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.

Evaluating appropriateness and potential efficiency of *Cannabis Sativa* oil for patients with 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 a 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, prepared in specialised pharmacies starting from standardised plant material (cannabis flos) by means of Romano-Hazekamp extraction, and diluted in oil (1 g of cannabis in 10 g of olive oil). The primary outcome was the change in pain intensity (considering Visual Analogue Scale, Present Pain Intensity, 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). 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 favourable 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 *Cannabis Sativa* oil provided was effective and well tolerated in patients with BMS. Further bigger and properly defined randomized controlled trials, with different therapeutic approaches or placebo-controlled, are however needed.

Key words: THC; oil; open-label; BMS; outcome.

Introduction

The International Headache Society has defined the burning mouth syndrome (BMS) 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 disease has been mostly classified under the header “Painful cranial neuropathies”.

The reported pain is described as moderate to severe, quite comparable to tooth ache 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, more commonly occurring in middle-aged and elderly women [3]. Many patients with BMS report benefit 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, in the majority of cases, is a chronic neuropathic pain condition, consisting of 2 main subgroups, peripheral and central [4].

BMS management should be directed to reduce symptoms and pain, but no therapy has been shown to be more effective than others; primary patients’ treatment has been based on the avoidance of possible causes of oral irritation and the provision of psychological support [5,6]. Recent evidences showed that the use of antidepressants (e.g. clonazepam) and alpha-lipoic

acid could provide favourable 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, Δ^9-tetrahydrocannabinol (THC) [9]. The plant's behavioural and psychotropic properties are attributed primarily to THC, which is produced mainly in the leaves and flower buds of the plant; besides it, there are also non-psychoactive cannabinoids with several medicinal functions, such as cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG), and many others [9].

In Italy, use of *Cannabis sativa* for therapeutic purposes (CTP) was first authorized in 2006. Suggestions for its use include chronic pain, nausea and vomitus associated to chemotherapy, appetite stimulation, hypotension effect in glaucoma, and lessening of uncontrolled body and facial movements [10]. Magistral formulations of CTP are prepared by extraction from standardized products, obtained from dried and minced cannabis inflorescences (containing standardized THC and CBD concentration) which that are imported from the Dutch Office of Medicinal cannabis [10]: Bedrocan® (mean amounts of 22% for THC, and <1% for CBD), Bedrobinol® (13.5% for THC, and <1% for CBD), Bediol® (6.3% for THC, and 8% for CBD), and Bedrolite® (0.4% THC, and 9% CBD) [11].

Introduced in 2007, Bediol® is the brand name for the cultivar *Cannabis sativa* L. ‘Elida’. *Cannabis sativa* L. ‘Elida’ is one of the first cannabis cultivars developed specifically to have a higher CBD content. The effects of CBD are distinctly different from 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 oral reported pain not related to a specific clinical mucosal alteration. We tested our hypothesis in a prospective, open-label study, by giving a galenic preparation of therapeutic *Cannabis sativa* in a cohort of subjects with reported oral burning sensation and/or pain, classified as BMS according the International Headache Society criteria. We decided to perform this preliminary evaluation to test logistics and gather information prior to a larger randomized controlled trial regarding sample size, exclusion criteria and materials needed; 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 (CIR-PO-2017/01), and was registered on ISRCTN registry (#XXX).

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

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: a) oral symptoms for at least 12 months; b) age ≥ 18 years; c) no detectable oral mucosal lesions; d) ability to complete the present clinical trial; e) unresponsive to any provided treatment in the previous six months, and yet suffering of oral pain. Exclusion criteria were: a) inability or unwillingness to provide informed consent; b) noteworthy psychiatric or cognitive impairment; c) existence of other diagnoses that could explain the neuropathic pain; d) previous diagnosis of Sjögren Syndrome on the basis of AECG criteria [12]; e) previously head and neck radiotherapy; f) hepatitis C infection; g) pregnant or breast-feeding women; h) patients in treatment with psychotropic drugs; i) 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 influence on oral health were assessed by Visual Analogue Scale (VAS) [consisting of a 100 mm-vertical line, marked wit 0 (=no pain) to 100 (=most severe pain experienced)], McGill Pain Questionnaire, Present Pain Intensity (PPI), and by 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 investigated.

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

Treatment provided

Medical cannabis consists of the dried, pulverised and homogenised flowers of *Cannabis sativa*, cultivated under standardised 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): Bediol®, which 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 in specialised pharmacies starting from standardised cannabis plant material (cannabis flos) by means of Romano-Hazekamp extraction, and diluted in oil (1 g of cannabis in 10 g of olive oil) [16]. Prescription was provided as not-refillable receipt with 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 with a liquid chromatography – mass spectrometry system, as required by the current Italian legislation.

