Seven-Year Follow-up of Patients Diagnosed with Atypical Odontalgia: A Prospective Study

Maria Pigg, DDS, PhD
Assistant Professor
Department of Endodontics
Faculty of Odontology
Malmö University
Malmö, Sweden

Peter Svensson, DDS, PhD
Professor
Department of Clinical Oral Physiology
School of Dentistry
Aarhus University
MINDLab, Center of Functionally Integrative Neuroscience
Aarhus University Hospital
Aarhus, Denmark

Mark Drangsholt, DDS, PhD
Associate Professor
Departments of Oral Medicine and Oral Health Sciences
University of Washington
Seattle, Washington, USA

Thomas List, DDS, PhD
Professor
Department of Stomatognathic Physiology
Faculty of Odontology
Malmö University
Malmö, Sweden
Department of Rehabilitation Medicine
Skane University Hospital
Lund, Sweden

Correspondence to:
Dr Maria Pigg
Department of Endodontics
Faculty of Odontology
Malmö University
Carl Gustafs väg 34
SE-20506 Malmö, Sweden
Fax: +46 40 6658577
Email: maria.pigg@mah.se

Aims: *To examine the long-term prognosis of 46 previously examined atypical odontalgia (AO) patients.* ***Methods:*** *In 2002 and 2009, AO patients completed validated instruments measuring pain characteristics (pain frequency and intensity), physical functioning (Graded Chronic Pain Severity, GCPS) and emotional functioning (Symptoms Checklist, SCL-90R). The main outcome was global improvement. Baseline data on quantitative somatosensory testing and responsiveness to lidocaine injection were available for a subgroup of patients. Paired tests compared baseline and follow-up data, and logistic regression explored the possible prognostic value of baseline data.* ***Results:*** *Data from 37 patients (80%) were obtained. Thirteen patients (35%; 95% confidence intervals [CI] 20.2%–52.5%) rated their overall pain status as significantly improved, 22 (60%; 95% CI 42.1%–75.3%) as a little improved or unchanged, and two patients (5%; 95% CI 0.7%–18.2%) as worse. Five patients (14%; 95% CI 4.5%–28.8%) were pain-free, indicated by a characteristic pain intensity score of 0. Average pain intensity decreased (from 5.7 ± 2.0 to 3.5 ± 2.4;* $P < .001$*). Pain frequency (*$P < .001$*) and GCPS (*$P < .001$*) also decreased, whereas SCL-90R scores remained unchanged and 26 of the 37 patients reported ongoing treatment. Low baseline pain intensity was the only factor predictive of favorable outcome.* ***Conclusion:*** *A third of the AO patients improved considerably over time, but for many of the patients, AO was a persistent and treatment-resistant condition.* J OROFAC PAIN 2013;27:151–164. doi: 10.11607/jop.1033

Key words: neuropathic pain, orofacial pain, prognosis, prospective study, trigeminal nerve

The prognosis for pain resolution is an important matter of concern to patients afflicted with a severe pain condition. Longitudinal studies examining the development of chronic pain over time are rare, and the prognosis has mostly been studied relative to short-term interventions. Chronic pain conditions are complex and often have a strong impact on daily activities and well-being, with patients suffering from comorbid disorders and high levels of distress.[1,2]

In medicine, a naturalistic study is one in which subjects are observed with a minimum interference approach.[3] In more rare pain conditions, randomized clinical trials are difficult to conduct. A naturalistic study design, where pain-management allocation follows a patient-oriented, clinical pattern (as opposed to being randomly assigned), has been recommended as an option to gain information about prognosis and treatment effect.[4,5] Because patients' preferences for therapy are accommodated and choice and duration of treatment are decided by clinical requirements rather than more rigid treatment schedules, naturalistic studies have been reported to

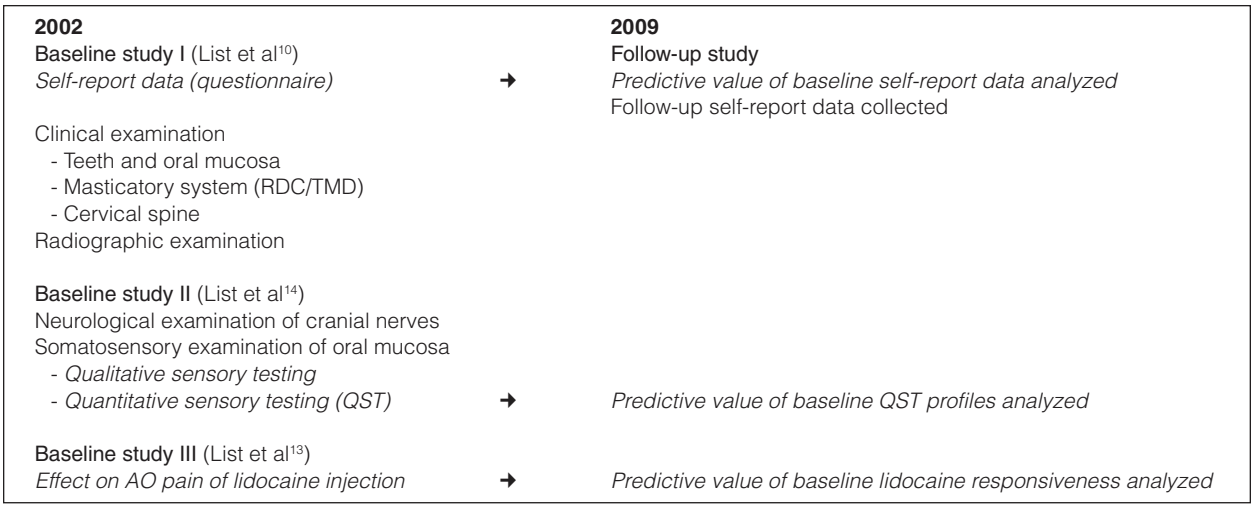


Fig 1 Data collection for the 7-year prospective study. Detailed patient and pain characteristics and experimental results are presented in baseline studies I–III (List et al[10,13,14]).

better reflect the clinical situation and assess clinical effectiveness of treatment.[6]

Atypical odontalgia (AO; also known as persistent idiopathic facial pain, phantom tooth pain, and persistent dentoalveolar pain disorder) is a chronic and most often continuous pain condition, located in or around the teeth and described as tooth-related pain or pain located at a site typically where a tooth was extracted. Clinical or radiographic evidence of relevant pathology is lacking.[7] The terminology and diagnostic criteria are still under discussion,[8] and the underlying pain mechanisms are debated. Recently, a systematic review found a 3.4% prevalence of non-odontogenic persistent pain more than 6 months after endodontic treatment[9] and in 83% of AO cases, pain onset occurred after dental treatment.[10] Current research supports the view that the pain, at least in some AO patients, is mediated through neuropathic mechanisms,[11–13] possibly caused by deafferentation of nociceptive primary afferents in the tooth pulp, but it has not been confirmed that AO is a neuropathic pain condition. Involvement of central sensitization mechanisms has been suggested; somatosensory abnormalities were reported in 85% of patients[14] and a large proportion of the AO patients exhibited changes in blink reflex induced by noxious stimuli[12] and no response to local anesthetic block.[13] Long pain duration and repeated care-seeking are often reported for these patients and may reflect diagnostic difficulties, unsuccessful compliance with treatment, or inadequate pain relief. This is in agreement with reports of confirmed neuropathic pain conditions, where clinical trials suggest that many patients experience insufficient pain relief.[15] A previous study of chronic idiopathic orofacial pain, likely including a proportion of AO patients, reported that 22% of the patients were free of orofacial pain after 9 to 19 years,[16] but risk factors for the development of AO and the long-term prognosis are largely unknown. The present prospective study explored the prognosis of AO in a sample of well-examined patients earlier described in several studies.[10–14,17] Using an observational naturalistic study approach, the aims were to examine the long-term prognosis of 46 previously examined AO patients. A global improvement estimate, Patient Global Impression of Change (PGIC) was the main outcome measure, supplemented by other outcome measures as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for chronic pain trials[18] and orofacial pain studies.[19]

The underlying hypotheses were that baseline clinical and self-report characteristics are potential prognostic factors and that clinical signs of neuropathic involvement, such as disturbed sensory function and non-response to peripheral anesthesia, may predict unfavorable long-term outcome.

