Comparative Efficacy of SSRIs and Amisulpride in Burning Mouth Syndrome: A Single-Blind Study

Giuseppe Maina, M.D.; Alberto Vitalucci, M.D.;
Sergio Gandolfo, M.D.; and Filippo Bogetto, M.D.

Introduction: Although a significant amount of evidence indicates the efficacy of some antidepressants in treating psychogenic pain and somatoform disorder, very few studies have investigated their possible therapeutic action in burning mouth syndrome (BMS). The purpose of this 8-week, single-blind study was to provide preliminary data on the efficacy and tolerability of amisulpride and the selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline for patients with BMS.

Method: Seventy-six patients with BMS (diagnosed according to the criteria in the literature and integrating the Diagnostic Interview Schedule-Revised for a complete psychiatric assessment), with no possible local or systemic causes and without concurrent major depression, were randomly assigned to receive amisulpride (50 mg/day), paroxetine (20 mg/day), or sertraline (50 mg/day). Efficacy assessments included a visual analogue scale (VAS) for pain intensity, the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Rating Scale for Anxiety (HAM-A), and the Clinical Global Impressions scale (CGI).

Results: All 3 treatment regimens resulted in a significant improvement from baseline in burning mouth symptoms at week 8 as demonstrated by the quantitative (mean reduction in VAS, HAM-D, and HAM-A scores) and qualitative (percentage of responders) analyses. Amisulpride showed a shorter response latency than the SSRIs. No serious adverse events were reported, and the incidence of side effects did not differ among the 3 groups. None of the patients who received amisulpride withdrew from the trial, whereas withdrawal from the trial occurred within the first week of treatment in 11.5% of patients (N = 3) treated with paroxetine and in 21.7% of patients (N = 5) treated with sertraline.

Conclusion: The data suggest that amisulpride and SSRIs may be effective treatments for BMS; they are equally effective and equally well tolerated in the short-term treatment of BMS. Amisulpride is associated with better compliance within the first week of treatment and with a shorter response latency in comparison with SSRIs. This finding may indicate that amisulpride is especially useful at the beginning of drug therapy of BMS. Double-blind, placebo-controlled trials are needed to further document the efficacy of amisulpride and SSRIs in the treatment of BMS.

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Received April 20, 2001; accepted July 31, 2001. *From the Department of Neuroscience, Psychiatric Unit (Drs. Maina, Vitalucci, and Bogetto), and the Department of Oral Medicine and Periodontology (Dr. Gandolfo), University of Turin, Turin, Italy.*

Reprint requests to: Giuseppe Maina, M.D., Department of Neuroscience, Psychiatric Unit, University of Turin, Via Cherasco 11, 10126 Turin, Italy (e-mail: bogetto@molinette.unito.it).

Burning mouth syndrome (BMS) is defined as burning or painful sensations in an oral cavity with a normal mucosa.[1–7] Epidemiologic studies on BMS have estimated a prevalence of 2.6% to 5.1%, and the rate of occurrence of this disorder in men is less than 20% of that in women.[1,4,5,8] Furthermore, the frequency of the disorder in women is peculiar: large variations in prevalence are found at different ages, with the greatest frequency in women beyond middle age.[1,4,6] The variation in prevalence between different ages is less in men, with the syndrome most frequent between 30 and 59 years of age.[1,8]

Apart from a burning or painful feeling in the mouth, these patients usually report other oral symptoms,[6,7] such as gustatory changes or xerostomia,[6,8] and several associated general symptoms, such as muscle pain, headache, or dizziness.[5,8]

Because of its characteristic epidemiology and its peculiar clinical features, many authors consider this disorder a distinct clinical entity. Evidence offered in support of this argument included our previous findings[8] that, for most patients, the onset of BMS chronologically precedes the onset of an additional psychiatric diagnosis and that the demographic and clinical features of BMS are not influenced by the presence of a comorbid psychiatric syndrome; moreover, a substantial percentage of patients with BMS (nearly 30%) exhibit this disorder in the absence of any other psychiatric diagnosis. The most prevalent comorbid diagnoses are major depressive episode (actual comorbidity: 20%, lifetime comorbidity: 23%) and generalized anxiety disorder (actual comorbidity: 25%, lifetime comorbidity: 29%); no other Axis I psychiatric disorders have been found to be significantly associated with BMS in comparison with healthy controls.[8]

