Efficacy of Amitriptyline for Treatment of Somatoform Pain Disorder in the Orofacial Region: A Case Series

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Aims: *To determine the efficacy of amitriptyline and the optimal dosage for treating a somatoform pain disorder in the orofacial region.* ***Methods:*** *Thirty outpatients with orofacial pain who fulfilled the criteria of pain disorder were recruited for the study. Twenty-three patients had specific precipitating events in their past history, which they considered to be the origin of the pain. Amitriptyline was administered and the dose was gradually increased up to a daily dose of 250 mg. The response to treatment was evaluated using a numeric rating scale and the Clinical Global Impression Scales.* ***Results:*** *Five patients dropped out and 25 patients (83%) completed the trial. Twenty-two patients became pain free or nearly pain free, while 3 patients who also completed the study did not respond at all, even though they took a daily dose of 250 mg amitriptyline. For responders, the mean daily dose of amitriptyline was 77.5 ± 51.5 mg (range, 10 to 200 mg). Four patients (16%) obtained pain relief with a daily dose of less than 50 mg, while 3 patients (12%) needed a daily dose of 150 mg or more for pain relief. Adverse side effects were observed in 19 patients.* ***Conclusion:*** *Amitriptyline was effective in relieving pain associated with a somatoform pain disorder in the orofacial region. The dose of amitriptyline may need to be as high as that used to treat a major depression.* J OROFAC PAIN 2006;20:234–240

Key words: orofacial pain, pain disorders, amitriptyline, tricyclic antidepressants (TCAs), precipitating event

Physicians and dentists in orofacial pain clinics often encounter patients with organically unexplained pain.[1] Usually, such patients have already received various physical examinations and treatment without any positive findings or response. It may be possible to diagnose such patients with pain disorder (PD), a diagnosis listed under somatoform disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[2] (Fig 1) or as somatoform pain disorder in the International Classification of Diseases-10.[3] It is a common disorder, with an estimated prevalence of up to 40% of patients who complain of pain.[4] Thus, when the pain cannot be explained by organic factors and the criteria of pain disorder according to the DSM-IV-TR are met, a diagnosis of PD can be made.

It has been hypothesized that PD is caused by a dysfunction of the serotoninergic and noradrenergic systems, and therefore the first line of therapy is the prescription of tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors.[5,6] The efficacy and optimal dosage of amitriptyline for treating PD in the orofacial region has not been evaluated yet.[6] It is generally assumed that therapy for chronic pain requires a considerably lower dose of TCA than that necessary for the treatment of major depression.[7–11] It has also been suggested that a high dose be used if the chronic pain does not respond to lower doses.[12–15] However, since PD is thought to be a psychological disorder, like major depression, the appropriate therapeutic dose of TCA should not be derived from the results of studies in which TCAs have been used to treat chronic pain but should be determined by means of clinical studies with such patients. The aim of this study was therefore to investigate the efficacy of amitriptyline in the treatment of PD and the optimal dose for treating PD in the orofacial region.

Fig 1 Criteria of Pain Disorder (DSM-IV-TR)

A. Pain in one or more anatomical sites is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention.
B. The pain causes clinically significant distress or impair ment in social, occupational, or other important areas of functioning.
C. Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain.
D. The symptom of deficit is not intentionally produced or feigned (as in factitious disorder or malingering).
E. The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet the criteria for dyspareunia.

Code as follows:
307.80 Pain disorder associated with psychological factors: psychological factors are judged to have the major role in the onset, severity, exacerbation, or maintenance of the pain. (If a general medical condition is present, it does not have a major role in the onset, severity, exacerbation, or maintenance of the pain.) This type of pain disorder is not diagnosed if criteria are also met for somatization disorder.

Specify if:
Acute: duration of less than 6 months.
Chronic: duration of 6 months or longer.

307.89 Pain disorder associated with both psychological factors and a general medical condition: both psychological factors and a general medical condition are judged to have important roles in the onset, severity, exacerbation, or maintenance of the pain. The associated general medical condition or anatomical site of the pain (see below) is coded on the Axis III.

Specify if:
Acute: duration of less than 6 months.
Chronic: duration of 6 months or longer.

Excerpt from the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* reprinted with the permission of the American Psychiatric Association.

Materials and Methods

Thirty outpatients who attended the orofacial pain clinic of Shizuoka Municipal Shimizu Hospital, Shizuoka, Japan, between June 1, 2002 and May 31, 2003 who fulfilled the criteria of PD according to the DSM-IV-TR (code 307.80 or 307.89) (Fig 1) were recruited. Patients with general medical conditions were excluded on the basis of biochemical examinations including C-reactive protein and radiographic examinations (pantomography, computed tomography, magnetic resonance imaging). Twenty-seven patients were female and 3 were male, and their ages ranged from 26 to 73 years (mean ± SD, 47.1 ± 14.6) (Table 1). Patients with other affective disorders, including major depressive disorder, were excluded by interview with a psychiatrist. None of the participants had any severe medical or neurological disorders. The study was approved by the ethics committee of Shizuoka Municipal Shimizu Hospital, and each patient signed a written informed consent.