Before starting the protocol, patients were instructed how to take the drug and informed about its possible side effects. Dose prescribed ranged from 10 to 40 drops, as the ideal dosing schedule is currently unknown, since 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 follow: 5 drops twice daily for 5 days, 10 drops twice daily for 5 days, 15 drops twice daily for 5 days, 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 (considering VAS, PPI, McGill Pain Questionnaire and Oral Health Impact Profiles) at t2, t3 and t4.

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

At every follow-up moment ($t_{1\text{-}2\text{-}3\text{-}4}$), 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 median and interquartile range (median [IQR]), whereas categorical variables as frequencies and percentages. Non-parametrical Friedman test was used to assess whether there were any differences among the distributions of each score (HADS score, GDS score, MC-GILL Pain, PPI, OHIP-14 score, OHIP-49 score, DN4 score and VAS) at four different times (t1, t2, t3, t4). Five pairwise comparisons (t2 *vs* t1, t3 *vs* t1, t4 *vs* t1, t3 *vs* t2 and t4 *vs* t2) for each score have been performed using the non-parametrical Wilcoxon signed-rank test, standard and adjusted (using the Bonferroni multiple testing correction method) p-values were computed. All statistical analyses were carried out using R software (version 3.6.2). Statistical significance was defined at P value of <0.05.

Results

Initially 34 patients were selected; 2 of these were not included because presenting exclusion criteria (diagnosis of Sjögren Syndrome, and treatment with psychotropic drugs). Fifteen patients refused to be part of this study.

Seventeen patients completed the treatment provided for 4 weeks, of whom 14 were women (82.4%); the mean age at presentation was 71 years.

Table 1 reported the sociodemographic characteristics, risk factors and haematological evaluation at baseline; only 1 patient (5.9%) showed a positive patch test, in particular for nickel, but none dental allergen was detected in the oral cavity.

Table 2 shows the frequency of oral symptoms, their description, and site of

involvement; xerostomia and dysgeusia were frequently reported; tongue was the most common affected site (more than 70%).

Table 3 shows the frequency of systemic diseases and the daily medication intake in the study group. The most commonly detailed systemic diseases were hypertension and hypothyroidism, followed by osteoporosis.

Subjects were previously treated with different medication 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

Scores distribution at different times is described in Table 4 and Figure 1. 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 pointed-out times and corresponding results. The MGP, PPI, OHIP-14, OHIP-49, DN4 and VAS statistically diminished at t2, t3 and t4 if compared to 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. Comparing data after 12 and 24 weeks with data after 4 weeks of treatment provided, 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 provided, displaying a favourable 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 comparing results obtained immediately after the end of therapy (t2) with baseline (t1), HADS and GDS score did not show a statistical difference if adjusted, whereas HADS alone showed a statistically significant reduction ($p < 0.05$) 24 weeks after end of therapy if compared to baseline (Table 5). Similarly, for reported pain, comparing data after 12 and 24 weeks (after the end of the therapy) with data after 4 weeks of treatment provided, no statistical significances were detected (t3 *vs* t2 and t4 *vs* t3) (similarly if 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, not causing any significant treatment modifications, the most frequent of which were dizziness (17.6%), headache (11.8%) and constipation (5.9%). All

reported effects were transient and disappeared in 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 remain a challenge and is considered a high urgency in oral medicine [18, 19]. Used therapies include hormone replacement therapy, anticonvulsants, antidepressants, capsaicin, benzodiazepines, analgesics, alpha-lipoic acid, photobiomodulation with laser and cognitive therapies; nevertheless, none of them appeared to be superior [20]. This wide-ranging diversity should require more detailed studies to assess which treatment should be the gold standard for this condition.

Cannabinoids display their actions due to selective binding to specific receptors. Among these, cannabinoids receptors types 1 and 2 (CBR1 and CBR2) are the main receptors, being G protein-coupled receptor superfamily (GPCR) [21]. CB1 is predominantly expressed in the central nervous system, particularly in cerebral cortex, cerebellum, and hippocampus, being activated by widespread signalling endocannabinoid system, through endogenous cannabinoids, such as anandamide and 2-arachidonyl glycerol [22], where it is involved in different pathways of neuronal plasticity, exerting a role of neuromodulators, rather than neurotransmitters. Specifically, CBR1 and CBR2 receptors are coupled directly to Gi/o proteins to down-regulate of 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 glutamate and GABA at synaptic level, can be regulated [23] in cortical and medullar pathways of locomotion, memory, and pain [24]. However, CBR1 is also expressed in gastrointestinal, urogenital, and cardiovascular system, despite its function is under scrutiny [25]. CBR2 is also expressed in immune systems, occurring also in neurons, glials and endothelial cells of substantia nigra, cerebral cortex and hippocampus, with activity and role still undefined when compared to CB1 [24].

