Trazodone in Burning Mouth Pain: A Placebo-Controlled, Double-Blind Study

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Aims: *An 8-week parallel, placebo-controlled, double-blind trial evaluated the efficacy of the antidepressant trazodone in the treatment of chronic burning mouth pain.* **Methods:** *Thirty-seven carefully selected women aged 39 to 71 (mean 58.6 years) were randomized to receive either 200 mg of trazodone or a placebo in a similar manner. Pain and pain-related symptoms were evaluated on a visual analogue scale and other measures at 0, 2, 4, and 8 weeks.* **Results:** *There were no significant differences between the groups in treatment effects for pain or pain-related symptoms. Seven patients in the trazodone group and 2 in the placebo group failed to complete the trial because of side effects. The most common side effects were dizziness and drowsiness.* **Conclusion:** *In this controlled trial, trazodone failed to relieve burning mouth pain.*

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Key words: burning mouth, oral mucosal pain, chronic pain, trazodone, antidepressants

Burning mouth syndrome (BMS) is characterized by a burning mucosal pain without clinically detectable lesions on the oral mucosa. The pain is typically reported at more than one oral site, the tongue, the palate, and the lower lip mucosa being the most frequently affected sites.[1,2] Patients with BMS also frequently complain of dry mouth and loss of or altered taste.[3] The prevalence of prolonged oral burning is about 8%, with less than 1% of those with the disorder suffering from constant burning pain symptoms.[4] The etiology and pathophysiology of BMS is unknown, but many causative factors of a local, systemic, or psychogenic nature have been proposed, including hyposalivation, oral candidiasis, the preanemic stage of nutritional deficiencies (especially of iron, B_{12} vitamins, and folate), hyperglycemia, and hormonal changes at menopause. However, controlled studies have not provided confirmation for the proposed etiologies,[1] and treatment based on any of these etiologies is usually unsatisfactory.[5,6] Burning mouth syndrome can be considered a chronic pain syndrome, with symptoms that usually last from several months to several years.[7,8] The pain is experienced as quantitatively similar

but qualitatively different from toothache pain. The verbal descriptor most commonly chosen by BMS subjects is "burning."[9] Burning pain is considered characteristic of chronic neuropathic pain conditions in general, and some recent data seem to suggest peripheral or central nervous system involvement as a possible underlying factor in BMS.[3,10–12]

Antidepressants are frequently used for the treatment of different chronic pain conditions, such as chronic neuropathic pains. In particular, tricyclic antidepressants have been shown to be effective in the treatment of different pain conditions.[13–15] The use of tricyclic antidepressants, eg, amitriptyline, has also been recommended in the treatment of BMS pain,[3,5,16] but their anticholinergic side effects, especially dry mouth, may make them unsuitable. The evidence of the efficacy of newer antidepressants in chronic pain is insufficient, but their use has been recommended in cases in which tricyclics cannot be used because of their adverse effects.[17]

Trazodone is a triazolopyridine derivative that is chemically and pharmacologically unrelated to other currently available antidepressants. Its pharmacologic activity is thought to be modulated via antagonism at serotonin 5-HT_2 receptors; the precise mechanism of action in humans is, however, not fully understood.[18] It is reported to lack almost totally any anticholinergic side effects, which can be considered an important aspect in trying to find effective pain medication for a pain problem that is often associated with the feeling of a dry mouth. Trazodone has been compared with amitriptyline in patients with mainly a burning type of pain. Both drugs appeared to be equally effective in relieving pain, but trazodone caused significantly less dry mouth.[19] With this background, the present study was designed to find out whether trazodone would be effective and suitable for the treatment of chronic BMS pain.

Material and Methods

The material of the study consisted of 37 women (aged 39 to 71 years, mean 58.6 years) selected over a 5-year period (from 1992 to 1996) from 146 consecutive female patients who were referred to the Department of Oral Diseases at Turku University Central Hospital because of oral mucosal burning pain. One of the investigators performed a screening evaluation of all subjects. The patients underwent a thorough clinical examination, including measurement of whole salivary flow, blood samples (blood count and levels of glucose, B_{12} vitamins, and folate), and diagnosis of candidiasis. The investigators asked patients about pain intensity and duration, overall health, and medications.

Altogether, 35 patients whose pain could possibly be related to some physical finding were excluded to obtain a strictly diagnosed group of patients with burning mouth pain (16 patients had oral mucosal lesions, 14 patients had oral candidiasis, 3 patients had hyposalivation, 1 had hyperglycemia, and 1 had low serum folate). In addition, 13 patients who used centrally acting pain medications or anxiolytics, as well as 2 patients who were considered to suffer from dementia, were excluded.

Criteria for inclusion were daily, or almost daily, oral burning pain that had lasted 6 months or longer and had a moderate to severe intensity (at least 30 on a visual analogue scale [VAS] of 0 to 100 mm). Forty-one of the remaining patients were not eligible, 30 because the pain did not occur daily or almost daily, 8 because of mild pain intensity, and 3 because of recent onset of the pain problem. Eligible patients received information about the study, and those willing to participate were included after granting informed, written consent. Eighteen patients refused to participate.