Materials and Methods

Participants and Study Procedures

The study examined a sample of 46 consecutive patients diagnosed with AO recruited from 4 orofacial pain clinics in the Swedish cities of Linköping, Jönköping, Kalmar, and Malmö. All patients had chronic pain for at least 6 months, localized to a region where a tooth had been endodontically or surgically treated, and with no plausible pain cause detectable in a comprehensive clinical and

radiographic examination. An experienced orofacial pain specialist (TL) examined and diagnosed all AO patients. The self-reported characteristics and clinical data from 2002 were reported in a previous study (baseline study I[10]). Of the original 46 patients participating in baseline study I, three were deceased at the time for follow-up. The remaining 43 were sent a comprehensive questionnaire by mail in 2009, along with a prepaid return envelope. When no response was received within 2 weeks, a new questionnaire was sent, and patients who still did not respond were then contacted by telephone. If the patients were not willing to complete the written questionnaire, they were asked to answer a shorter version over the telephone. The 2009 questionnaire was essentially the same as the one used in 2002, supplemented with a few questions concerning events during the 7-year study period. Figure 1 describes baseline and follow-up data collection. No new clinical examination was included in the present study.

In agreement with the 1964 Declaration of Helsinki (2008 revision, www.wma.net), the Regional Ethics Review Board at Lund University approved the study (daybook no. 2009-530), and all participants were asked to sign an informed-consent form. The subjects received no monetary compensation for their participation.

A short description is given below of the measures and instruments included in the questionnaire, assessing the main (global improvement) and secondary (pain, physical functioning, and emotional functioning) outcome domains.

Global Improvement

As the main outcome measure, patients were asked to rate their overall status at follow-up compared to baseline, thereby including all of the components of their pain experience, using the 7-point PGIC scale.[18,20] Perceived overall situation change over the 7 years was described as very much improved, much improved, a little improved, unchanged, a little worse, much worse, or very much worse. The ratings "very much improved" and "much improved" were considered as clinically relevant improvement in this study. Baseline data were analyzed in relation to the global impression of change after 7 years. The PGIC scale was included in both the full (written) questionnaire and the shorter (telephone) version.

Pain

Intensity. Characteristic Pain Intensity (CPI, 0–100 score) is a compound measure that is calculated by taking the mean of current pain, average pain, and worst pain in the last 6 months (all measured on a 0–10 numeric rating scale, NRS) and multiplying by a factor of 10.[21] CPI has been reported to have good reliability, validity, and temporal stability for orofacial pain.[22] When looking specifically at the pain intensity measure, a CPI score of 0 was defined as freedom of pain at follow-up.

Frequency. Continuous, recurrent, occasional, or no pain was assessed.[21]

Descriptors. A Swedish short form of the McGill Pain Questionnaire (SF-MPQ) with 15 descriptors (11 sensory and 4 affective) was used, each item scored on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).[23,24] Total sensory and affective scores for each patient were calculated by adding the intensity scores for each item for sensory and affective descriptors, respectively.

Widespread Pain. Patients were asked to mark the areas where pain is experienced on an anatomical drawing. A maximum of 10 areas can be marked: head, face, mouth (intraoral), throat, neck/shoulder, back, chest, abdomen, upper extremities, and lower extremities.

Pain intensity and frequency and number of pain areas but not verbal pain descriptors were included in the shorter telephone questionnaire.

Physical Functioning

Quality of Life. The generic health-related quality of life measure Short Form 36-Item Health Survey (SF-36) was used; it covers eight domains: physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional functioning, and mental health.[25]

Disability from Pain. The Graded Chronic Pain Severity (GCPS) Scale is a measurement of pain and its impact, grades 0 to IV (grade 0 = no pain and thus no disability from pain; grades I–II = low disability; grades III–IV = high disability).[21]

Jaw Function. The 0 to 10 graded Jaw Function Limitation Scale (JFLS-14), which includes 14 items evaluating jaw function,[26] was also used.

The GCPS Scale was included in the shorter telephone questionnaire, whereas the other physical functioning measures were not.

Emotional Functioning

Psychological Status. Scores for depression (20 items) and nonspecific physical symptoms (12 items) included in the Symptoms Checklist (SCL-90R) of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) were

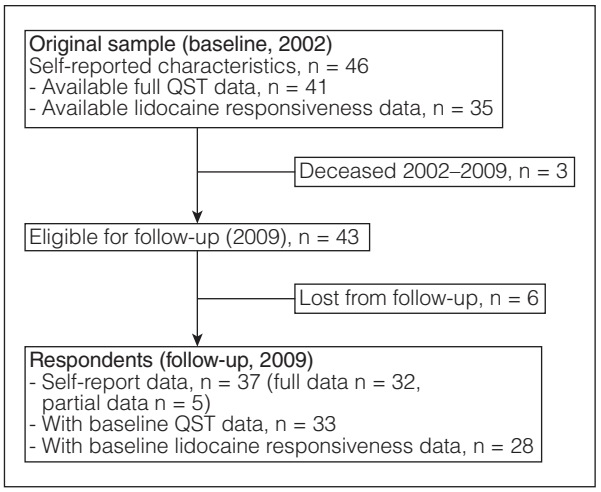


Fig 2 Flow chart of patients from baseline in 2002 to follow-up in 2009, and data available for analysis.

used.[21] According to this instrument, patients were grouped as normal status or as having moderate or severe symptoms. The instrument has exhibited good reliability and validity.[22]

The SCL-90R was not included in the shorter telephone questionnaire.

Treatment, Pain Explanation, and Compensation

In addition to the above variables, at follow-up the investigators recorded patient-reported present ongoing pain treatment (pharmacological and nonpharmacological), number and type of dental treatments performed in the pain region during the last 7 years, whether the patients thought they had received a satisfactory explanation for the pain problem, and whether they had received any monetary compensation for costs brought on by the pain condition (from insurance or otherwise). The questions on pain treatment, dental treatment, and pain explanation were also included in the shorter telephone version. Baseline data were available on what treatments patients had tried (pharmacological treatment, surgical treatment, stabilizing treatment, sensory stimulation, manual treatment, and relaxation).[10]

Somatosensory Measures

Included among the clinical measures of the initial assessment in 2002 was qualitative and quantitative sensory testing (for a comprehensive description of the procedures, see baseline study II[14]). Nine quantitative sensory testing (QST) measures were applied: mechanical detection threshold (MDT), mechanical pain threshold for pinprick (MPT), pressure pain threshold (PPT), dynamic mechanical allodynia for brush (DMA-brush) and vibration (DMA-vibration), wind-up ratio for repetitive pinpricks (WUR), and thermal thresholds for cold (CDT), warmth (WDT) and heat pain (HPT). The present study did not examine the patients clinically, but baseline QST data were analyzed to examine a possible relationship between somatosensory status and long-term prognosis for pain. For a majority of the patients, a Z-score describing the individual's somatosensory profile could be created and then compared to a control group. Each patient was rated as either having no or only minor sensory abnormalities (MiSA), or as having major sensory abnormalities (MaSA). At least two abnormal QST measures (out of the nine possible) were required for a Z-score to be rated as MaSA.