Of the components of Cannabis, THC is the most abundant compound, being responsible of the most intense psychoactive properties [26]. THC has ability to bind to both CBR1 and CBR2, differently from 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 preference for CBR2 rather than CBR1 [27]. THC has been largely known for its psychoactive effects, and it is approved treatment for chemotherapy-induced nausea and vomiting, and as appetite stimulant amid cachectic patients [26]. On the other hand, CBD has been reported to bear analgesic, anti-inflammatory and neuroprotective properties, being deployed with encouraging outcomes in the management of anxiety, post-traumatic stress disorder [28,29], being approved by FDA as antiepileptic for rare disorders [30].

The main strength of this study relies on the novelty of the intervention, being, to the best of our knowledge, the first study analysing role of cannabinoids in management of unresponsive BMS. Our hypothesis derived from previous

assessment of the potentialities of THC/CBD formulation in the management of other neuropathic disorders [15,31].

Concerning route of administration, oral and inhaled formulations have been approved by Italian Ministry of Health [32], with decoction being the preferential pharmaceutical form, whereas inhaler route should be considered in those cases where oral form would not be able to provide its therapeutic properties. As presented in this work, oil extract form is also allowed. Despite inhalation being more often studied in literature and considered as more effective [33], for the present pilot study we considered oral drops as being more patient-friendly, giving also a better control on the daily dosage among the elderly. Furthermore, literature showed that 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 preparation among BMS patients, who notoriously require pain relief over an extended period of time [34]. Furthermore, such formulation was preferred to facilitate reproducibility, due to the fact that inhaled formulation is not allowed in some countries [26], and that use of vaporizers or similar devices could encourage, if not reinforce, the habit of smoking in some patients.

Bediol® formulation, despite the relatively high concentration of THC (6.3%), notoriously responsive of psychoactive effects [35], did not lead to serious adverse effects in the present study. On the other hand, the well-balanced composition of Bediol® in terms of similar concentration of CBD (8%) and THC (6.3%) 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 six months after end of treatment (t4), with a sole exception of a minimal increase of OHIP-49 from t3 (average 29.00) to t4 (average 32.00), still insufficient to jeopardize the scale of reduction of OHIP-49 from t4 to t1, where starting average of OHIP-49 was 88.00. On the other hand, despite what reported in literature with regards to the ability for THC/CBD to facilitate management of anxiety and/or depression [28,29], Bediol® did not provide any immediate antidepressant nor 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 value at six months after end of treatment were compared to 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 BMS' etiopathogenetic theories, 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. Such smallness of sample is a consequence of the strict eligibility criteria aforementioned. On the other hand, the short-term therapy was decided due to the novelty of the product and the absence of empirical evidence in literature regarding its application in oral medicine. In this sense, future research should compare Bediol® with a different formulation, such as Bedrolite®, to assess if 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 can provide a reliable and safe treatment for long-term management of BMS both in terms of symptom relief and quality of life [37]. Even Clonazepam, considered effective for symptom remission in patients with BMS, as showed in a recent meta-analysis [38], bears important repercussions, especially in the form of potential addiction in the long-term [39,40]. On the other hand, controversy still remains with regards to which variables can influence dependence to Cannabis derivates, with some studies providing positive correlation with high THC content [41] and other focusing on patient-related variables [42]. Moreover, it should be highlighted that evidence on these aspects are often provided in samples of young individuals, whereas limited data is available on effectiveness and safety of cannabis in older subjects, where comorbidity, polypharmacy and increased susceptibility to cognitive disorders have to be carefully assessed [26,43].

Finally, despite limitations in patients' enrolment, which might arise due to potential impairment caused by THC while driving or at workplace [28], in the specific scenario of BMS patients, such restriction is almost marginal, with most of BMS patients being diagnosed as elderly women of 60-69 years of age, and frequently retired from work [44,45]. In the present work, only 17.8% of patients were employed (Table 1) and in no case impairment at workplace was experienced.

With elderly patients being the most commonly affected by BMS, further bigger and properly defined randomized controlled trials, with different therapeutic approaches or placebo-controlled, are needed in order to

ascertain the clinical efficacy of THC products compared with standard medical treatments for BMS patients.

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Table 1. Sociodemographic characteristics, risk factors and haematological evaluation at baseline of 17 analysed patients

Demographical variables	
Age (median [IQR]), years	71.00 [62.00, 72.00]
Gender = male (%)	3 (17.6)
Married = yes (%)	14 (82.4)
Employed = yes (%)	3 (17.6)
Education level, mean (SD), years	8.9 (5.9)
Risk factors	
BMI (median [IQ])	22.31 [21.05, 23.23]
Smoker = yes (%)	1 (5.9)
Alcohol consumer = yes (%)	3 (17.6)
Haematological evaluation	
Vitamin B1, mean (SD), µg/dl	62 (8.6)
Vitamin B6, mean (SD), µg/l	26.1 (16.3)
Vitamin B12, mean (SD), pg/ml	393.2 (121.6)
Folic acid, mean (SD), ng/ml	14 (8.5)
Serum iron, mean (SD), µg/dl	123.2 (22.9)
Serum ferritin, mean (SD), µg/l	93.6 (40.8)
Transferrin, mean (SD), mg/dl	261 (26.6)
Fasting blood glucose, mean (SD), mg/dl	97.1 (16.5)
Zinc, mean (SD), mg/l	0.86 (0.1)