The design of the trial was a double-blind, randomized, parallel-group, placebo-controlled study. Identical capsules of trazodone and of passive placebo were packed in the same way. Randomization was performed in blocks of 6 by the manufacturer of the drug (Orion). The trial protocol was approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital.

Patients began taking one 100-mg capsule of trazodone in the evening for the first 4 days, and after this, the medication was increased to two 100-mg capsules in the evening. Control patients took the placebo in a similar manner. The trial lasted for 8 weeks. Patients were evaluated at 0, 2, 4, and 8 weeks by the other investigator.

Visual analogue scales were used at each time point to measure the intensity of BMS pain; the influence of the pain on eating, speaking, and sleeping; and the suffering caused by the pain. At the beginning and end of the trial (0 and 8 weeks), the intensity and character of the pain were further defined by the use of the Finnish version[20] of the McGill Pain Questionnaire.[21] Possible depression was measured with the Beck Depression Inventory. The pain threshold of the subjects was

assessed at the beginning of the trial by asking them to estimate the intensity of the pain they experienced when taking a regular blood test. The patients' assessment of their total improvement and benefits of the treatment in relation to side effects were obtained separately at the end of the trial.

During the trial, subjects kept diaries on possible side effects and on other pain medication they had taken. Patient compliance was estimated by counting the capsules left in the bottle at the final visit. The randomization code was not opened during the trial. During the trial, nothing suggested that the blind had not remained intact for the patients. The examiner could not guess the treatment of the subjects.

Statistical Analysis

Analysis of variance of repeated measurements was used to analyze the treatment and time effects, as well as the interaction of treatment and time for normally distributed responses. If necessary, the logarithm or square-root transformation was applied. The analysis of variance was carried out with a mixed procedure on SAS software (SAS Institute, Garry, NC), which allows missing data in follow-up and includes the possibility of modeling the covariance structure of measurements. For categorical responses, the statistical comparison between treatment and placebo was carried out with the Fisher exact test separately at each time point. For ordinal scaled outcome variable, the Kruskal-Wallis test was applied. P values of less than 0.05 were interpreted as significant, and the level in confidence intervals was 95%. Statistical calculations were performed with SAS System for Windows, release 6.12 (1996).

Results

Of 37 patients, 18 received trazodone and 19 received a placebo. The mean duration of pain in the trazodone group was 3.0 years (6 months to 17 years) and in the placebo group it was 2.8 years (6 months to 20 years). The mean age of the patients in the trazodone group (61.1 years) was slightly higher than in the placebo group (56.2 years). The groups had a baseline difference in pain intensity at the start of the medication, the mean VAS in the trazodone group being 12.6 mm higher than in the placebo group ($P < 0.05$). Patients randomized in the trazodone group considered taking a blood test somewhat more painful (mean VAS 7.6) than patients in the placebo group (mean VAS 5.4), but the difference was not statistically significant. There were no other baseline differences between the groups. No other pain medications for BMS pain were used by the patients, but 2 patients in the trazodone group and 2 in the placebo group used anti-inflammatory analgesics for other pain conditions regularly or almost regularly.

Seven subjects in the trazodone group and 2 in the placebo group failed to finish the trial because of side effects, mainly because of dizziness. In the trazodone group, 4 subjects withdrew soon after the start of the trial and 3 subjects withdrew after 2 to 4 weeks. In the placebo group, 1 subject withdrew during the first week and another withdrew after 6 weeks. Based on a count of the pills, compliance was excellent among the patients who completed the trial.

The difference between the groups in treatment effect or treatment by time interaction for pain intensity was not significant (Fig 1). The mean difference in pain reduction between the trazodone and placebo groups at 8 weeks, as shown by the VAS, was –4.8 (95% confidence interval, range: –20.3 to 10.7). However, there was a general reduction in the pain ratings. The mean pain VAS in the trazodone group at the beginning of the study was 59.2, and at 8 weeks it was 45.3; in the placebo group VAS values were 46.6 and 34.3, respectively. The decrease in pain intensity was significant ($P < 0.01$) in both groups. There were no significant differences between the groups in treatment effects or treatment by time interactions for the influence of the pain on eating, speaking, and sleeping, or for the suffering caused by the pain.

At the baseline, 17 subjects were identified by the Beck Depression Inventory as depressed, using a cut-off score of 13. There was no significant treatment effect or treatment by time interaction on the depression score, but the scores decreased significantly ($P < 0.01$) in both groups during the trial. The subgroup of depressed patients did not differ from the whole group with respect to any pain-related measurements, but the number of drop-outs was slightly higher (6 of 9) in this subgroup.

The mean score for the number of words chosen in the McGill Pain Questionnaire, which is thought to reflect the intensity of the pain experienced,[21] was 8.2 in the trazodone group and 7.5 in the placebo group at the baseline. There was no significant difference between the groups or within the groups at different time points.