Responsiveness to Local Anesthesia

In 2002, a subgroup of the patients (n = 28) also participated in a randomized controlled trial examining the effect of local anesthesia (20 mg/mL lidocaine and 12.5 μg/mL adrenaline) on AO pain (baseline study III[13]). The present study examined whether baseline responsiveness to local anesthesia could predict the long-term pain prognosis.

Statistical Analyses

Mean values and standard deviations (SD) at baseline and follow-up were calculated for all continuous variables, and comparisons were made using the paired samples *t* test. The Wilcoxon signed-rank test and the McNemar's chi-square test (for paired samples) were used for categorical variables.

Independent samples *t* test (continuous variables) and Pearson's chi-square test (categorical variables) were used to compare the patients participating in the follow-up to the patients lost from follow-up with regard to sex, baseline age, pain frequency, pain intensity, pain duration, disability from pain, and emotional functioning.

The Wilcoxon signed-rank test was also used to analyze PGIC in relation to baseline data (continuous variables dichotomized at median value). Comparisons between PGIC and other possible outcome measures were made using the Wilcoxon signed-rank test and McNemar's chi-square test, and correlations between *(1)* various outcome measures and *(2)* ongoing treatment types and PGIC were determined using Spearman's rank correlation coefficient (ρ).

Because of the relatively modest sample size, multivariate regression was not used; to determine the predictive values of baseline status, simple logistic regression analyses were performed with favorable PGIC as the dependent factor ("very much improved" or "much improved"). The odds ratio (OR) for a favorable PGIC was calculated in relation to each variable separately. All variables (covariates) were undichotomized when analyzed.

The data from the previous studies on lidocaine injection responsiveness (28 patients) and on Z-score QST profiles (33 patients) were reanalyzed in this study, since long-term outcome data were not available for all the original patients of these studies.

For proportion outcomes, exact 95% Clopper-Pearson confidence intervals (CIs) were calculated; these are recommended for small sample size with binomial outcome distribution and applicable also when proportions are low. CIs were calculated at the 95% confidence level.

All inferential statistical tests were done two-tailed and at the 5% significance level. Predictive Analytics SoftWare (PASW, Windows version 18.0, IBM SPSS) and Microsoft Excel (version 14.2.3 for Mac) were used for all statistical calculations.

Results

Demographic Data, Response Rate, and Follow-up Sample Representativity

Figure 2 describes study samples and available data. Thirty-one women and six men completed the study. The mean age was 62.8 years (SD 10.8, range 38 to 81 years). There was no significant difference in age between women and men ($P = .351$). The total response rate was 80% (37/46); 32 patients provided full data (returning the mailed questionnaire) and a further 5 provided partial data (telephone interview). Of the remaining eligible 6 patients, 2 reported themselves too old and ill to answer the questions, 1 was in a nursing home (and according to the staff unable to reliably complete the questionnaire) and 1 had no known address. A further 2 patients were unwilling to participate in the follow-up study. The reasons given were desire to put the issue behind them (1 patient) and disappointment with pain treatment outcome (1 patient).

When baseline data for the patients who participated in the follow-up (n = 37) were compared to data of the patients who did not (n = 9), no significant differences occurred in sex, pain (intensity and frequency), or physical or emotional functioning ($P = .308$ to $.959$). The patients lost from follow-up were significantly older at baseline (mean age 65 years compared to 55 years; $P = .04$) and had longer pain duration (mean duration 14 years compared to 6 years; $P = .003$) than the patients available for follow-up. The median pain duration at baseline was 5 years for the original sample (n = 46) and 4 years for the follow-up subgroup (n = 37).

The 37 patients available for follow-up were thus considered representative of the original sample of 46 AO patients in the essential domains. Following this assumption, all subsequent analyses used n = 37 as the denominator.

PGIC

Thirteen patients out of 37 (35%; 95% CI 20.2%–52.5%) reported clinically relevant improvement based on PGIC ratings "much improved" (7 patients) or "very much improved" (6 patients). Fifteen patients reported no change in overall status, and 7 perceived themselves as a little improved. Two patients reported that they were worse after the 7 years: 1 patient a little worse and 1 much worse.

Comparison of Baseline and Follow-up Data

Baseline and follow-up status of the AO patients in the secondary outcome domains pain, physical functioning, and emotional functioning are described in Tables 1 and 2, and Fig 3.

Table 1 and Fig 3a show the pain characteristics. Average pain intensity, worst pain intensity, and CPI scores were all significantly lower at follow-up. Fifty-one percent (95% CI 34.4%–68.1%) reported at least 30% decrease in CPI over the 7 years. Pain frequency was also lower at follow-up ($P < .001$). Five patients (14%; 95% CI 4.5%–28.8%) were pain-free at follow-up, reporting a CPI score of 0. Two of them also reported pain frequency as "no pain," two gave no report on pain frequency on follow-up, and one reported pain frequency as "recurrent" but absent for the 6 months preceding follow-up.

The number of painful areas (widespread pain) assessed by the anatomical drawings did not change over time.

Table 2 and Fig 3b show changes over time in physical functioning. The quality of life SF-36 scores were significantly higher at follow-up compared to baseline for the domains bodily pain ($P < .001$), social functioning ($P = .013$), and role-emotional functioning ($P < .001$), indicating improved quality of life in these aspects.

For disability from pain assessed by GCPS, 13 patients reported lower disability at follow-up than at

Table 1 Pain and Patient Characteristics of the Patients with AO (mean and SD) in 2002 and 2009

	2002 (n = 46)	2002 (n = 37)	2009 (n = 37)	*P**
Average pain intensity, NRS 0–10	5.6 (1.9)	5.7 (2.0)	3.5 (2.4)	< .001
Worst pain intensity, NRS 0–10	7.3 (2.0)	7.4 (2.0)	4.7 (3.1)	< .001
CPI, 0–100 score	59 (18)	61 (19)	39 (25)	< .001
Number of painful areas, 0–10	3.5 (2.4)	3.5 (2.2)	3.4 (2.1)	.793
Pain duration, years	7.7 (7.8)	6.0 (4.6)	13.0 (4.6)	
Age, years	56.9 (12.9)	55.8 (10.8)	62.8 (10.8)	
Sex, % females	85	84	84	

**P* values for comparison between 2002 and 2009 with n = 37; ie, the same 37 patients who participated in the baseline (2002) and follow-up (2009) studies.