Only a few studies have been published concerning drug treatment of BMS, and most of them were uncontrolled trials and/or were not conducted by psychiatrists. Several substances such as capsaicin,[9,10] sucralfate,[11]

dyclonine HCl,[12] and benzydamine hydrochloride[13] have been tested in topical administration without showing significant effects on mouth pain.

Several uncontrolled trials investigated the efficacy of benzodiazepines in the treatment of BMS: in open trials, diazepam and chlordiazepoxide showed poor efficacy with regard to the burning symptomatology.[14,15] Two naturalistic observations[16,17] revealed that clonazepam may be effective in treating BMS: partial-to-complete remission was described in approximately 45% of patients, but with a significant percentage—about 25%—of dropouts due to side effects, usually drowsiness.

Although a significant amount of evidence indicates that some antidepressants have an analgesic effect in psychogenic pain and in somatoform disorders,[18] very few studies have investigated their possible therapeutic action in BMS. Several uncontrolled trials tested tricyclic antidepressants: taken together, no significant advantage over diazepam and over placebo could be found for amitriptyline and for clomipramine with regard to BMS.[14,15,19,20] A possible therapeutic effect of mianserin[20] and of doxepin[4] also has been investigated in open-label trials, which suggested that both drugs are not more effective than placebo. The only double-blind comparison of trazodone and placebo in the treatment of BMS that has been performed showed poor efficacy of the active drug.[21] Among selective serotonin reuptake inhibitors (SSRIs), a case report described a very good therapeutic effect of sertraline combined with psychodynamic therapy.[22] Several clinical studies indicate that substitute benzamides have therapeutic efficacy in somatoform disorders (for example, see Mucci et al.[23]), and in a preliminary open-label study, we had suggested that amisulpride has equal clinical global efficacy in treating BMS.[8] Amisulpride is a substituted benzamide related to sulpiride, with specific dopamine D_2 and D_3 receptor blocking and little effect on other receptors. It has been shown to be as effective against negative symptoms, where 100 mg/day seems optimum.[24] In Italy, amisulpride is licensed for dysthymia on the basis of a number of studies that have shown a low dose (50–100 mg/day) to have some efficacy in dysthymic disorder.

The aim of this prospective randomized, single-blind study was to compare the efficacy and tolerability of amisulpride and SSRIs (sertraline and paroxetine) over 8 weeks of treatment in a group of patients suffering from BMS.

METHOD

Sample

Subjects for this study were recruited at the Department of Oral Medicine and Periodontology of the University of Turin. Inclusion criteria were a diagnosis of BMS, on the basis of literature criteria,[2,25–27] with the exclusion of any possible local or systemic cause. Subjects with a lifetime diagnosis of schizophrenia or other psychotic disorders and subjects with concurrent major depression, according to DSM-IV, were excluded from the study. Diagnostic assessment was made through a structured interview (Diagnostic Interview Schedule-Revised [DIS-R]).[28] Patients who had severe medical illness, were pregnant or lactating, or had positive history of breast cancer, allergy, or intolerance to the agents used in the study were excluded. None of the patients had taken any psychoactive drug for at least 4 weeks before the time at admission, and no other concomitant treatment, neither psychotropic nor psychotherapeutic, was allowed for the duration of the study.