The chief complaint of 15 patients was tooth pain. Of these patients, 9 complained of pain in a single tooth, while 3 complained of pain in 2 or 3 adjacent teeth. Twenty-three patients (77%) reported a specific pain-precipitating event: 7 had had a root canal treatment, including pulp extirpation; 4 had received a prosthesis; 3 had had a tooth extraction; 3 had undergone minor surgery, including ophthalmic surgery; and for the remainder, various other events had precipitated the pain (Table 1).

All patients were treated with amitriptyline. The dose was gradually increased until the occurrence of either significant improvement or adverse side effects, up to a daily dose of 250 mg. The dosage of amitriptyline was increased slowly and carefully in each case. When a patient experienced an adverse side effect, the dosage of amitriptyline was maintained for a certain period until she/he acquired tolerance for this dosage. Symptoms and adverse side effects were checked once a month. A daily dose of amitriptyline of less than 50 mg was

Table 1 Baseline Characteristics and Precipitating Events

Patient no.	Age	Sex	Duration of illness (mo)	Pain location	Precipitating event
1	68	F	48	Face (bilateral), tension-type headache	Placement of prosthesis
2	49	F	4	Left masseter	Loss of job
3	59	F	180	Nuchal pain	None
4	28	F	2	Head, neck, and back	None
5	26	F	10	4(15), right side of face	Root canal treatment
6	34	F	120	2(17)	Root canal treatment
7	67	F	84	Right side of face	A stressful relationship
8	67	F	24	12(24), 13(25)	None
9	45	F	72	10(22)	Minor ophthalmic surgery
10	52	F	144	Face (bilateral), tension-type headache	Doctor's critical words
11	39	F	120	Mandible (bilateral)	TMD treatment
12	37	F	84	Right cheek	Root canal treatment
13	59	F	20	28(44), 29(45)	None
14	58	F	18	20(35)	Cementation of inlay restoration
15	53	F	24	18(37)	Tooth extraction
16	37	F	8	Right cheek	Root canal treatment
17	40	F	240	2(17)	Root canal treatment
18	73	M	36	2(17) through the 15(27)surrounding gingiva	Tooth extraction
19	51	F	3	2(17)	None
20	27	M	24	5(14)	Cementation of crown restoration
21	44	F	12	Palate, tongue	None
22	39	F	48	9(21), 10(22)	Root canal treatment
23	35	F	120	20(35)	Root canal treatment
24	30	F	60	4(15), 5(14), 6(13) and right cheek	Placement of prosthesis
25	26	F	27	4(15)	None
26	67	F	36	Tongue	Implant surgery
27	49	F	120	4(15), 5(14), 12(24), 13(25), 28(44), 29(45)	Mucocele surgery
28	69	F	48	2(17), 3(16), 30(46), 31(47)	Cementation of crown restoration
29	31	M	84	Neck (bilateral)	Motor vehicle accident
30	53	F	48	Left side of face	Tooth extraction
Mean ± SD	47.1 ± 14.6		62.3 ± 57.9		

Universal (FDI) tooth numbers shown. F = female; M = male; TMD = temporomandibular disorders.

defined as a low dose; 50 to 150 mg/d was defined as a moderate dose; more than 150 mg was considered a high dose. Patients who withdrew from treatment because of intolerance of adverse side effects before reaching the dosage of 150 mg/d amitriptyline were considered dropouts. During the investigation period, subjects did not take any other medication, including other antidepressants, benzodiazepines, neuroleptics, analgesics, or anticonvulsants.

A baseline electrocardiogram was performed for all patients at the beginning of the study. All patients receiving more than 150 mg/d amitriptyline were also monitored by electrocardiogram throughout the study.

At baseline and the end of the trial, the severity of pain was evaluated subjectively by the patients using a numeric rating scale (NRS) where 0 indicated no pain and 10 the greatest pain possible. The Clinical Global Impression of Severity (CGI-S) scale[16] and the Clinical Global Impression of Improvement (CGI-I) scale[16] were also used to assess pain. Adverse side effects were recorded on the basis of the patients' reports.