Table 2 Baseline and Follow-up Data for Physical Functioning (SF-36, GCPS, JFLS) and Emotional Functioning (SCL-90R)

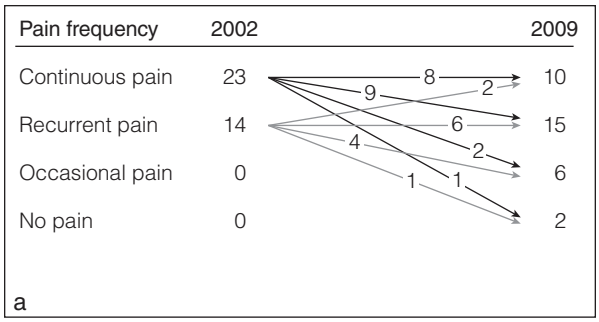
	2002	2009	*P*
SF-36*, mean scores (SD)			
Physical functioning	76.4 (24.5)	73.0 (26.5)	.694
Role-physical	44.6 (42.1)	54.2 (45.5)	.133
Bodily pain	40.7 (20.8)	54.8 (24.4)	< .001
General health	58.1 (30.0)	56.6 (27.9)	.602
Vitality	50.1 (26.8)	48.6 (31.4)	.800
Social functioning	66.6 (27.6)	77.0 (22.1)	.013
Role-emotional	51.4 (43.5)	81.5 (27.9)	.001
Mental health	68.1 (24.4)	69.4 (22.7)	.709
GCPS disability†, n (%) of patients			< .001
Grade 0	0	5 (13.5)	
Grades I–II	25 (67.6)	28 (75.7)	
Grades III–IV	12 (32.4)	4 (10.8)	
JFLS-14‡ mean scores (SD)	4.6 (5.4)	3.7 (4.4)	.689
SCL-90R§ Depression, n (%) of patients			
Normal	11 (30)	11 (30)	
Moderate	9 (24)	7 (19)	
Severe	17 (46)	14 (38)	
Mean scores (SD)	1.23 (.88)	1.08 (.82)	.069
SCL-90R§ Nonspecific physical symptoms, n (%) of patients			
Normal	9 (24)	8 (22)	
Moderate	7 (19)	4 (11)	
Severe	21 (57)	20 (54)	
Mean scores (SD)	1.18 (.89)	1.19 (.81)	.962

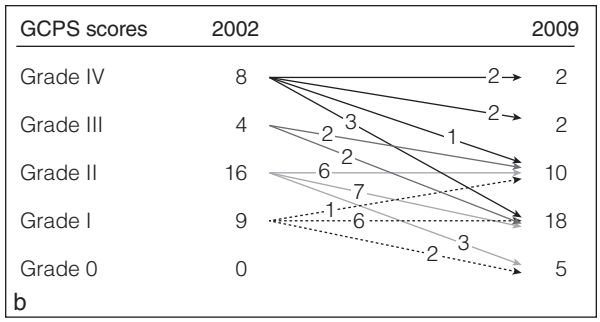
*Eight domains. Higher scores indicate better quality of life,
†*P* values from Wilcoxon signed-rank test.
‡Jaw Function Limitation Scale (14-item). No change over time was seen for any JFLS domain; only total scores are reported here.
§Symptoms Checklist 90R of Research Diagnostic Criteria for Temporomandibular Disorders, RCD/TMD. *P* values from Wilcoxon signed-rank test. Five patients (13%) did not report SCL-90 at follow-up.

baseline (5 patients moved from low disability to no disability from pain, and 8 moved from high disability to low disability). Twenty-four patients reported the same disability level on both occasions (20 of these patients had low disability and 4 had high disability from pain). No patient reported higher disability at follow-up compared to baseline.

No significant differences were seen in JFLS-14 between baseline and follow-up ($P = .689$).

Table 2 and Fig 3c show changes over time in emotional functioning. There was a tendency for depression scores of SCL-90R to be higher at baseline; uncategorized mean scores for depression corresponded to "severe" signs at baseline and to





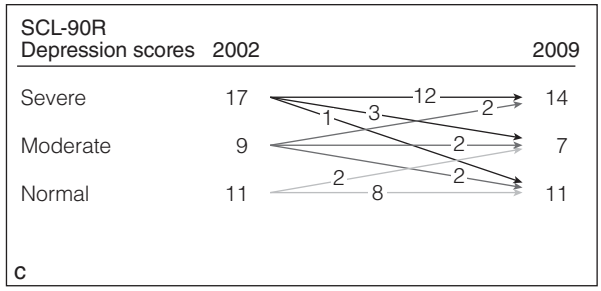


Fig 3 Changes in *(a)* pain frequency, *(b)* physical functioning (Graded Chronic Pain Severity, GCPS scores), and *(c)* emotional functioning (Symptoms Checklist, SCL-90R scores) in the patients with atypical odontalgia (AO) from 2002 to 2009. Numbers represent number of patients in each of the categories. Four patients did not report pain frequency and five patients did not report SCL-90R in 2009. Grades III–IV are considered high disability, grades I–II low disability, and grade 0 no pain/disability from pain.

Table 3 Relationship Between the Main Outcome Measure (Patients' Graded Impression of Change; PGIC) and Alternative Outcome Measures

	Average pain decrease ≥ 30% (n = 37)			CPI decrease ≥ 30% (n = 37)			Decreased pain frequency (n = 33)*		
	Yes	No	ρ (*P*)	Yes	No	ρ (*P*)	Yes	No	ρ (*P*)
PGIC improvement (n = 13)	12	1	–.55 (< .001)	12	1	–.65 (< .001)	7	3	.44 (.011)
No PGIC improvement (n = 24)	10	14		7	17		10	13	

Average pain decrease ≥ 30%, CPI decrease ≥ 30%, and decrease in pain frequency over time are shown; grey fields indicate agreement between outcome measures. Spearman's rank correlation coefficient (ρ), *P* value, and number of patients reporting different outcomes are presented.
ρ values range from –1 to 1, and high correlation between measures is indicated by values approaching these values.
PGIC improvement is defined as much or very much improved overall status after 7 years.
*Four patients did not report pain frequency on follow-up.

"moderate" signs at follow-up. Although no statistically significant differences occurred in categorized data on the group level in depression (P = .590), there were differences on the patient level; six patients had improved, scoring in a lower depression category at follow-up than at baseline, while four patients had deteriorated, scoring in a higher depression category at follow-up compared to baseline.

For nonspecific physical symptoms, both baseline and follow-up scores corresponded to "severe" symptoms. Similar changes occurred on the patient level for nonspecific physical symptoms as for depressive symptoms; five patients had improved from baseline to follow-up (three went from severe to moderate and two from moderate to normal scores), and four patients had deteriorated from baseline to follow-up (one patient went from normal to severe and two from moderate to severe nonspecific physical symptoms).

Alternate Outcome Measures and Their Relationship to PGIC

Other possible (and commonly used) outcome measures include average pain intensity, CPI, and pain frequency.

