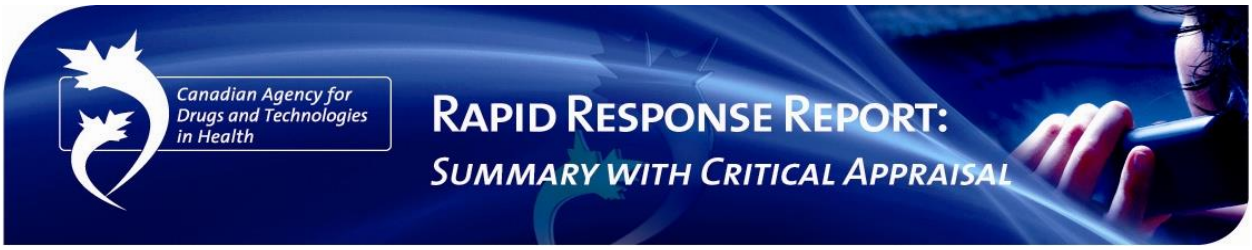

TITLE: Interventions for Atypical Facial Pain: A Review of Clinical Effectiveness and Guidelines

DATE: 01 April 2016

CONTEXT AND POLICY ISSUES

Atypical facial pain (AFP), also referred to as persistent idiopathic facial pain (PIFP), is a chronic condition which involves localized, lancinating pain to the craniofacial region that is not characteristic of common cranial neuralgias, and which has no apparent cause; the pain is present daily and often lasts throughout the day.[1] The prevalence of AFP in Canada is unclear but considered to be rare;[2] the lifetime prevalence of AFP based on a study in the German population has been estimated at 0.03%.[3] According to the International Headache Society's classification system (2nd edition of The International Classification of Headache Disorders; ICHD-II), it includes atypical odontalgia (AO), which refers to unilateral, continuous pain in the teeth or tooth socket without an identifiable dental cause.[1] AFP is differentiated from classical trigeminal neuralgia (TN) by the types of pain episodes; TN is characterized by the ICHD-II as consisting of brief episodes of extreme facial pain in the trigeminal nerve regions lasting up to a maximum of two minutes.[4] The Burchiel classification system of TN is another commonly used method for describing these conditions, delineated into TN Types 1 and 2 (TN1 and TN2).[5] The Burchiel classification of TN1 is consistent with the ICHD-II description of classical TN, whereas TN2 most closely corresponds with the ICHD-II definition of AFP; TN2 is characterized as idiopathic, constant facial pain that lasts for at least half of the day, that may include some intense, episodic pain.[5]

Due to the vague terminology used to describe AFP and the lack of identifiable physical or structural causes, diagnosis and subsequent treatment are difficult. Treatment options explored for the management of AFP may include those typically used for classical TN, such as first-line pharmacotherapy with antiepileptic medication (e.g., carbamazepine, oxcarbazepine, gabapentin, pregabalin) or neurosurgery for patients who do not experience symptom relief or cannot tolerate the adverse effects of medication.[6,7] There are several neurosurgical options for TN, including microvascular decompression (MVD) and ablative procedures (e.g., neurectomy and rhizotomy), which address the neurovascular compression of the trigeminal nerve and demyelination that are common in classical TN.[6,7] However, AFP does not have a clear etiology that can be easily targeted for treatment, and it has been suggested that neurosurgery and

other invasive treatments are not effective for this condition.[8] In order to inform clinical practice, evidence regarding the safety and effectiveness of treatment options for AFP, as well as guidelines for their use, is required.

The purpose of this report is to review the available published literature relating to pharmacological and non-pharmacological interventions for the treatment of AFP in adults.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of pharmacological and non-pharmacological interventions for patients with atypical facial pain?