Table 2 Outcome After Administration of Amitriptyline

Patient no.	Final dose (mg/d)	Time elapsed until relief (mo)	NRS baseline	NRS after treatment	CGI-S scale baseline	CGI-S scale after treatment	CGI-I scale after treatment	Adverse events
1	50	12	9	0	6	1	1	U
2	100	4	5	0	4	1	1	
3	40	5	5	0	4	1	1	
4	75	14	9	0	6	1	1	
5	75	10	7	0	5	1	1	D, S, U
6	50	11	7	0	5	1	1	
7	50	7	7	0	5	1	1	
8	50	3	5	0	4	1	1	
9	50	4	10	0	7	1	1	S
10	20	30	7	0	5	1	1	
11	100	13	9	0	6	1	1	S
12	10	1.5	5	0	4	1	1	
13	100	1.5	9	1	6	1	1	D
14	50	3	5	1	4	2	2	S, D
15	200	8	3	1	3	2	2	S, C
16	150	9	9	1	6	2	2	D, C
17	100	14	5	1	4	2	2	W
18	75	4	7	1	5	2	2	T
19	10	2	7	1	5	2	2	S
20	75	4	3	1	3	2	2	S
21	75	18	10	1	7	2	2	C, W
22	200	9	5	3	4	3	3	C
23	(250)		7	7	5	5	5	D, C
24	(250)		9	9	6	6	5	
25	(250)		9	9	6	6	5	D, C
26	(100)		10		7			D, S
27	(100)		7		5			C
28	(75)		7		5			D, C
29	(20)		9		6			
30	(30)		7		5			W
Mean ± SD	77.5 ± 51.5	8.5 ± 6.7						

The dosages for patients who either dropped out or reached the maximum dose without relief are given in parentheses. C = constipation; D = dry mouth; S = sedation; T = tremor; U = urinary retention; W = weight gain.

Scores of CGI-S were as follows: 1 (none), 2 (borderline), 3 (mild), 4 (moderate), 5 (marked), 6 (severe), and 7 (extreme). Scores of CGI-I were as follows: 1 (very much improved), 2 (much improved), 3 (moderately improved), 4 (minimally improved), 5 (no change), 6 (minimally worse), 7 (moderately worse), 8 (much worse), 9 (very much worse).

Results

All patients were diagnosed with PD, because there was no evidence of a general medical condition on the basis of clinical examinations. The mean pain duration was 62.3 ± 57.9 months.

Five patients (17%) dropped out and 25 patients (83%) completed the trial. Three of the 5 patients who dropped out could not reach a dose of 150 mg/d because of intolerable adverse side effects. Two patients were unable to continue the trial because they could not come to the clinic.

Of the 25 patients who completed the trial, 4 patients (16%) were treated with a low dose of amitriptyline, 16 (64%) with a moderate dose, and 5 (20%) with a high dose. For responders, the mean daily dose of amitriptyline was 77.5 ± 51.5 mg (range, 10 to 200 mg).

NRS scores at baseline and after treatment are shown in Table 2. After treatment, 12 of 30 patients (40%) recruited stated that the pain had completely disappeared, and 10 (33%) stated that the pain had mostly disappeared. Three (10%) reported no change despite taking amitriptyline at a daily dose of 250 mg for more than 4 weeks.

CGI-S scores at baseline and after treatment and CGI-I scores after treatment are shown in Table 2. After treatment, 13 (43%) of 30 recruited were very much improved and 8 (27%) were much improved. Three (10%) reported no change, even though they took amitriptyline at a daily dose of 250 mg for more than 4 weeks.

Amitriptyline was effective in providing pain relief for a total of 22 patients: 73% of the patients (22/30) in the last observation carried forward (LOCF), which was an analysis of data from all recruited patients, including dropouts, and 88% of the 25 patients who completed the trial. In these patients, the mean duration required for pain relief was 8.5 ± 6.7 months.

Adverse side effects occurred in 19 patients. Eight subjects reported dry mouth, 8 constipation, 8 sedation, 3 weight gain, 2 urinary retention and 1 tremor. No change of cardiac rhythm, including prolonged QT interval, was observed.

Discussion

Amitriptyline was effective in providing pain relief for 22 (73%) of the 30 PD patients recruited; 12 patients (40%) became pain free. However, when calculations were based on the 25 patients who completed the trial, the number experiencing pain relief increased to 88%.

There were, however, 2 issues the authors wished to address with respect to the diagnosis and treatment of PD. The first was the search for the optimal dose for treating PD. Traditionally, it has been reported that the management of chronic pain requires lower doses of TCA than those needed for the treatment of major depression.[7–11] However, the present study showed that some patients required several dose increases until amitriptyline was effective. Only a minority of participants responded to a low dose of amitriptyline, while the majority needed 50 mg/d or more. Since the mean daily dose of amitriptyline necessary for pain relief was 77.5 ± 51.5 mg, it seems that less than half of the usual dose required for an antidepressant effect (150 to 300 mg/d) is sufficient for an analgesic effect. This study therefore supports the viewpoint of Feinmann and Harris, who suggested that most cases of this type can be managed by a suitably trained dentist.[15] However, 10% to 20% of cases require a psychiatrist to provide diagnostic and therapeutic support.[15] The most appropriate way to treat these patients is in a liaison with dentists and psychiatrists.