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

Oral symptoms	
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 3. Incidence of systemic diseases and daily medication consumption in 17 BMS patients [frequency and (%)]

Systemic disease	
None	2 (11.8)
Hypertension	5 (29.4)
Hypercholesterolemia	3 (17.8)
Osteoporosis	4 (23.5)
Hypothyroidism	5 (29.4)
Type II diabetes mellitus	2 (11.8)
Rheumatoid arthritis	3 (17.8)
Gastro-Esophageal 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	3 (17.8)
Proton pump inhibitors	3 (17.8)
Statins	2 (11.8)
Vitamin D	3 (17.8)

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

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 Analogue 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), Geriatric Depression Scale (GDS).

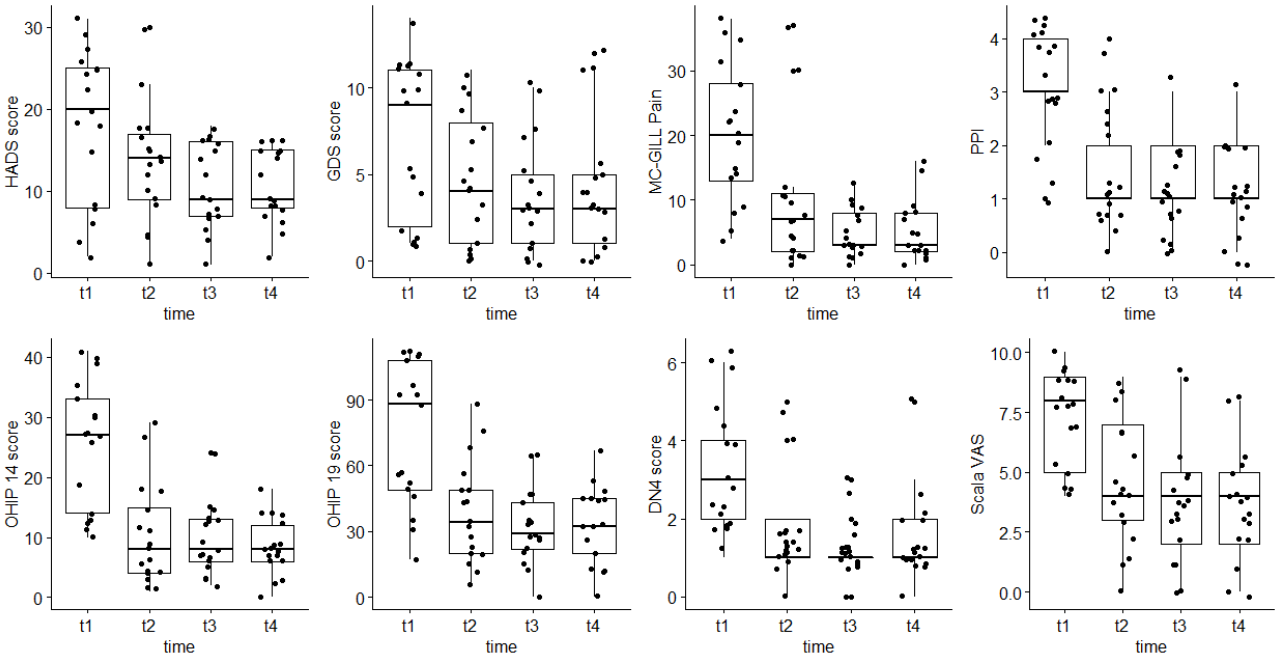
Table 5. Distributions of the scores'[§] differences between the pointed-out times* (median [IQR]) and corresponding results from the Wilcoxon signed-rank test (both unadjusted and Bonferroni-adjusted) (p-value in bold are statistically significant)

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

[§]SCORES. Visual Analogue 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), 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]
	pvalue	**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]
	pvalue	**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]
	pvalue	**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]
	pvalue	**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]
	pvalue	**0.003**	**0.000**	**0.000**	0.166	0.766
	p-value adj.	**0.013**	**0.002**	**0.002**	0.828	1.000

Figure 1. Box plot of each score's[§] distribution at the different times* (black points correspond to individual values)



*t1=baseline; t2=4 after the end of therapy; t3=12 weeks after t2; t4=24 weeks after t2.

[§]SCORES. Visual Analogue 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), Geriatric Depression Scale (GDS).