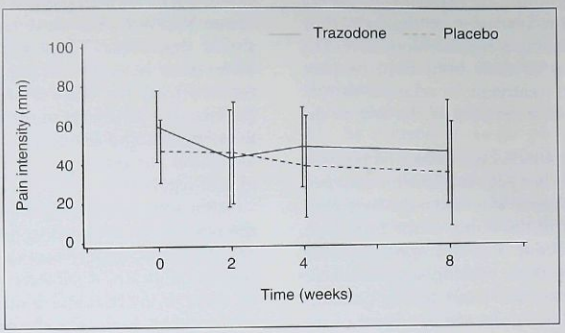

Fig 1 Graph showing changes in pain intensity. The mean values and standard deviations of pain intensity on a 100-mm visual analogue scale in trazodone and placebo groups are shown at different follow-up points.

Table 1 Side Effects Reported by Patients

	Treatment	
Side effect	Trazodone (n = 18)	Placebo (n = 19)
Dizziness	11	1
Drowsiness	9	2
Abdominal pains	5	4
Headache	3	2
Palpitations	2	2
Tremor	2	1
Dry mouth	3	1
Nightmares	0	2
Urinary incontinence	1	0

Patients in the trazodone group reported significantly more dizziness ($P < 0.001$) and drowsiness ($P < 0.05$) than patients in the placebo group (Table 1). Two patients in the trazodone group and 8 in the placebo group reported no side effects. There were no significant differences between groups in the patients' global assessment of improvement or benefits of the treatment (Tables 2 and 3).

Discussion

Burning mouth syndrome remains an ill-defined condition that presents both diagnostic and treatment problems.[3,22] We tried to select our patient material very carefully according to the latest understanding of the nature of the problem and only included patients for whom no obvious cause for the burning mucosal pain was evident in order to get material with "true" burning mouth symptoms.[22] For this reason, and because only patients with chronic, frequent, and moderate to severe

Table 2 Patients' Global Assessment of Improvement at the Final Visit

	Treatment	
Assessment	Trazodone (n = 11)	Placebo (n = 17)
Improved	8 (73%)	13 (76%)
No effect	2 (18%)	4 (24%)
Worse	1 (9%)	0 (0%)

Table 3 Patient Assessment of Benefits in Relation to Side Effects

	Treatment	
Assessment	Trazodone (n = 11)	Placebo (n = 16)
Efficient	6 (55%)	13 (81%)
Neutral	4 (36%)	3 (19%)
Inconvenient	1 (9%)	0 (0%)

intensity pain were included, the recruiting of the patient material took a long time. Also, the great number of patients who were unwilling to participate in the trial added to the problem. The reasons for refusal were various and included long-distance travel, negative attitudes in general toward medications, and ability to cope with the pain. The pain of those who refused was of a slightly shorter duration but had the same mean intensity as that of the participants.

According to the results of this trial, trazodone failed to relieve burning pain or pain related symptoms. There were no significant differences in treatment effects with trazodone compared to the placebo. Considering the range of the confidence limits of the main outcome of this study, the conclusion seems warranted since the reduction in pain VAS compared to placebo was +10.7 at its best and –20.3 at its worst.

Our trial lasted 8 weeks, which should be long enough to detect treatment effects of antidepressants in pain treatment. Trazodone dosages used in the treatment of depression can vary: older patients are reported to tolerate dosages of up to 300 or 400 mg per day.[18] We used a lower dosage, 200 mg, which was comparable to that used in other studies on trazodone in pain patients and possibly explains the lack of efficacy on depression in this study. Ventafridda et al[19] reported receiving comparable treatment effects on pain with 75 to 225 mg of trazodone and 25 to 75 mg of amitriptyline. In the only trial on pain patients in which trazodone was titrated as high as side effects allowed, the mean dosage remained at 201 mg.[23] The rather high occurrence of side effects reported by our patients might have rendered the use of any higher dosages difficult. The side effect profile corresponded to that reported on trazodone in general.[18] Some patients in our material, as well as in other studies,[23,24] have also reported dry mouth.

In contrast to the positive findings presented by Ventafridda et al,[19] the present study suggested that trazodone lacks analgesic efficacy in chronic pain. This is in line with some previous placebo-controlled studies on trazodone.[23,24] The results on BMS patients were not encouraging: the efficacy was comparable to that of the placebo, and side effects were common.

In general, there is growing evidence to support the effectiveness of antidepressants in the treatment of chronic pain,[13,14] but their mode of action is poorly understood.[14,17,25] Tricyclic antidepressants with mixed serotonergic and noradrenergic biochemical profiles have the strongest evidence to support their efficacy in the treatment of different chronic pain conditions, but there are no controlled trials on their use in BMS pain.

The only earlier controlled trial of pain management in BMS has been the work by Loldrup et al.[26] In their placebo-controlled study, which included patients with different idiopathic pains, they treated a group of 77 burning mouth pain patients with clomipramine, an antidepressant with serotonergic biochemical profile; mianserin, a noradrenergic antidepressant; or a placebo. No statistically significant difference between the 3 treatments was found in patients with BMS.

Considering the fact that BMS pain can continue for years and can, at worst, be experienced as severe, daily, continuous pain, it is understandable that there is a real need to try to find effective treatment for the symptoms. In the present placebo-controlled trial, trazodone failed to relieve burning mouth pain. Obviously, the search for an effective treatment for burning mouth pain must continue.

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