An average pain decrease of ≥ 30% was reported by 22/37 patients (59%; 95% CI 42.1%–75.3%), 19/37 patients (51%; 95% CI 34.4%–68.1%) reported 30% or larger CPI decrease, and 17/33 patients (52%; 95% CI 33.5%–69.2%) reported lower pain frequency at follow-up compared to baseline. Table 3 presents how these alternate measures were related to PGIC outcome. An average pain change in agreement with the PGIC rating (meaning that a PGIC rating representing substantial improvement corresponded with an average pain decrease ≥ 30% and a PGIC rating representing less or no improvement corresponded with the absence of

Table 4 Effect of Baseline Variables on Long-Term Prognosis

Variable	OR	95% CI	*P* value
Age	1.00	0.93–1.06	.895
Sex[a]	2.10	0.33–12.3	.411
Educational level[b]	1.50–1.80	0.15–15.5	.592–.793
Average pain	1.52	1.02–2.28	.042*
Worst pain	1.36	0.94–1.95	.100
CPI[c]	1.56	1.02–2.39	.041*
Pain frequency[d]	1.71	0.43–6.83	.445
Pain duration in years	1.00	0.86–1.17	.963
Number of pain areas	1.28	0.88–1.88	.203
MPQ sensory descriptors[e]	1.10	0.96–1.25	.159
MPQ affective descriptors[e]	1.05	0.86–1.28	.618
GCPS[f]	1.36	0.94–1.96	.104
SCL-90R depression[g]	1.02	0.94–1.11	.683
SCL-90R non-specific physical symptoms[g]	1.02	0.94–1.11	.622
SF-36[h]	1.00–1.03	0.97–1.06	.072–.807
Number of treatments tried	0.76	0.47–1.22	.252
Effect of pharmacological treatment[i]	1.88	0.44–7.99	.395
QST profile[j]	1.11	0.51–2.39	.793
Pain relief from lidocaine injection[k]	1.22	0.24–6.32	.811

Logistic regression analysis with each variable analyzed separately. Odds ratios (OR) for a Patient Global Impression of Change (PGIC) outcome of "much improved" or "very much improved," calculated per unit of decrease for continuous variables and with n = 37 patients unless otherwise specified.

[a]OR for male gender compared to female.

[b]OR range for university degree, high-school degree, and 9-year compulsory school compared to less than 9 years of education (no significance found for any educational level) (n = 34).

[c]Characteristic Pain Intensity; OR increase per 10 CPI units decrease.

[d]OR for recurrent pain compared to continuous pain.

[e]McGill Pain Questionnaire (n = 36).

[f]Graded Chronic Pain Severity; OR increase per GCPS disability point decrease (based on raw data).

[g]Symptom Checklist 90R of Research Diagnostic Criteria for Temporomandibular Disorders; OR increase per 0.1 SCL-90R unit decrease (based on raw data).

[h]Short Form 36-Item Health Survey; OR range for domains physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional functioning, and mental health (no significance found for any domain). OR increase per unit SF-36 increase.

[i]OR on positive effect of pharmacological treatment compared to no treatment effect (n = 34).

[j]Quantitative Sensory Testing; OR increase per unit increase of normal parameters (n = 33).

[k]OR on experiencing ≥ 50% pain reduction after lidocaine injection compared to no effect of injection (n = 28).

such a decrease in average pain) was reported by 26/37 patients (70%). For CPI change, the corresponding figure was 29/37 (78%), and for pain frequency change, 20/33 (61%).

Relationship Between Self-Reported Baseline Data and Outcome

Table 4 shows the results of the exploratory logistic regression analyses for outcome in relation to baseline self-reported data (based on raw data), baseline QST test results and lidocaine responsiveness, and treatment variables.

The demographic variables age, sex, and educational level did not significantly affect outcome. Mean age at baseline was 56 years (SD 11; range 31 to 74; median 58 years). Among the 13 patients who reported clinically relevant improvement (favorable PGIC), 6 were younger and 7 were 58 years or older. Thirty-one patients were female and 6 were male. Among the 13 patients who improved, 3 were male. Eight of the patients (22%) had an education level corresponding to a university degree, 12 (32%) had a high-school degree, and 8 (22%) had completed 9-year compulsory education (or older equivalents). Six patients (16%) had lower education, less than 8 years of elementary school (old school system). Three patients did not report educational level.

Mean average pain intensity at baseline was 5.7 (SD 2.0; range 2 to 10) on a 0 to 10 NRS; mean worst pain was NRS 7.4 (SD 2.0; range 2 to 10). The mean CPI score was 61 (SD 19; range 20 to

100). Low baseline average pain intensity and low CPI score increased the likelihood of improvement. At baseline, 23 patients reported continuous pain and 14 reported recurrent pain. Mean pain duration at baseline was 72 months (SD 55; range 6 to 240 months). The median duration was 48 months, and of the 13 patients who improved, 6 patients had had their pain for less than 48 months and 7 patients for at least 48 months. The number of pain areas ranged from 1 to 9, and the mean number was 3.5 (SD 2.2). Pain frequency, pain duration, and presence of widespread pain did not affect the outcome significantly.

The mean total score of the SF-MPQ sensory descriptors used was 9.5 (SD 6.8; range 2 to 28), and for affective descriptors it was 2.9 (SD 3.6; range 0 to 12). Intensity scores for sensory and affective descriptors did not significantly affect outcome.

No quality of life SF-36 domain scores predicted the outcome. The results of the regression analysis were as follows: physical functioning, OR 1.0 (P = .546); role-physical functioning, OR 1.0 (P = .807); bodily pain, OR 1.0 (P = .171); general health, OR 1.0 (P = .729); vitality, OR 1.0 (P = .491); social functioning, OR 1.0 (P = .072); role-emotional functioning, OR 1.0 (P = .189); and mental health, OR 1.0 (P = .790).

GCPS scores did not predict outcome, but the trend was that the higher the grade of GCPS disability that a patient reported at baseline, the less likely was a favorable outcome. Baseline GCPS grade IV category patients had an OR for improvement of 0.114 (P = .086), grade III OR 0.267 (P = .322), and grade II OR 0.480 (P = .386), all compared to patients in grade I category at baseline. This tendency did not reach statistical significance.

Emotional functioning as assessed by SCL-90R scores also did not predict outcome. Severe symptoms of depression had an OR for favorable PGIC outcome of 0.729 (P = .714) and moderate symptoms an OR of 1.4 (P = .714), both compared to normal SCL-90R scores.

Relationship Between Baseline Diagnostic Tests Results and Outcome

This section describes the association between the clinical findings in baseline studies II and III and the long-term outcome.

QST Profiles. Baseline data on complete QST Z-scores were available for a subgroup of 33 patients, and 31 (94%) of these had at least one abnormal parameter. Eleven patients had improved substantially according to their PGIC rating, and 22 had not. Eleven patients (33%) had a MiSA profile with 0 to 1 abnormal parameters (out of 9 possible); 3 of these patients reported clinically relevant improvement (27%). Twenty-two patients (67%) had MaSA profiles (two or more abnormal parameters) and out of these, 8 patients had improved substantially (36%); the difference was not statistically significant (P = .999) and the sensory profiles did not predict outcome (Table 4).

Responsiveness to Local Anesthesia. Data from the investigation of responsiveness to injection of a local anesthetic agent in the pain area were available for 28 of the 37 patients. Thirteen patients had experienced at least 50% pain reduction by 30 minutes after lidocaine injection, and out of these 4 (31%) also reported clinically relevant improvement after 7 years. For the 15 patients who experienced less or no effect of lidocaine injection, the corresponding number was 4 (27%); the difference was not statistically significant (P = .166) and the responsiveness to local anesthesia did not predict outcome (Table 4).

