiction in the long term [39, 40]. On the other hand, controversy remains with regard to which variables can influence dependence on cannabis derivates, with some studies providing positive correlations with high THC content [41] and others focusing on patient-related variables [42]. Moreover, it should be highlighted that evidence on these aspects is often provided from samples of young individuals, and limited data are available on the effectiveness and safety of cannabis in older subjects, in whom comorbidity, polypharmacy, and increased susceptibility to cognitive disorders have to be carefully assessed [26, 43].

Finally, although limitations on patients' enrollment might arise due to potential impairment caused by THC while driving or at the workplace [28], in the specific scenario of patients with BMS, such restrictions are marginal, with most patients diagnosed with BMS being women 60 to 69 years of age and frequently retired from work [2, 44]. In the present study, only 17.8% of patients were employed (Table 1), and in no case was impairment at the workplace experienced.

With older patients being most commonly affected by BMS, additional larger and properly defined randomized controlled trials with different therapeutic approaches or placebo control are needed to ascertain the clinical efficacy of THC products as compared with standard medical treatments for patients with BMS.

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Ethical approval and informed consent: All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments. For this study, written informed consent was obtained from all participants included.

All authors have contributed to the work. Each author has read and approved the final version of the manuscript. All authors agreed to have their name added to the article.

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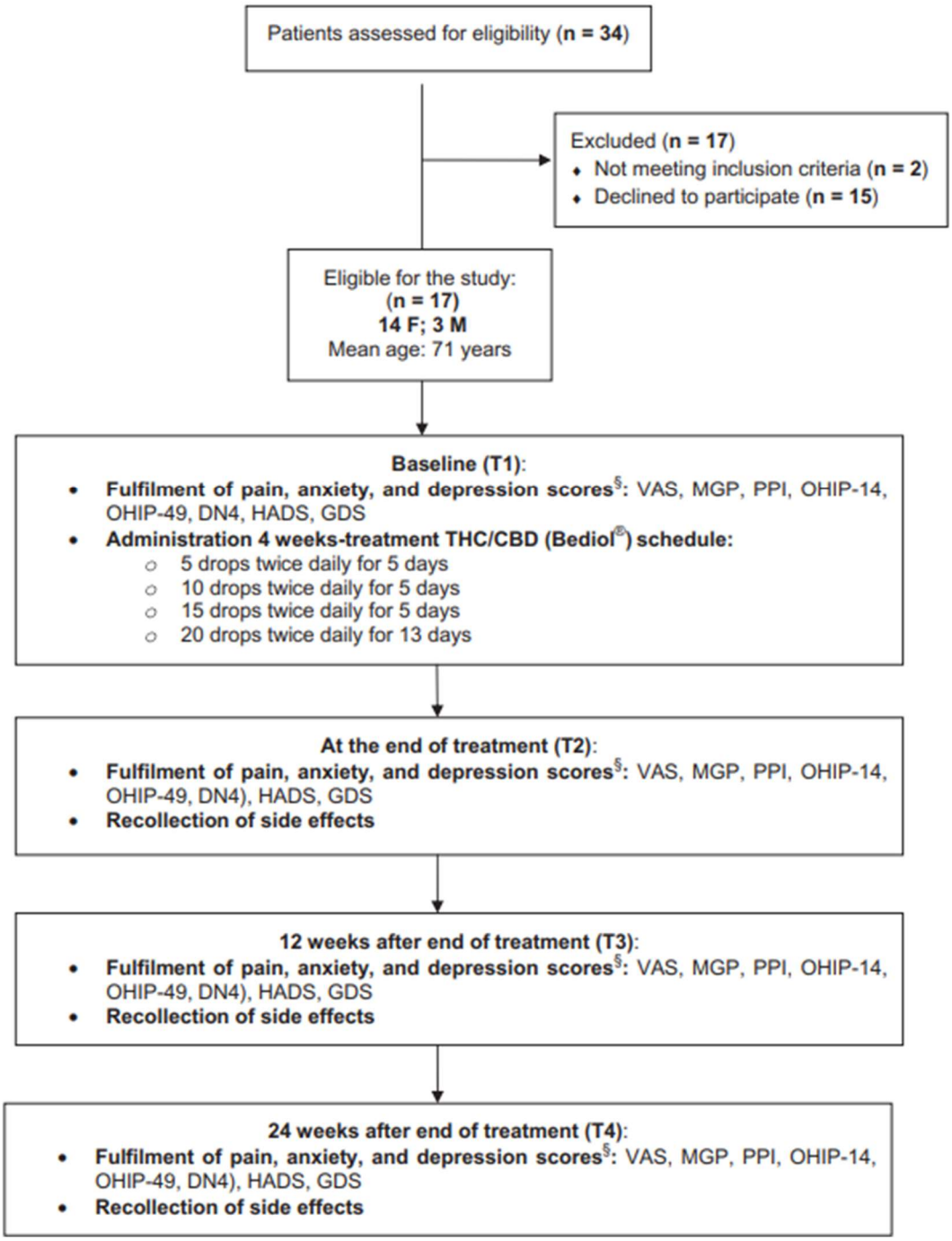