Sadock et al[17] stated that TCAs are dose-dependent drugs with widely varying rates of absorption and metabolism, leading to 30- to 50-fold differences in the plasma concentrations in patients receiving the same dosage. The results of this study confirm that the administration of TCA to treat orofacial pain should not be stopped at a low dose but should be gradually increased until the occurrence of either significant improvement or adverse side effects, as in the treatment of major depression and affective disorders.[12,17,18]

Previous studies of psychogenic facial pain and atypical odontalgia (AO) have suggested that, when TCAs alone do not lead to sufficient pain relief, a low dose of an antipsychotic agent (neuroleptic) such as perphenazine or trifluoperazine sometimes promotes improvement.[15,19–22] For 3 of the 4 patients in the present study who failed to respond to amitriptyline alone (patients 23 through 26), the addition of 2 mg risperidone (a serotonin-dopamine antagonist) provided marked pain relief. Thus, though the number of cases was small, it seems that it may be worthwhile to add a low dose of an antipsychotic agent for those patients who do not respond to TCA alone in adequate doses. However, as antipsychotics have a risk of tardive dyskinesia,[23] they should be used only when a TCA trial with a sufficient dose and duration has failed.

The most common adverse side effects with high doses of amitriptyline were constipation, sedation, and dry mouth, although these were well tolerated by most patients, even at higher doses. Indeed, only 3 patients dropped out because of adverse side effects. The reason for the good tolerance was likely related to individual titration and to the slow and careful dosage increase. Moreover, the results indicated that these adverse side effects may occur independently of amitriptyline dosage.

The second issue related to the diagnosis and treatment of PD that should be discussed was the view that AO may be a localized form of PD. In about half of the patients, the pain was localized to a single tooth or several teeth, which matches the diagnostic criteria of AO.[24] Although the pathophysiology of AO has not been elucidated, the 2 major views are that AO might be neuropathic or psychogenic in nature.[22,24,25] Pain experts who were trained with a strong emphasis on physical diseases tend to view unexplained symptoms as neuropathic. However, with the recent progress in biological psychiatry, psychiatric disorders, including major depressive disorders and pain disorders, have also been considered to be due to a dysfunction of the central nervous system. In this view, PDs are caused by a dysfunction of the serotoninergic and noradrenergic systems.[4] Therefore, the distinction between neuropathic pain and pain due to psychiatric disorders has become blurred. Thus, AO could be a localized form of a more diffuse facial PD, as both AO and PD share the following 4 clinical features. First, the pain can occur in a person with no recent his-

tory of local trauma (patients 8, 13, 19, 21, and 25 in Table 1). Second, the pain can be precipitated by a specific unpleasant event and aggravated by psychosocial stressors,[4,14,26] as in patients 2, 7, and 10 in the present study. Third, the pain can recur after having completely disappeared. In the cases presented here, and in previously reported cases of AO,[24] recurrence of pain was not rare. It is difficult to explain the mechanism of pain recurrence once it has completely disappeared if the pain is neuropathic in nature. On the other hand, psychiatric disorders, including orofacial PDs, recur frequently,[15] so that continuous medication may be needed to prevent pain relapse, just as in the case of major depression disorders. Fourth, the pain is not localized to a dermatome and, in case of AO, it often spreads far from the original site and may even cross the midline,[27,28] possibly because of central sensitization.[28]

PD is a classic disorder within the framework of the biopsychosocial model.[29] Psychosocial factors are therefore potentially as important as biological ones in its onset. In this study, 77% of the PD patients reported specific precipitating oral or medical events, and most of these patients also remembered having clear anxiety or fear during those events, which is consistent with earlier observations.[30] Unfortunately, the sensitivity and specificity of the criteria used to diagnose a PD have not been established,[5] so that there is no definitive way to differentiate PD from a neuropathic pain. A careful history and examination, however, may indicate that certain pain patterns do not match the features of neuropathic pain; for example, pain localization may be inconsistent with the anatomic distribution of the nervous system, or responses to medications, including local anesthetics, may be unusual. Furthermore, the pain in PD is usually fluctuating and is often exacerbated by stressors such as emotional stress, social environment, temperature, and humidity.[3]

It is important to interpret the results of the present study with great caution, because this study was a case series. Furthermore, plasma amitriptyline levels were not measured because of lack of research funds, and adverse side effects were recorded based only on patient reports, which may have lead to underreporting. To obtain more detailed results, a systematic questionnaire such as the UKU side-effect rating scale[31] should have been applied. To confirm these preliminary results, a larger, randomized double-blind study is warranted.

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