2. What are the evidence-based guidelines regarding interventions for patients with atypical facial pain?

KEY FINDINGS

A number of therapeutic options are available for managing atypical facial pain, including surgical interventions, non-surgical non-drug interventions, and drug treatments. Seven non-randomized studies on surgical procedures for atypical facial pain were identified that reported generally poor outcomes related to pain relief and complications or adverse events among this patient population. Likewise, limited evidence of the clinical effectiveness of non-surgical interventions (drug and non-drug) was reported by five non-randomized studies and two randomized controlled trials; non-surgical approaches were found to attenuate pain symptoms in some patients, but not all patients responded well to these treatment modalities. These findings warrant careful interpretation in light of several limitations, including small sample sizes, the retrospective nature of included studies, and the fact that many studies had no control group. The applicability of the identified published literature is also limited for the Canadian context given the lack of studies conducted in this setting.

One evidence-based guideline was identified that recommends first-line treatment with pharmacologic agents for the management of atypical facial pain, followed by minimally-invasive surgical intervention for patients who are uncontrolled on drug therapy.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and February 22, 2016.

Selection Criteria and Methods

Two reviewers independently screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and

assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with atypical facial pain (also known as idiopathic facial pain and persistent idiopathic facial pain) or Burchiel classification TN2
Intervention	Pharmacological interventions (e.g., anticonvulsants, antidepressants, anti-inflammatories, opiates, cannabis, nabilone); Non-pharmacological interventions (including surgical modalities [e.g., MVD, neurectomy, rhizotomy] and non-surgical interventions [e.g., cognitive behavioural therapy, acupuncture, motor cortex simulation])
Comparator	Q1: Interventions compared with each other; placebo; no comparator.
Outcomes	Q1: Clinical benefits and harms (e.g. pain relief, safety) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews and/or meta-analyses, randomized controlled studies, non-randomized studies, evidence-based guidelines

MVD = microvascular decompression; TN2 = trigeminal neuralgia Type 2.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2006. Guidelines were excluded if they did not clearly indicate a formal literature search and/or assessment of the quality of the evidence upon which the recommendations were based.

Critical Appraisal of Individual Studies

The methodological quality of included randomized and non-randomized clinical studies was assessed using the Downs and Black checklist.[9] Similarly, evidence-based guidelines were critically appraised using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[10] Summary scores were not calculated for the included studies or published guidelines; rather, a review of the strengths and limitations of each included study or evidence-based guideline was performed and described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 470 citations were identified in the literature search. Following screening of titles and abstracts, 443 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. One additional relevant record was retrieved from the grey literature search. Among the articles selected for full-text review, 13 articles were excluded due to the study population (i.e., indications that did not include AFP, or mixed patient populations without outcome reporting separated by indication), and a total of 15 publications met the inclusion criteria and were included in this report. Appendix 1: Selection of Included Studies presents a flow diagram of the study selection process, including reasons for exclusion of full-text publications.

Summary of Study Characteristics

A brief overview of the characteristics of 14 included studies and guideline publication can be found in Appendix 2: Characteristics of Included Publications.

Study Design

Among the 14 clinical studies selected for inclusion, six (43%) were retrospective chart reviews,[11-16] four (29%) were uncontrolled before-and-after studies,[17-20] two studies (14%) adopted an analytic cross-sectional design,[21,22] and two were randomized controlled trials (RCTs).[23,24]

One evidence-based guideline[8] met the inclusion criteria for this review. This guideline was developed using an evidence grading approach developed by Guyatt et al. (2006)[25] and assigned scores to available published literature on interventional pain management techniques.

Country of Origin

The majority of included studies were conducted across different European settings; namely, there were two studies from France,[11,18] two from Denmark,[13,23] and one each from the Netherlands,[12] Turkey,[22] Croatia,[19] Germany,[16] and Sweden.[24] Three studies were conducted in the United States,[15,17,21] and there was one study from Brazil[14] and Taiwan,[20] respectively.