Approximately 140 subjects with BMS were screened consecutively for inclusion in this study, and 101 were referred to the Psychiatry Unit of the University of Turin for psychiatric evaluation, because all likely local or systemic causes were excluded. Of these 101 patients, 59 (58.4%) had at least 1 other concomitant psychiatric disorder: 51 had another diagnosis in addition to BMS (pain disorder, according to DSM-IV), and 8 had 3 Axis I diagnoses. Nineteen patients were subsequently excluded for concurrent major depression, and 4 patients were excluded for comorbid psychotic disorders. Seventy-six patients (60 women and 16 men) gave their written consent to participate in the study (2 refused to participate). Of the 76 patients included in the study, 42 met diagnostic criteria for BMS only (pain disorder, according to DSM-IV), with no other current diagnoses; 29 had another diagnosis in addition to BMS; and 5 had 3 diagnoses. The most frequent disorders were mood and anxiety disorders: concurrent generalized anxiety disorder was diagnosed in 21 patients; dysthymic disorder, in 9 patients; specific phobia, in 6 patients; depressive disorder not otherwise specified, in 5 patients; and panic disorder, in 1 patient. Two patients had concomitant hypochondriasis.

Study Design

At the time of enrollment, each patient was randomly assigned to 1 of the 3 eight-week standardized treatments of amisulpride, paroxetine, or sertraline. The ratings were all made under blind conditions, but patients were not blinded to which medication they were taking. The dosing schedules were as follows: group 1 (amisulpride), 50 mg/day from day 1; group 2 (paroxetine), 20 mg/day from day 1; group 3 (sertraline), 50 mg/day from day 1. The occurrence of severe side effects (as defined by item 3 of the Clinical Global Impressions scale [CGI] "efficacy index"), lack of compliance (missing more than 2 consecutive doses of the drug), or withdrawal of patients' consent were criteria for premature discontinuation of the study.

Clinical Assessment

The patients were clinically assessed by scoring a vertical 10-cm visual analogue scale (VAS)[29]; they were asked to indicate the mean pain intensity for the week preceding

the consultation. Depressive symptoms were evaluated according to the Hamilton Rating Scale for Depression (HAM-D),[30] anxiety symptoms were evaluated according to the Hamilton Rating Scale for Anxiety (HAM-A),[31] and clinical efficacy and tolerability of the treatment were assessed using the CGI.[32] The rating scales were administered at baseline and every 2 weeks until the end of the study by 2 trained psychiatrists (G.M., A.V.) blinded to the treatment group.

Statistical Procedures

Analysis of variance (ANOVA) was used to test for comparability of treatment groups for continuous variables such as index age, age at onset, and baseline scores for the VAS, HAM-D, HAM-A, and CGI. A chi-square test was used to compare sex ratio among groups.

The analyses of rating scale results were performed on the groups of patients who did not prematurely withdraw from the study (efficacy sample). Treatment efficacy within groups was analyzed using the Student t test for paired samples. Comparisons between SSRI treatments and amisulpride treatment were also made using the Student t test.

A comparative qualitative evaluation of treatment response was also performed by calculating the percentage of responders in each group. The adopted criteria for response consisted of a reduction of the VAS score > 50% from baseline together with a score < 3 on the CGI-Global Improvement scale. A survival analysis (using BMDP Statistical Software[33]), in which responders were considered to be "dead cases" and nonresponders were considered to be "survivors" at the end of the treatment period (week 8), was performed. This analysis allowed us to calculate the cumulative percentage of responders to each treatment together with the mean latency (i.e., mean survival time) of the therapeutic effect of the 3 drugs.

Safety analysis was performed on the "intent-to-treat safety" patient sample that consisted of those patients randomly assigned into the trial who took at least 1 capsule of study medication and had at least 1 valid postbaseline safety evaluation while on drug treatment. The number and percentage of patients experiencing each specific adverse event for treatment-emergent signs and symptoms were calculated for all treatment groups. Treatment-emergent signs and symptoms were defined as experiences that appeared for the first time during the single-blind period or experiences that were already assessed at baseline, but increased in severity during the single-blind period. Chi-square contingency tables were constructed to compare the rates of adverse events among the 3 treatment groups.

RESULTS

Of the 76 patients who were recruited for the study, 27 were randomly assigned to receive amisulpride; 26, to receive paroxetine; and 23, to receive sertraline. A summary of demographic information, including gender, index age, and age at onset of BMS, is displayed by treatment group in Table 1. Moreover, the 3 treatment groups did not differ significantly in respect to baseline rating scale total scores (VAS, HAM-D, HAM-A, and CGI-Severity of Illness) and in respect to actual comorbidity rates with other psychiatric disorders.