Treatments Tried at Baseline and Reported Outcome

Grouped after type of treatment, 92% of the patients had tried pharmacological treatment at baseline (analgesics, sedatives, antidepressants, or anticonvulsants), 73% had tried additional surgical interventions (endodontic treatment, tooth extraction, or any form of surgical treatment in the pain area), 68% treatment aimed at stabilizing the occlusion (occlusal appliance or equilibration), 57% sensory treatment (transcutaneous electrical nerve stimulation [TENS], acupuncture), 30% manual treatment (physiotherapy or chiropractic treatment), and 19% relaxation. Of the 29 patients who had tried analgesics at baseline, 18 (62%, 95% CI 42.3%–79.3%) reported that the treatment had had at least some effect on the pain. For antidepressants and for anticonvulsants (carbamazepine or gabapentin), the corresponding results were 3/11 patients (27%, 95% CI 6.0%–61.0%) and 4/12 patients (33%, 95% CI 9.9%–65.1%), respectively.

The median number of treatment-type groups that patients had tried at baseline was three, and 25 (68%) of the 37 patients had tried treatments from three or more groups. Of these 25, 9 patients (36%) also reported clinically relevant improvement. For the 12 patients who had tried fewer than three treatment types, the corresponding figure was 4 patients (25%). The number of treatment groups tried did not significantly affect outcome (Table 4). Eleven of the 34 patients who reported they had tried pharmacological pain treatment stated that they had some pain-reducing effect from it. Of these, 5 also reported favorable PGIC outcome.

Ongoing Treatment and Reported Outcome

All patients responded to the question whether they were currently under any form of pain treatment, and 26 (70%) of them stated that they were. Thirteen patients reported taking benzodiazepines, 9 patients took analgesics, 6 took antidepressants, and 5 took gabapentin or pregabalin (no patient was currently on carbamazepine). Two patients reported acupuncture treatment and 1 patient TENS. Six patients reported physiotherapy as ongoing treatment, 4 patients relaxation, and 2 patients chiropractic treatment. Fourteen patients used occlusal appliances. The mean number of ongoing treatments was 1.7 (SD 1.6, range 0 to 5).

In total, 13 patients reported a clinically relevant improvement. Among those, 6 (46%) reported ongoing treatment. Of the 24 patients who had not improved significantly over the study period, 20 (83%) reported ongoing treatment.

Sixteen patients reported that they were currently on (some form of) pharmacological treatment, whereas 18 were on nonpharmacological treatment. When PGIC was correlated to ongoing treatment type, favorable PGIC was correlated to nonpharmacological treatment by $\rho = -0.438$ ($P = .008$) and pharmacological treatment by $\rho = -0.252$ ($P = .138$).

Dental Treatment During the Study Period

Some patients had had new dental treatment in the pain area, although the response rate was low for this question. Eight patients (question answered by 25 patients) reported having received crowns or fillings, 4 (question answered by 14 patients) had had endodontic treatment, and 2 (question answered by 14 patients) tooth extractions. No patient reported having endodontic surgical treatment in the pain area (question answered by 13 patients).

Pain Explanation and Economic Compensation

Twenty patients (54%) reported that they had not received a satisfactory explanation for the pain. Of the 13 patients who had improved, 7 (54%) were satisfied with the explanation given, and among patients who did not improve, the corresponding figure was 10/24 (42%).

Twenty-six of 29 patients (90%) reported having had no economic compensation for costs brought on by the pain problem; 8 had improved PGIC and 14 had not. Eight patients chose not to answer this question.

Discussion

Long-Term Outcome in AO

This study's main finding was that about one-third of the patients (35%) with AO improved considerably over time, indicated by the patient-reported overall status assessment on the PGIC measure and supported by significantly decreased pain intensity, frequency, and disability over time. Watson and coworkers studied 156 patients with postherpetic neuralgia for up to 11 years and found that 47% were doing well at their final assessment appointment.[27] Allerbring and Hägerstam assessed patients with persistent idiopathic facial pain by a questionnaire and found 22% of patients to be free of orofacial pain at 9 to 19 years after their first consultation. Pain resolution was attributed to a range of reasons, including dental treatment (prosthodontic, endodontic, or surgical treatment), pharmacological treatment (analgesics, or steroid treatment for rheumatic disease), replacement of all amalgam fillings with other materials, and acupuncture.[16] In addition, the study was retrospective and had a 39% dropout rate, and the inclusion criteria were not strict (patients were included on grounds of not having received any diagnosis on consultation), which suggests difficulties in comparing materials between studies.

Another important finding in the present study was that although many patients improved, most still experienced pain of some degree many years (on average 13 years) after pain onset. Around half of the patients reported no change or even deterioration despite repeated treatment efforts. Few patients reported complete remission from pain. In comparison, a longitudinal study on TMD pain—considered mainly musculoskeletal in origin—reported complete remission in 49% of cases.[28] The difference in findings indicates that there are important differences between atypical tooth pain and TMD pain, for example, in mechanisms underlying pain maintenance.

Nine patients were lost to follow-up, the majority due to death or old age. In accordance, the dropouts were significantly older than the ones participating in follow-up, and perhaps not surprisingly also reported longer pain duration at baseline (being older to begin with, they also had had pain for a longer time, assuming equal onset age). Long pain duration is generally considered a risk factor for continuing pain, and although the average baseline pain duration in the remaining sample was still long (6 years), it is possible that the loss of these older patients to follow-up introduced bias towards an overestima-

tion of the prognosis. Because the 9 dropouts did not differ from the 37 followed in other aspects, data were analyzed with 37 patients as the denominator (sample size). However, in analyzing best-case and worst-case scenarios, there is also the possibility that all of the 6 still living dropouts in fact experienced clinically relevant improvement (or even complete remission of pain) after 7 years, or alternately experienced unchanged or increased pain. The same possibility exists for the deceased 3 patients regarding pain status at the time of death. A best-case scenario assuming that all 9 dropouts were significantly improved would render a PGIC improvement rate of 48% (95% CI 32.4%–63.1%). The opposite, worst-case (none of the 9 dropouts were improved) renders a PGIC improvement rate of 28% (95% CI 16.1%–43.5%). For complete remission of pain, the corresponding figures are 30% (95% CI 17.7%–45.8%) for all 9 being pain-free and 11% (95% CI 3.6%–23.6%) for none of the 9 being pain-free from their AO condition at follow-up (or time of death, respectively). Thus, even assuming these worst-case or best-case scenarios, the present findings suggest that significant improvement over 7 years as measured by the PGIC instrument lies in the range of about a third to half of the AO patients, and that complete remission of pain can be expected for less than one in four.

PGIC, which reflects patients' satisfaction with the overall situation, may be a more relevant measure than those assessing only a single or a few aspects of the complex pain experience.[29] Recommended by IMMPACT as a core outcome measure in chronic pain trials, PGIC has been widely used in studies of various painful conditions.[30–34] In treatment studies, PGIC ratings usually describe perceived change over a comparatively short time period (3 to 6 months). In the present study, patients were asked to rate their perceived change over 7 years, which may present a memory bias problem.[35] However, the global rating correlated reasonably well with other frequently used outcome measures—pain intensity and frequency—indicating that the reported improvement is robust. Similarly, Farrar et al found a consistent relationship between the PGIC ratings "very much improved" or "much improved" and a 30% reduction in pain intensity on a NRS, regardless of age, sex, or disease type, in a meta-analysis of pregabalin treatment for chronic pain conditions.[34] The present study used identical scales and cutoff points and so the results may be generalizable for AO patients in this aspect. The alternate outcome measures (30% or more average pain reduction/CPI reduction, and reduction in pain frequency) implied better long-term outcome than the PGIC ratings. This finding highlights that the pain experience is complex and not easily assessable.