The included clinical practice guideline was the product of collaboration between clinicians and researchers from the Netherlands, Belgium, and the United States, endorsed by the World Institute of Pain.[8]

Patient Population

The target populations across included clinical studies generally comprised adult patients experiencing chronic facial pain localized to one or both sides of the face. There was considerable variability in terms of the description of the pain condition across studies, including mention of persistent idiopathic facial pain (PIFP),[11,16,19,20] atypical facial pain (AFP),[12,14,15,18,22] atypical odontalgia (AO),[23,24] as well as trigeminal neuralgia type 2 (TN2) pain based on the Burchiel classification system.[13,15,17,21] With the exception of one before-and-after study which exclusively recruited patients with PIFP,[20] and two RCTs which focused specifically on patients with AO,[23,24] most of the included studies comprised heterogeneous samples of patients with diverse craniofacial diagnoses; thus, patients with AFP were frequently subgroups among larger study samples. Patients across a number of study samples reported a history of chronic facial pain before undergoing the studied interventions; duration of pre-procedure pain was reported across three included studies and spanned the period between 3 years up to 12 years.[12,13,21] Moreover, six (43%) included studies reported on patients who were treatment experienced,[11,13-15,17,18] while there were three (21%) treatment-naive study samples.[21,23,24] Prior treatment experience was not reported among five (36%) studies.[12,16,19,20,22] Patients across 50% of included studies received one type of intervention or procedure during the time of the study,[12,15,17,18,21,23,24] while patients in other studies underwent one or more procedures.[11,13,14,16,19,20,22] Reasons for repeated procedures were not reported in any of the included studies. Participants across the majority of study samples were aged on average above 50 years; the mean age of participants in two studies was above 45 years.[20,23]

The intended users of the included evidence-based guideline were described as pain specialists whose responsibility consists of confirming a PIFP diagnosis of a referring physician prior to the onset of interventional pain management; the guideline is intended for use among any clinicians with an interest in pain management.[8]

Interventions and Comparators

Three major types of interventions were identified across the included studies: surgical interventions (6 studies), non-surgical non-drug interventions (5 studies), and drug treatments (2 studies).

More specifically, surgical interventions comprised:

- alcohol neurolysis of the sphenopalatine ganglion under CT guidance[11]
- radiofrequency thermocoagulation of the shenopalatine ganglion[12]
- percutaneous glycerol injection or rhizotomy[13]
- microvascular decompression[13,21]
- repeat posterior fossa exploration[17]
- trigeminal tractotomy-nucleotomy under CT guidance[22]
- radiofrequency percutaneous rhizotomy with or without neurovascular decompression[14]

Non-surgical non-drug interventions included:

- repetitive transcranial magnetic simulation of the motor cortex contralateral to pain[18]
- Gamma knife radiation surgery[15]
- occipital nerve block[16]
- low level laser therapy[19,20]

Drug therapies comprised local anesthetics ketamine or fentanyl,[23] and lidocaine or adrenaline,[24] whose efficacy was specifically assessed among patients with AO.

Given that the majority of included studies adopted a single-arm, pre-post design with no control group, with the exception of two placebo-controlled RCTs, active treatment comparators were not reported across clinical studies.

Outcomes

The primary outcome of interest across all included studies was pain relief. However, there was considerable variation in the way this outcome was measured. Namely, seven studies (50%) measured mean pain relief using a Visual Analogue Scale (VAS),[11,12,18,20,22-24] two studies measured self-reported pain relief (no structured instrument described),[17,21] one study used a vector-based pain diagram,[13] and four used other rating methods or grading scale approaches.[14-16,19] Secondary outcomes comprised adverse events or complications among nine (64%) studies,[11-14,16,17,22-24] and the recurrence of pain was assessed in one study.[11]

The included evidence-based guideline provided recommendations on diagnosis and therapeutic options and presented a clinical practice algorithm. The evidence for different interventional pain management techniques was rated.[8]

Summary of Critical Appraisal

A detailed overview of the strengths and limitations of each study selected for inclusion can be found in Appendix 3: Critical Appraisal of Included Publications.

What is the clinical effectiveness of pharmacological and non-pharmacological interventions for patients with atypical facial pain?