Table 1. Patient Characteristics in the 3 Treatment Groups

Characteristic	Amisulpride (N = 27)	Paroxetine (N = 26)	Sertraline (N = 23)	p Value
Gender, N (%)[a]				NS
Female	21 (77.8)	20 (76.9)	19 (82.6)	
Male	6 (22.2)	6 (23.1)	4 (17.4)	
Age, mean ± SD, y[b]	64.3 ± 7.2	63.4 ± 6.7	62.8 ± 5.9	NS
Age at onset, mean ± SD, y[b]	62.7 ± 4.2	62.0 ± 4.0	61.4 ± 4.1	NS
Illness duration, mean ± SD, y[b]	1.4 ± 0.4	1.5 ± 0.5	1.4 ± 0.3	NS

[a]Chi-square test.
[b]Analysis of variance.

Three patients were excluded from the efficacy sample: 2 patients for lack of compliance (1 treated with paroxetine and 1 treated with sertraline) and 1 patient for taking disallowed concurrent medications (treated with sertraline). A further 5 patients prematurely discontinued the study by withdrawal of their consent: 3 subjects refused to continue the study as a result of side effects (1 treated with paroxetine and 2 treated with sertraline) and 2 of them (1 treated with paroxetine and 1 treated with sertraline), because of lack of efficacy. Since all 8 of these subjects withdrew within the first week of treatment, they were not considered for the efficacy analysis. The safety analysis included all patients randomly assigned into the study because they all took at least 1 capsule of drug and had at least 1 valid postbaseline safety evaluation for drug.

All 3 treatment regimens resulted in a significant improvement from baseline in burning mouth symptoms at week 8 (Table 2), as demonstrated by the VAS total scores at the end of the study; a significant improvement was also shown by the final HAM-D and HAM-A total scores compared with the respective baseline values.

Both the CGI-Severity of Illness (CGI-S) and -Global Improvement (CGI-I) scales showed steady improvement over the 8 weeks of therapy with all drugs. The mean ± SD CGI-S scores were 3.9 ± 0.9 at baseline and 2.3 ± 1.2 at week 8 in the amisulpride group ($p < .001$), 3.95 ± 0.9 at baseline and 2.0 ± 1.0 at week 8 in the paroxetine group ($p < .001$), and 4.05 ± 1.05 at baseline and 2.1 ± 1.0 at week 8 in the sertraline group ($p < .001$). On the VAS and the HAM-D, mean scores decreased without any statistical difference among the 3 treatments at weeks 4 and 6 and the final on-therapy evaluation, but amisulpride was associated with significantly greater improvement as measured by these rating scales than both

Table 2. Mean VAS, HAM-D, and HAM-A Total Scores During Treatment With Amisulpride, Paroxetine, and Sertraline (efficacy sample)[a]

Treatment Group	VAS		HAM-D		HAM-A	
	Baseline	Week 8	Baseline	Week 8	Baseline	Week 8
Amisulpride (N = 27)						
Mean	7.2	3.2*	10.5	7.2*	15.5	10.4*
SD	1.2	1.7	2.4	3.0	8.2	7.0
Paroxetine (N = 23)						
Mean	7.0	3.3*	10.3	7.2*	15.9	11.1*
SD	1.2	2.1	2.4	2.7	7.7	6.1
Sertraline (N = 18)						
Mean	7.2	2.8*	10.9	7.4*	16.1	11.6*
SD	1.0	2.4	2.6	1.8	7.1	7.4

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, VAS = visual analogue scale.
*p < .001, Student t test.