Physical functioning improved over the study period, as indicated by the decreased GCPS scores for one-third of the patients, and possibly also by the significantly improved quality of life in the SF-36 bodily pain domain. The domain is closely associated with disability from pain; one of the two items concerns the impact of pain on work and household activities. It is thus possible that the improvement partly results from a decrease in expected work activities with increasing age and changes in domestic arrangements; the reported number of pain areas did not change over time. The relationship between number of painful areas, reported pain levels, and reported disability from pain is likely also complex.

Emotional functioning did not improve over time at the group level. The change patterns at the individual level, with almost as many deteriorating as improving from baseline to follow-up, may indicate bias from confounding life events, for example, concomitant health problems. The relationship between emotional functioning and pain cannot be readily described in this material.

Outcome Prediction—Self-Report Measures

This study used self-report measures on various aspects of the pain itself—and of its effects on the individual—in two ways. First, data between "baseline" in 2002 and "follow-up" in 2009 were compared to measure and describe changes over time at the group and individual levels. This method gives straightforward information on how patients with AO fare over time. In contrast to many follow-up studies concerned with treatment efficacy, the patients in this material had not been subjected to a defined treatment regime but were heterogeneous in many respects, and differences in study design obstruct direct comparison between studies.

Second, the study aimed to explore the predictive value of each measure's baseline value and thus identify prognostic factors for persisting pain. Since AO is a relatively rare condition, the material is not large in number. Instead of performing a logistic regression analysis with multiple covariates simultaneously, each factor was examined separately. Due to the moderate sample size and wide CI for a favorable outcome in terms of PGIC, all attempts to identify prognostic factors among baseline self-report data and clinical test results must be regarded as exploratory.

Based on *(1)* dichotomization of baseline values of each parameter and relating them to a dichotomized PGIC—clinically relevant improvement or not—and

(2) logistic regression analysis with each covariate studied separately, only one factor was predictive of a favorable outcome. This was low baseline pain intensity, represented by a low CPI score and low average pain intensity (nested within the CPI measure). The data suggest that the chance of perceived overall improvement over 7 years increases with 56% for each baseline NRS point reduction in pain intensity; however, the finding must be regarded with the reservation of a 95% CI lower limit approaching 1. Statistical analysis of a relatively low number of patients does not permit predictor identification with a high degree of certainty, and interactions between factors were not possible to investigate in this material, so results must be interpreted with caution. Other factors that seemed to promote favorable outcome, but failed to reach statistical significance, were low worst pain intensity, male gender, and low grade of disability from pain at baseline.

Outcome Prediction—Clinical Findings

The clinical diagnostic tests, QST and lidocaine injection in the pain area, were also analyzed in terms of their prognostic values.

Most AO patients (94%) had at least one somatosensory abnormality at baseline, and 67% had two or more. This compares favorably to a recent large study describing various neuropathic pain conditions, where 92% of the patients had at least one abnormality.[36] Further studies are needed to determine more precisely the range of normal values for intraoral QST in parallel with reported ranges for other neuropathic pain conditions[36,37] and to describe AO subgroups that may help identify mechanisms for pain maintenance and guide treatment choice.[15]

The baseline study examined responsiveness to lidocaine injection. Local anesthesia produced a pain reduction of 50% or more in only 54% of the patients, and the interpretation was that for many AO patients, pain cannot be the result of peripheral sensitization and nociception alone but may involve a substantial sensitization of higher-order trigeminal neurons and/or impairment of endogenous pain inhibitory systems.[13] Indeed, it has been suggested that central sensitization plays a major role in chronic neuropathic pain maintenance,[38] and therefore the authors hypothesized that patients who do not respond to peripheral anesthetic injections (indicating predominantly centrally based mechanisms for pain maintenance) would have a less favorable prognosis.

In the present study, neither limited signs of somatosensory dysfunction nor pain relief by local anesthesia appeared to be predictive of a favorable long-term prognosis, but the material may have been too small to reveal such correlations. Further studies are warranted.

Treatment Effectiveness

Treatment effectiveness was examined in subgroups of patients who had tried various treatment regimes. A therapeutic algorithm for AO based on a number of AO studies has been recommended, with tricyclic antidepressants or serotonin and norepinephrine reuptake inhibitors as the first line of pharmacological treatment,[39] but randomized controlled trials (RCTs) investigating treatment outcome are lacking. In the present study, the proportions of patients reporting some pain relief were 33% for anticonvulsants and 27% for antidepressants. In concordance, two recent Cochrane reviews reported that carbamazepine treatment in neuropathic pain conditions provided better pain relief than placebo (70% vs 12% improved),[40] and an approximate number needed to treat of 3 for tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine) in neuropathic pain treatment.[41] A crossover RCT reported only moderate effectiveness of venlafaxine for the treatment of atypical facial pain (a condition suggested to closely resemble AO).[42]

Ongoing Treatment at Follow-up

A majority (70%) of patients reported ongoing treatment at follow-up. Ongoing treatment was more common in patients who reported no clinically relevant improvement (83%) compared to patients who perceived themselves substantially improved (46%). This may reflect that patients who are troubled by pain are more likely to pursue treatment of some kind. Watson et al found that 60% of patients with postherpetic neuralgia with poor outcome and 46% with good outcome were on medication, which is consistent with the present findings.[27] An alternative interpretation is that although pharmacological treatment provides pain relief to some extent, patients may discontinue treatment because of negative side effects, as others have found.[42] This is possibly supported by the finding that there was a significant correlation between favorable PGIC and nonpharmacological treatment, but not pharmacological treatment. Among the nonpharmacological treatments, occlusal appliances were frequently used; patients may perceive that the appliance prevents loading and protects the painful region. A high prevalence of concomitant TMD pain has been reported and may be another explanation.[10,43]

Pain Explanation and Patient Communication

In 2002, patients received detailed information of the findings, diagnosis, and implications. Recommendations for future attitudes to dental care were also made, for example, to avoid invasive treatment in the pain region since neuropathic pain was suspected. It is noteworthy that despite these precautions, 54% of patients considered that they had not received a satisfactory pain explanation. At least 16% had received further invasive treatment. Wolf and coworkers reported in a qualitative study that patients with chronic (nonspecific) orofacial pain express dissatisfaction with consultations and difficulties in communication and understanding, suggesting unsatisfactory communication between patient and caregiver and difficulties in developing coping strategies.[44] In managing treatment-resistant pain, complementary psychological interventions, such as cognitive and behavioral self-management strategies, are strongly recommended.[4,45,46] One path of future research could be to investigate the relationship between patient-caregiver interaction, patient ability to cope, and long-term prognosis of orofacial pain.

Study Strengths and Limitations

The strength of this study was that a wide range of well-established instruments were included, examining various aspects of the complexity of AO pain, although aspects such as sleep quality, anxiety, and stress were not covered. The original sample of AO patients was well-characterized and the response rate in the high range, which may vouch for good generalizability to the AO patient population.

One of the limitations of the study was sample size, which although one of the largest presented on AO pain, did not allow a more robust regression analysis with examination of interactions between baseline conditions. Due to the complex pain situation of many patients, it was impossible to know whether ongoing pharmacological treatment was exclusively aimed at the orofacial pain or was partly related to other pain problems or distress.