The assessment of included studies by methodological quality domains of the Downs and Black checklist[9] revealed that major concerns across studies were associated with external validity, internal validity (confounding), and statistical power, while the reporting and internal validity (bias) domains contributed to a lesser extent to the overall risk of bias between and within studies. More specifically, less than half (43%) of included studies provided sufficient information on the recruitment of participants to inform the representativeness of the study sample,[13,17,20,21,23,24] two of which (14%) further described the representativeness of subjects who were willing to participate in the study.[13,20] In addition, it was generally unclear whether the implementation of the intervention was representative of that in use in the source population. Although randomization of participants and concealment of treatment allocation were only possible for the two included RCTs, one of two studies was successful in blinding outcome assessors.[23] While patients in retrospective studies were recruited in a consecutive manner, it was unclear whether analyzed subgroups of patients, such as patients with AFP, were the product of planned or unplanned analyses. Furthermore, participants across studies were recruited over the same time period, and six of 14 studies (43%) used intention-to-treat analysis.[12,13,15,17,18,21] None of the included studies performed a power estimation or provided justification for the number of recruited participants; as a result it was difficult to assess whether study samples were sufficiently powered to detect a clinically relevant treatment effect, and the validity of inferences made based on small samples reported across many of the included studies remains questionable. Finally, while most studies fared relatively well on items relating to reporting and internal validity, five (36%) of the included studies did not report potential adverse events associated with the specified interventions, and none of the participants across uncontrolled studies were blinded to the intervention they received. The risk of bias from lack of blinding of study participants, however, was difficult to prevent owing to the nature of the interventions under study. Moreover, the use of different outcome measures limited comparison across included studies, and it was unclear which measures were responsive to changes in symptoms among patients with AFP.

Given the number of threats to both internal and external validity, results of included studies should be interpreted cautiously. Finally, the risk of publication bias cannot be ruled out.

What are the evidence-based guidelines regarding interventions for patients with atypical facial pain?

Methodological quality of the included evidence-based guideline was evaluated using the AGREE-II instrument.[10] The quality of this guideline document is strengthened by several factors, including a clear description of the objective and the intended users, well-designed methods for formulating recommendations, consideration for health benefits, adverse effects, and risks in formulating recommendations, and guidance on how the recommendations can be put into practice. However, reporting regarding guideline development was unclear. Namely, it was unclear whether systematic methods were used to search for evidence, and stakeholder involvement did not appear to consider the views and preferences of patient representatives or

clinicians other than anesthesiology specialists. In addition, it was unclear whether the guideline has been externally reviewed by experts prior to publication, and the guideline does not describe facilitators and barriers to its application. Finally, potential conflicts of interest were not reported.

Summary of Findings

A detailed synthesis of results of each included study and guideline recommendation can be found in Appendix 4: Main Study Findings and Author's Conclusions.

What is the clinical effectiveness of pharmacological and non-pharmacological interventions for patients with atypical facial pain?

Clinical effectiveness of the following three categories of interventions for the management of atypical facial pain was assessed across the selected studies: surgical interventions (6 studies), non-surgical non-drug interventions (5 studies), and drug treatments (2 studies). Results of these studies along with the authors' conclusions are summarized below.

Surgical interventions

Alcohol neurolysis of the sphenopalatine ganglion (SPN) under CT guidance was found to be a safe and effective surgical treatment for patients with PIFP uncontrolled on pharmacologic therapy.[11] This finding was based on a retrospective file review study of 42 patients with chronic facial pain, 10 of which had a PIFP diagnosis and underwent a total of 21 procedures; all study participants were followed-up for a period of up to 48 months. In the PIFP subgroup, this intervention was successful in 18 of 21 procedures (effectiveness rate = 85.7%, defined as more or equal to a 50% pain reduction on a VAS lasting for one month or longer); however, recurrence of pain was observed in 16 of 18 (89%) successful procedures. While the number of treatment-related complications occurring in the PIFP subgroup was not reported, the overall rate of short-term (e.g., local hematomas and post-procedural pain) and long-term complications (e.g., persisting hemipalate paresthesia and anesthesia) among a total of 58 procedures was 25.6% and 6.9%, respectively.