Figure 1. Diagram of patients' enrollment and experimental design. Scores: visual analog scale (VAS), McGill Pain Questionnaire,

Present Pain Intensity (PPI), Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49), Douleur Neuropathique en 4

Questions (DN4), Hospital Anxiety and Depression Scale (HADS), and Geriatric Depression Scale (GDS)

Demographic variables	
Age, years, median [IQR]	71.00 [62.00, 72.00]
Gender = male, n (%)	3 (17.6)
Married = yes, n (%)	14 (82.4)
Employed = yes, n (%)	3 (17.6)
Education level, years, mean (SD)	8.9 (5.9)
Risk factors	
Body mass index, median [IQR]	22.31 [21.05, 23.23]
Smoker = yes, n (%)	1 (5.9)
Alcohol consumer = yes, n (%)	3 (17.6)
Hematologic evaluation	
Vitamin B1 (reference values: 28–85 µg/dL), mean (SD)	62 (8.6)
Vitamin B6 (reference values: 3.6–18 µg/dL), mean (SD)	26.1 (16.3)
Vitamin B12 (reference values: 197–771 pg/mL), mean (SD)	393.2 (121.6)
Folic acid (reference values: 3.89–26.8 ng/mL), mean, (SD)	14 (8.5)
Serum iron (reference values: 53–167 µg/dL), mean (SD)	123.2 (22.9)
Serum ferritin (reference values: 30–400 µg/L), mean, (SD)	93.6 (40.8)
Transferrin, mean (reference values: 200–360 mg/dL), mean, (SD)	261 (26.6)
Fasting blood glucose, (reference values: 70–100 mg/dL), mean (SD)	97.1 (16.5)
Zinc (reference values: 0.75–1.1 mg/dL), mean (SD)	0.86 (0.1)

Table 1 Sociodemographic characteristics, risk factors, and hematologic evaluation at baseline of 17 analyzed patients

Oral symptoms	**n** (%)
Xerostomia	12 (70.6)
Dysgeusia	9 (52.9)
Pain or burning every day of the week	17 (100)
Pain or burning only in the morning	1 (5.9)
Persistent intensity during the day	9 (52.9)
Pain or burning during meals	15 (88.2)
Pain or burning during the night	11 (64.7)
Sites of involvement	
Tongue	15 (88.2)
Palate	9 (52.9)
Lips	5 (29.4)
Buccal mucosa	3 (17.6)
Gingiva	5 (29.4)
Throat	1 (5.9)

Table 2 Reported oral symptoms, their description, and site of involvement in 17 patients with BMS [frequency and (%)]

Systemic disease	n (%)
None	2 (11.8)
Hypertension	5 (29.4)
Hypercholesterolemia	3 (17.8)
Osteoporosis	4 (23.5)
Hypothyroidism (compensated under levothyroxine regimen)	5 (29.4)
Type II diabetes mellitus	2 (11.8)
Rheumatoid arthritis	3 (17.8)
Gastroesophageal reflux disease	2 (11.8)
Neurological	1 (5.9)
Medication consumption	
None	4 (23.5)
Antiplatelets	2 (11.8)
Beta-adrenergic receptor blockers	2 (11.8)
Calcium antagonists	2 (11.8)
Metformin	1 (5.9)
L-thyroxin	5 (29.4)
Proton pump inhibitors	3 (17.8)
Statins	2 (11.8)
Vitamin D	3 (17.8)

Table 3 Incidence of systemic diseases and daily medication consumption in 17 patients with BMS [frequency and (%)]