Table 3. Rating Scale Total Scores (mean ± SD) Obtained During Treatment With Amisulpride, Paroxetine, or Sertraline (efficacy sample)[a]

Scale	Amisulpride (N = 27)	Paroxetine (N = 23)	Sertraline (N = 18)	p Value vs. Amisulpride[b]	
				Paroxetine	Sertraline
VAS					
Baseline	7.2 ± 1.2	7.0 ± 1.2	7.2 ± 1.0	NS	NS
Week 2	4.9 ± 1.6	5.8 ± 1.3	5.9 ± 1.2	.025	.025
Week 4	3.4 ± 1.7	4.1 ± 2.1	3.9 ± 2.1	NS	NS
Week 6	3.3 ± 1.8	3.3 ± 2.1	3.5 ± 2.1	NS	NS
Week 8	3.2 ± 1.7	3.3 ± 2.1	2.8 ± 2.4	NS	NS
HAM-D					
Baseline	10.5 ± 2.4	10.3 ± 2.4	10.9 ± 2.6	NS	NS
Week 2	8.1 ± 2.7	10.0 ± 2.7	10.7 ± 2.6	.025	.005
Week 4	7.5 ± 3.0	8.2 ± 2.9	8.0 ± 1.9	NS	NS
Week 6	7.4 ± 3.1	7.3 ± 2.8	7.7 ± 1.9	NS	NS
Week 8	7.25 ± 3.0	7.2 ± 2.7	7.4 ± 1.8	NS	NS
HAM-A					
Baseline	15.5 ± 8.2	15.9 ± 7.7	16.1 ± 7.1	NS	NS
Week 2	12.7 ± 8.2	15.2 ± 7.6	14.1 ± 7.8	NS	NS
Week 4	11.0 ± 7.1	12.5 ± 6.4	12.55 ± 7.5	NS	NS
Week 6	10.7 ± 6.9	11.4 ± 6.4	11.9 ± 7.4	NS	NS
Week 8	10.4 ± 7.0	11.1 ± 6.1	11.6 ± 7.4	NS	NS

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, VAS = visual analogue scale.
[b]Statistically significant differences favored amisulpride.

paroxetine and sertraline at week 2 (Table 3). No statistically significant differences in HAM-A total score were observed among the 3 groups at any time.

Neither the CGI-S nor the CGI-I confirmed any statistical difference among the 3 treatments from week 4, but scores on both CGI scales were significantly lower for amisulpride at week 2 (mean ± SD CGI-S scores: 3.25 ± 0.9 in the amisulpride group vs. 3.95 ± 0.9 in the paroxetine group [p < .005] and 3.8 ± 1.1 in the sertraline group [p < .05]; mean ± SD CGI-I scores: 2.9 ± 0.8 in the amisulpride group vs. 3.8 ± 0.7 [p < .01] in the paroxetine group and 3.7 ± 0.7 [p < .01] in the sertraline group).

Table 4. Cumulative Proportion of Responders at Weeks 2, 4, 6, and 8 During Treatment With Amisulpride, Paroxetine, or Sertraline (efficacy sample)[a]

Time	Amisulpride (N = 27)		Paroxetine (N = 23)		Sertraline (N = 18)		p Value	
	N	%	N	%	N	%	Overall Comparison	SSRIs vs. Amisulpride
Week 2	6	22.2	0	0	1	5.6	< .05	< .05
Week 4	14	51.8	12	52.2	10	55.6	NS	NS
Week 6	18	66.7	15	65.2	12	66.7	NS	NS
Week 8	19	70.4	16	69.6	13	72.2	NS	NS

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 5. Treatment-Emergent Signs or Symptoms in the 3 Patient Groups (intent-to-treat safety sample)

Side Effect	Amisulpride N = 27		Paroxetine N = 26		Sertraline N = 23	
	N	%	N	%	N	%
Nausea/dyspepsia	0	0	4	15.4	3	13.0
Sedation	0	0	2	7.7	1	4.3
Dry mouth	0	0	2	7.7	2	8.7
Constipation	0	0	2	7.7	1	4.3
Insomnia	3	11.1	1	3.8	1	4.3
Anxiety	4	14.8	0	0	0	0
Tremor	3	11.1	0	0	0	0
Asthenia	0	0	2	7.7	2	8.7
Headache	1	3.7	2	7.7	1	4.3
No side effects	22	81.5	19	73.1	18	78.3

The percentage of response at week 8 was quite high in all treatment groups (ranging from 69.6% to 72.2%), with no significant differences between groups (Table 4) and between patients with and without current comorbid diagnoses. Moreover, the mean ± SE survival time (which reflects the mean latency of the therapeutic response) was 26.7 ± 2.8 days for the amisulpride group, 33.8 ± 2.5 days for the paroxetine group, and 33.5 ± 2.1 days for the sertraline group, with a significant difference between amisulpride and SSRIs (p < .05).