Findings from another retrospective chart review study of 15 patients, 10 of whom were initially diagnosed with AFP, revealed that radiofrequency thermocoagulation (RFT) of the sphenopalatine ganglion appeared as an effective surgical intervention in the treatment of AFP.[12] The authors of this study also concluded that patients with facial pain and headache were frequently misdiagnosed; four out of 10 patients initially diagnosed with AFP were found to have been correctly diagnosed following reassessment using the International Classification of Headache Disorders (ICHD) criteria. Of these four AFP patients, two experienced almost complete pain reduction (as measured by VAS) following single RFT, one had adequate pain reduction secondary to infection following two RFT procedures, and one patient did not experience pain reduction following single RFT.

Pain relief following surgical intervention with percutaneous glycerol injection (GI), microvascular decompression (MVD), or rhizotomy (RIZ) was assessed in a retrospective chart review study of 70 patients with trigeminal neuralgias type 1(TN1) and type 2 (TN2); 22 (31%) sample participants were diagnosed with TN2.[13] In this file review study, clinically significant pain relief ranged from complete pain relief to low-grade chronic dull pain, and was measured by a visual numerical rating scale or vector-based diagram. Findings revealed that one year

after the procedure, 73%, 33%, and 30% of patients with TN2 experienced a clinically significant positive effect following MVD, RIZ, and GI, respectively. After three years, the percentage of TN2 patients with a clinically significant positive effect decreased to 28%, 0% and 14% following MVD, RIZ, and GI, respectively; the number of TN2 patients receiving each procedure or multiple procedures was not specified. Furthermore, the number of TN1 and TN2 patients who experienced treatment-related complications was generally low, with the exception of 89% of overall patients with RIZ-related postoperative facial hypoesthesia. The authors concluded that while MVD and RIZ may be considered reasonably safe and effective among TN1 patients, the surgical outcomes among TN2 patients are still very poor.

MVD surgical outcomes were also evaluated in an analytic cross-sectional study of 95 treatment-naive patients with TN1 and TN2; 28 (29%) study participants were diagnosed with TN2.[21] Pain relief was the primary clinical outcome of interest, as measured through patient self-report. After 36 or more months following the surgical procedure, seven (25%) TN2 patients were pain-free without medication (excellent outcome), 11 (39%) patients had mild or intermittent pain controlled with low-dose medication (good outcome), and 10 (36%) patients experienced severe persistent pain or need for additional surgical treatment (poor outcome). The authors concluded that the proportion of patients with TN2 pain who experienced long-term pain relief following MVD was low..

In an uncontrolled before-and-after study of 29 treatment-experienced patients with recurrent TN1 and TN2 pain, repeat posterior fossa exploration (PFE) was reasoned to be a safe and effective surgical option with comparable results to other destructive procedures.[17] Results among the five TN2 study participants showed that 27% were pain-free without medication at one and three years following surgical intervention, respectively. While a number of treatment-related complications, including facial numbness and post-partial nerve section trigeminal deficits, were common among all recruited patients, the number of complications among TN2 patients in particular was not reported. The authors drew the conclusion that patients with TN2 did poorly after repeat PFE, and that it remains unclear which surgical procedure would lead to better outcomes for this difficult-to-treat population.

Surgical outcomes following CT-guided trigeminal tractotomy-nucleotomy (TC-TN) were assessed in an analytic cross-sectional study of 65 patients with craniofacial pain, 21 of which had an AFP diagnosis.[22] Findings revealed that of the 21 patients with atypical facial pain, 15 (71%) had no pain following surgical intervention, four (19%) patients experienced partial satisfactory pain relief, one (5%) patient had partial non-satisfactory pain relief, and one (5%) patient had no change in pain. While treatment-related complications were relatively uncommon among all patients, adverse events experienced specifically by AFP patients were not reported. The authors concluded that the TC-TN procedure under CT guidance may be considered as an early approach to managing patients with craniofacial pain owing to its minimal invasiveness, high efficacy, and low complication rate.