Score†	t1	t2	t3	t4	*P* value
HADS	20.00 [8.00, 25.00]	14.00 [9.00, 17.00]	9.00 [7.00, 16.00]	9.00 [8.00, 15.00]	0.003
GDS	9.00 [2.00, 11.00]	4.00 [1.00, 8.00]	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	0.029
MGP	20.00 [13.00, 28.00]	7.00 [2.00, 11.00]	3.00 [3.00, 8.00]	3.00 [2.00, 8.00]	<0.001
PPI	3.00 [3.00, 4.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	<0.001
OHIP-14	27.00 [14.00, 33.00]	8.00 [4.00, 15.00]	8.00 [6.00, 13.00]	8.00 [6.00, 12.00]	<0.001
OHIP-49	88.00 [49.00, 108.00]	34.00 [20.00, 49.00]	29.00 [22.00, 43.00]	32.00 [20.00, 45.00]	<0.001
DN4	3.00 [2.00, 4.00]	1.00 [1.00, 2.00]	1.00 [1.00, 1.00]	1.00 [1.00, 2.00]	<0.001
VAS	8.00 [5.00, 9.00]	4.00 [3.00, 7.00]	4.00 [2.00, 5.00]	4.00 [2.00, 5.00]	<0.001

*t1 = baseline; t2 = after the end of therapy; t3 = 12 weeks after t2; t4 = 24 weeks after t2.

†Scores: visual analog scale (VAS), McGill Pain Questionnaire (MGP), Present Pain Intensity (PPI), Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49), Douleur Neuropathique en 4 Questions (DN4), Hospital Anxiety and Depression Scale (HADS), and Geriatric Depression Scale (GDS).

Table 4 Score distribution (median [IQR]) at four different time points* and corresponding results from the Friedman test

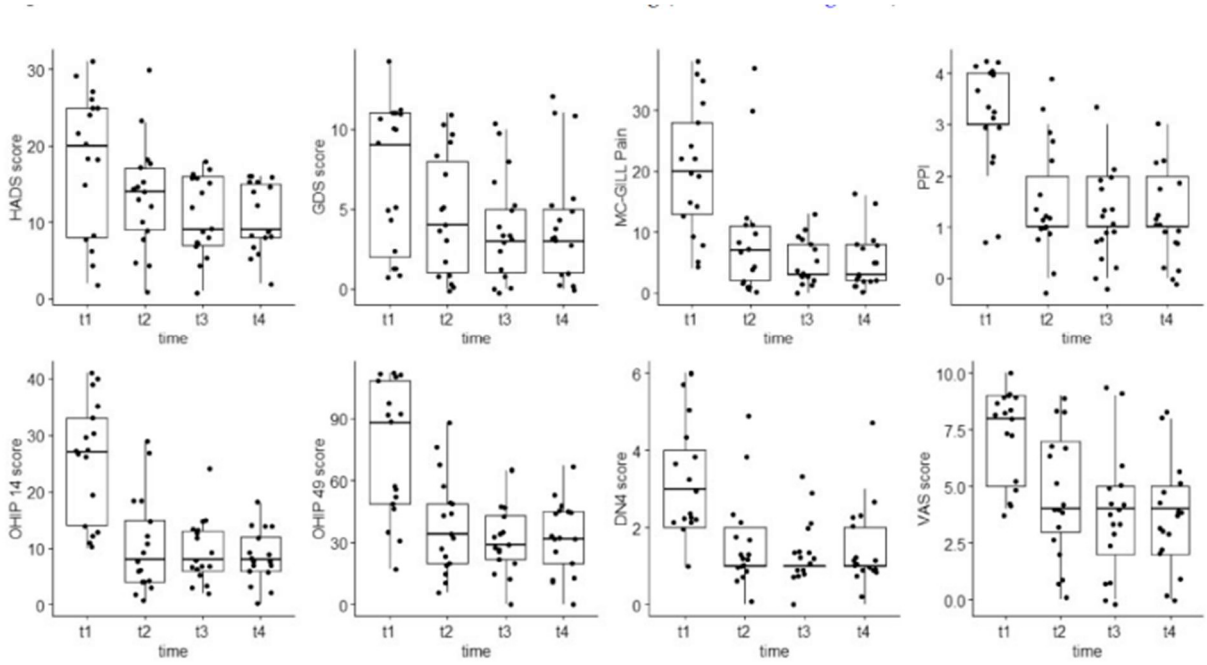

Figure 2. Levels of pain, anxiety, and depression: box plot of each score's distribution at the different times (black dots correspond to individual values). *t1 ¼ baseline; t2 ¼ 4 weeks after the end of therapy; t3 ¼ 12 weeks after t2; t4 ¼ 24 weeks after t2. Scores: visual analog scale (VAS), McGill Pain Questionnaire, Present Pain Intensity (PPI), Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49), Douleur Neuropathique en 4 Questions (DN4), Hospital Anxiety and Depression Scale (HADS), and Geriatric Depression Scale (GDS).