No serious adverse events were reported in any of the 3 groups. Table 5 shows the treatment-emergent signs or symptoms with an incidence of 5% or more in any one treatment group; chi-square analysis revealed no statistical difference among the 3 groups of patients.

DISCUSSION

To our knowledge, this is the first systematic study of amisulpride and SSRIs in the treatment of BMS using established research diagnostic criteria and rating scales and is the largest study ever performed in this syndrome. This study was single blind and without placebo control; therefore, any conclusions are tentative and preliminary. However, we found a significant improvement in symptomatology in BMS patients.

Of the 76 patients who were randomly assigned in the study, only 8 (10.5%) could not be considered for the efficacy analysis since they withdrew within the first week

of treatment. It is interesting that none of the patients who received amisulpride withdrew from the trial, whereas 11.5% of patients (N = 3) treated with paroxetine and 21.7% of patients (N = 5) treated with sertraline withdrew from the trial. The higher percentages of dropouts that we found in patients treated with SSRIs are consistent with those found in previous studies with different drugs[16,17] and suggest the difficult clinical management of these patients. Further double-blind trials to investigate whether amisulpride is associated with higher compliance at the beginning of pharmacologic treatment should be performed.

According to the results of this study, paroxetine, sertraline, and amisulpride showed similar efficacy profiles in the treatment of BMS, according to the mean reduction in VAS, HAM-D, and HAM-A scores (quantitative analysis). Concerning the qualitative evaluation of clinical response, the percentages of responders were quite high and similar in the 3 treatment groups, confirming the results derived by the quantitative analysis. The only difference that emerged was in response latency; amisulpride showed a mean latency of only 1 week. No serious adverse events related to the use of the 3 drugs were reported, and the incidence of side effects did not differ among the 3 groups.

Variables that might have affected the results were controlled: no significant differences were found in demographic and clinical variables among the 3 treatment groups. Moreover, the demographic and clinical features of our sample of BMS patients were broadly consistent with those reported by other studies; this may suggest that the results of this study are representative of the effect size of SSRIs and amisulpride in this patient population.

Three limitations of these results need to be noted. First, this study was performed on an open-label basis and without a placebo control. It should be noted that placebo response rates up to 50% have been reported in previous studies[20]; therefore, only a double-blind, placebo-controlled trial can determine the true therapeutic profile of amisulpride and SSRIs in the treatment of BMS. Although this study seems to indicate that the effects of amisulpride and SSRIs in the treatment of this somatoform disorder are specific and not only related to their effect on anxiety and/or depression—since they work equally well in BMS with and without comorbid diagnoses and since they reduce VAS scores—only a double-blind, placebo-controlled trial will be able to confirm the data. Second, a considerable percentage of patients with BMS (almost 20%) were not included in this study because they had an additional diagnosis of a major depressive episode. Additional investigations on the treatment of this subgroup of patients should be performed to test which drugs are more effective and to identify the proper daily dose. Third, the efficacy and tolerability of both SSRIs and amisulpride have been tested in short-term observations, but they also need to be investigated in long-term observations.

In conclusion, amisulpride and SSRIs are equally effective and equally well tolerated in the short-term treatment of BMS. Amisulpride is associated with better compliance within the first week of treatment and with a shorter response latency in comparison with SSRIs, possibly indicating that amisulpride is especially useful at the beginning of drug therapy of BMS. Further studies of this potentially important condition are needed, and the potential benefits of SSRIs and amisulpride should be confirmed under placebo-controlled conditions.

Drug names: amitriptyline (Elavil and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), diazepam (Valium and others), doxepin (Sinequan and others), paroxetine (Paxil), sertraline (Zoloft), sucralfate (Carafate and others).

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