The effectiveness of radiofrequency percutaneous rhizotomy (RPR) and neurovascular decompression (ND) on pain relief was assessed in a retrospective file review study of 367 treatment-experienced patients with facial pain; 16 patients had an AFP diagnosis.[14] Pain relief was measured by way of a pain grading scale developed by the study authors; surgical outcomes were assessed at one and four months after the initial procedure, and at every six months thereafter on an as-needed basis. Of the 16 patients with AFP, there were five patients with a Degree 1 pain score (pain relief, hypalgesia or analgesia, tactile sensitivity deficit at the trigeminal branch affected, no neurological complications) and one patient with Degree 3 pain

score (pain relief, anaesthesia at any facial area or corneal, transient functional deficit or ocular motor nerves or other nerves, paresthesia with need of medication, lesion of encephalic structures). Four patients had no pain alleviation with treatment and six patients experienced partial improvement in pain or residual pain treated with medication. Two AFP patients underwent further intervention with neurovascular decompression (ND), and the outcome for both patients was rated as Degree 3 pain relief. Furthermore, five AFP patients who received RPR (31.3%) and one AFP patient who underwent ND (50%) experienced post-operative complications (i.e., corneal hyporeflex, keratitis, and central pain). Recurrence of pain was observed in four AFP patients. The authors concluded that while RPR was an efficient surgical approach for certain types of facial pain, it was not a good technique for AFP and inflammatory pain.

Non-surgical non-drug interventions

Non-surgical interventional pain management using repetitive transcranial magnetic simulation (rTMS) of the motor cortex was assessed among 55 treatment-experienced patients with craniofacial pain in a single-arm before-and-after study.[18] A total of 15 patients with AFP of idiopathic or central cause participated in this study, and pain relief was measured on a visual numeric scale (0 to 10 points) at 15, 30, 90, and 180 days after onset of rTMS therapy. Findings revealed that 13 out of 15 patients (87%) with AFP were responders at 15 days following the initial procedure, as these patients experienced 30% or greater pain reduction compared to baseline. Conversely, the percentage of responders to rTMS who completed the "maintenance phase" of the protocol at 180 days was 53% (8 patients). The authors concluded that while the rTMS long-term maintenance protocol can be effective in controlling pain for several months in patients with chronic refractory facial pain, not all patients will respond to this technique.

Gamma knife radiation surgery (GKRS) was assessed in a sample of 446 treatment-experienced patients with TN1 and TN2 pain by way of a retrospective file review; there were 61 patients with TN2 pain and 32 patients with AFP (defined as facial pain of somatoform origin).[15] Pain relief, as measured by the Barrow Neurologic Institute (BNI) rating scale, was the primary outcome of interest, and it was measured at three months after the initial procedure. Results showed that 79.3%, 46.2%, and 29.3% of TN2 patients achieved scores BNI 1 to BNI 3 (treatment success) at one year, three years, and five years of follow-up, respectively. For patients with AFP at the same follow-up times, these proportions were 62.7%, 50.2%, and 9.2%, respectively. Moreover, the proportion of TN2 patients achieving BNI 1 (complete pain relief without medications) at one, three, and five years after the initial procedure was 47.5%, 25.2%, and 9.2%, respectively. The median time to pain relapse was 20.75 months for TN2 patients and 7.89 months for AFP patients. A potential overlap in outcome reporting may exist between patients diagnosed with AFP and TN2, as the definition of AFP used in this study may have included TN2 patients. Based on these findings, the authors drew the conclusion that the durability of GKRS for alleviating TN-type pain depends mainly on the type of pain experienced (TN1 or TN2), posttreatment BNI score, and treatment-related adverse events. In addition, pain relief among higher-risk TN2 patients, or those with recurrent trigeminal neuralgia or atypical facial pain, may be less dependent on the type of interventional pain management as compared with understanding the source of the pain.

Findings from another retrospective chart review study of 20 patients with facial pain or cranial neuralgias revealed that occipital nerve block (ONB) using lidocaine and dexamethasone appeared to be a more effective interventional approach for the treatment or trigeminal neuralgia than trigeminal neuropathic pain or PIFP.[16] Of the 20 included patients in this study,

five had a PIFP diagnosis. One (20%) patient with PIFP responded to ONB treatment, and the mean pain level among PIFP patients at three days following the initial procedure was 85.3% of baseline pain. One PIFP patient experienced cranial flush and local tenderness over the injection site. Given the minimally invasive nature of the procedure and mild adverse effects, the authors suggested that ONB be used before considering more invasive approaches.