Score†		t2 vs t1	t3 vs t1	t4 vs t1	t3 vs t2	t4 vs t3
HADS	Difference (median [IQR])	−5.00 [-11.00, -1.00]	−8.00 [-14.00, -1.00]	−9.00 [-13.00, 0.00]	−1.00 [-7.00, 0.00]	0.00 [0.00, 0.00]
	P value	**0.015**	**0.006**	**0.006**	0.064	0.796
	P value adj.	0.077	**0.030**	**0.031**	0.322	1.000
GDS	Difference (median [IQR])	−1.00 [-3.00, 0.00]	−2.00 [-5.00, -1.00]	−1.00 [-5.00, 0.00]	0.00 [-1.00, 1.00]	0.00 [0.00, 1.00]
	P value	**0.031**	**0.004**	**0.027**	0.526	0.188
	P value adj.	0.155	**0.019**	0.136	1.000	0.942
MGP	Difference (median [IQR])	−13.00 [-20.00, -2.00]	−17.00 [-21.00, -5.00]	−18.00 [-21.00, -5.00]	0.00 [-5.00, 1.00]	0.00 [-1.00, 0.00]
	P value	**0.002**	**0.001**	**0.001**	0.219	0.958
	P value adj.	**0.010**	**0.003**	**0.004**	1.000	1.000
PPI	Difference (median [IQR])	−2.00 [-3.00, -1.00]	−2.00 [-3.00, -1.00]	−2.00 [-3.00, -1.00]	0.00 [-1.00, 0.00]	0.00 [0.00, 0.00]
	P value	**0.003**	**0.000**	**0.000**	0.222	1.000
	P value adj.	**0.016**	**0.002**	**0.002**	1.000	1.000
OHIP-14	Difference (median [IQR])	−10.00 [-24.00, -9.00]	−14.00 [-26.00, -9.00]	−15.00 [-26.00, -12.00]	0.00 [-3.00, 1.00]	0.00 [-1.00, 1.00]
	P value	**0.000**	**0.000**	**0.000**	0.730	0.245
	P value adj.	**0.002**	**0.002**	**0.002**	1.000	1.000
OHIP-49	Difference (median [IQR])	−31.00 [-61.00, -12.00]	−34.00 [-71.00, -17.00]	−38.00 [-71.00, -18.00]	−3.00 [-22.00, 6.00]	0.00 [-1.00, 4.00]
	P value	**0.001**	**0.000**	**0.000**	0.227	0.528
	P value adj.	**0.003**	**0.002**	**0.002**	1.000	1.000
DN4	Difference (median [IQR])	−2.00 [-2.00, -1.00]	−2.00 [-3.00, -1.00]	−2.00 [-3.00, -1.00]	0.00 [-1.00, 0.00]	0.00 [0.00, 0.00]
	P value	**0.001**	**0.001**	**0.004**	0.429	0.371
	P value adj.	**0.005**	**0.005**	**0.022**	1.000	1.000
VAS	Difference (median [IQR])	−3.00 [-5.00, -1.00]	−4.00 [-5.00, -2.00]	−4.00 [-5.00, -2.00]	0.00 [-2.00, 1.00]	0.00 [0.00, 0.00]
	P value	**0.003**	**0.000**	**0.000**	0.166	0.766
	P value adj.	**0.013**	**0.002**	**0.002**	0.828	1.000

*t1 = baseline; t2 = after the end of therapy; t3 = 12 weeks after t2; t4 = 24 weeks after t2.

†Scores: visual analog scale (VAS), McGill Pain Questionnaire (MGP), Present Pain Intensity (PPI), Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49), Douleur Neuropathique en 4 Questions (DN4), Hospital Anxiety and Depression Scale (HADS), and Geriatric Depression Scale (GDS).

Table 5 Distributions of the score differences between the specified times* (median [IQR]) and corresponding results from the Wilcoxon signed-rank test (both unadjusted and Bonferroni adjusted) (P values in bold are statistically significant)