Conclusions and Clinical Implications

A third of the AO patients experienced a clinically meaningful improvement in overall status over time. A higher rate of improvement was suggested by less complex alternate outcome measures assessing single aspects, such as reported changes in pain intensity and pain frequency. Low baseline pain intensity, represented by low average pain and CPI scores, was the only predictor for decreased pain over a 7-year period that could be tentatively identified. The clinical implications of the findings are that although improvement to some degree can be expected over time for AO patients, especially if the baseline pain is low or moderate, the pain will persist in a majority of AO patients. Future studies examining the effect of various interventions are needed to identify the best management of pain in this group.

Acknowledgments

This work was supported by a grant from TePe Munhygienprodukter AB, Sweden. This company has no commercial interests in the field of pain research or pain management. The study was also supported by grants from the Swedish Dental Society, the South Swedish Dental Society, and by NIH grants K12 DE14069 and R21-DE018768. There were no conflicts of interest in the performance of this study.

References

1. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors? Int J Epidemiol 2006;35:468–476.
2. Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance. An epidemiologic investigation. Arch Gen Psychiatry 1990;47:239–244.
3. MedicineNet.Inc. www.medterms.com. Online web version of Webster's New World Medical Dictionary, ed 3. New York: Wiley, 2008.
4. Angst F, Verra ML, Lehmann S, Brioschi R, Aeschlimann A. Clinical effectiveness of an interdisciplinary pain management programme compared with standard inpatient rehabilitation in chronic pain: A naturalistic, prospective controlled cohort study. J Rehabil Med 2009;41:569–575.
5. Navarro A, Saldana MT, Perez C, Torrades S, Rejas J. Patient-reported outcomes in subjects with neuropathic pain receiving pregabalin: Evidence from medical practice in primary care settings. Pain Med 2010;11:719–731.
6. Leichsenring F. Randomized controlled versus naturalistic studies: A new research agenda. Bull Menninger Clin 2004;68:137–151.
7. Melis M, Lobo SL, Ceneviz C, et al. Atypical odontalgia: A review of the literature. Headache 2003;43:1060–1074.
8. Nixdorf DR, Drangsholt MT, Ettlin DA, et al. Classifying orofacial pains: A new proposal of taxonomy based on ontology. J Oral Rehabil 2012;39:161–169.
9. Nixdorf DR, Moana-Filho EJ, Law AS, McGuire LA, Hodges JS, John MT. Frequency of nonodontogenic pain after endodontic therapy: A systematic review and meta-analysis. J Endod 2010;36:1494–1498.
10. List T, Leijon G, Helkimo M, Oster A, Dworkin SF, Svensson P. Clinical findings and psychosocial factors in patients with atypical odontalgia: A case-control study. J Orofac Pain 2007;21:89–98.
11. Baad-Hansen L, List T, Jensen TS, Svensson P. Increased pain sensitivity to intraoral capsaicin in patients with atypical odontalgia. J Orofac Pain 2006;20:107–114.

12. Baad-Hansen L, List T, Kaube H, Jensen TS, Svensson P. Blink reflexes in patients with atypical odontalgia and matched healthy controls. Exp Brain Res 2006;172: 498–506.
13. List T, Leijon G, Helkimo M, Oster A, Svensson P. Effect of local anesthesia on atypical odontalgia–A randomized controlled trial. Pain 2006;122:306–314.
14. List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: A case-control study. Pain 2008;139:333–341.
15. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9:807–819.
16. Allerbring M, Hägerstam G. Chronic idiopathic orofacial pain. A long-term follow-up study. Acta Odontol Scand 2004;62:66–69.
17. Baad-Hansen L, Leijon G, Svensson P, List T. Comparison of clinical findings and psychosocial factors in patients with atypical odontalgia and temporomandibular disorders. J Orofac Pain 2008;22:7–14.
18. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.
19. Haythornthwaite JA. IMMPACT recommendations for clinical trials: Opportunities for the RDC/TMD. J Oral Rehabil 2010;37:799–806.
20. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: DHEW, 1976.
21. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
22. Ohrbach R, Turner JA, Sherman JJ, et al. The research diagnostic criteria for temporomandibular disorders. IV: Evaluation of psychometric properties of the Axis II measures. J Orofac Pain 2010;24:48–62.
23. Burckhardt CS, Bjelle A. A Swedish version of the short-form McGill Pain Questionnaire. Scand J Rheumatol 1994;23:77–81.
24. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–197.
25. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.
26. Ohrbach R, Larsson P, List T. The jaw functional limitation scale: Development, reliability, and validity of 8-item and 20-item versions. J Orofac Pain 2008;22:219–230.
27. Watson CP, Watt VR, Chipman M, Birkett N, Evans RJ. The prognosis with postherpetic neuralgia. Pain 1991;46: 195–199.
28. Ohrbach R, Dworkin SF. Five-year outcomes in TMD: Relationship of changes in pain to changes in physical and psychological variables Pain 1998;74:315–326.
29. Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: Is a single global assessment good enough? Pain 2001; 91:189–194.
30. Baron R, Brunnmuller U, Brasser M, May M, Binder A. Efficacy and safety of pregabalin in patients with diabetic peripheral neuropathy or postherpetic neuralgia: Open-label, non-comparative, flexible-dose study. Eur J Pain 2008;12:850–858.
31. Bolton JE. Sensitivity and specificity of outcome measures in patients with neck pain: Detecting clinically significant improvement. Spine (Phila Pa 1976) 2004;29:2410–2417; discussion 2418.
32. Dunkl PR, Taylor AG, McConnell GG, Alfano AP, Conaway MR. Responsiveness of fibromyalgia clinical trial outcome measures. J Rheumatol 2000;27:2683–2691.
33. Emshoff R, Emshoff I, Bertram S. Estimation of clinically important change for visual analog scales measuring chronic temporomandibular disorder pain. J Orofac Pain 2010;24:262–269.
34. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.
35. Stone AA, Schwartz JE, Broderick JE, Shiffman SS. Variability of momentary pain predicts recall of weekly pain: A consequence of the peak (or salience) memory heuristic. Pers Soc Psychol Bull 2005;31:1340–1346.
36. Maier C, Baron R, Tolle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150:439–450.
37. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain 2006;123:231–243.
38. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011;152:S2–S15.
39. Baad-Hansen L. Atypical odontalgia—Pathophysiology and clinical management. J Oral Rehabil 2008;35:1–11.
40. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults Cochrane Database Syst Rev 2011;(1):CD005451.
41. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: A Cochrane review. J Neurol Neurosurg Psychiatry 2010;81:1372–1373.
42. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: A randomized controlled trial. J Orofac Pain 2004;18:131–137.
43. Vickers ER, Cousins MJ, Walker S, Chisholm K. Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:24–32.
44. Wolf E, Birgerstam P, Nilner M, Petersson K. Patients' experiences of consultations for nonspecific chronic orofacial pain: A phenomenological study. J Orofac Pain 2006;20:226–233.
45. Turk DC, Audette J, Levy RM, Mackey SC, Stanos S. Assessment and treatment of psychosocial comorbidities in patients with neuropathic pain. Mayo Clin Proc 2010;85:S42–S50.
46. Wetering EJ, Lemmens KM, Nieboer AP, Huijsman R. Cognitive and behavioral interventions for the management of chronic neuropathic pain in adults–A systematic review. Eur J Pain 2010;14:670–681.