Clinical effectiveness of low level laser therapy (LLLT) was evaluated in two before-and-after studies with no control group.[19,20] In the first study, the effect of LLLT on patients' resolution of symptoms was investigated in a sample of 10 patient with PIFP and 11 patients with traumatic trigeminal neuropathy; findings revealed that among the 10 patients with PIFP, 70% achieved total resolution of symptoms, 20% achieved partial resolution of symptoms, and no improvement was noted in one patient (10%). In the second study, pain and discomfort (as measured by VAS) before and after treatment with a low-level energy diode laser was assessed among 16 patients with PIFP; results showed that the mean percent pain reduction among this patient population was 43.9%, and ranged between a 5.6% to 74% reduction in pain. The authors of both studies concluded that LLLT may be an effective treatment for PIFP.

Drug treatments

The effect of pharmacological treatment with *S*-ketamine (intravenous, 25 mg/mL) and fentanyl (intravenous, 50 mcg/mL) on ongoing pain relating to atypical odontalgia (AO) was compared in a randomized, double-blinded, placebo-controlled cross-over trial; 10 patients with spontaneous AO pain and 10 healthy adult volunteers without orofacial pain were recruited.[23] Findings among AO patients specifically showed that no difference in treatments was found in ongoing AO pain, as measured by an electronic VAS over a time period of 10 minutes. The authors concluded that compared with studies on other neuropathic pain conditions, fentanyl and *S*-ketamine in the specified doses failed to diminish AO pain.

In another multicentre, randomized, double-blinded, cross-over trial, the effect of lidocaine (intravenous, 20 mg/mL) and adrenaline (intravenous, 12.5 mcg/mL) was compared against placebo (saline) among 35 patients suffering from pain in the jaw and diagnosed with AO.[24] Pain relief and "unpleasantness" (not otherwise defined) was measured using a VAS, and comparative results showed that VAS pain scores at 15 to 120 minutes after lidocaine injections were significantly lower as compared with placebo injections. Similarly, VAS unpleasantness scores at 15 to 120 minutes after lidocaine injections were significantly lower as compared with placebo injections. Furthermore, treatment responders (defined as greater than 50% pain reduction from baseline within 30 minutes of injection) were significantly more numerous in the lidocaine group (54%) than in the placebo group (29%). Adverse events were common among study participants and included hypoesthesia, hyperesthesia, brush-evoked allodynia, and other treatment-related adverse effects. The authors concluded that AO patients experienced a significant, but not complete, pain relief from the administration of local anesthetics.

What are the evidence-based guidelines regarding interventions for patients with atypical facial pain?

The guideline produced by the World Institute of Pain recommends first-line treatment of AFP with drug therapy options such as tricyclic antidepressants and anticonvulsant medications. The primary choice is amitriptyline, with venlafaxine and fluoxetine as subsequent options. However, this recommendation is based on a limited evidence base which includes non-randomized studies with small sample sizes published more than 10 years ago. For patients whose

symptoms persist or are uncontrolled despite initial management with the suggested pharmacotherapies, pulsed radiofrequency treatment of the ganglion pterypalatinum is recommended.[8] This recommendation was made based on one retrospective file review study of patients with chronic head and face pain of various etiologies; this study was published more than 10 years ago.

Evidence-based guidelines for the management of patients with AFP in the Canadian context were not identified in the published literature.

Limitations

The methodological quality of included clinical studies was generally poor. Of particular concern is the large number of non-randomized studies with no control group, use of a retrospective study design, small samples of participants, inadequate adjustment for confounding in the analyses, and perhaps most markedly, reliance on a number of different outcome measures, limiting comparability across studies. Given that no Canadian studies were identified in the published literature, the applicability of findings to pain management in the Canadian setting may be limited.

The selected guideline recommendations were supported by published clinical evidence; however, there is uncertainty relating to the methodological rigour and stakeholder involvement in the guideline development process. The applicability of this guideline to clinical practice may be limited owing to the lack of high-quality evidence supporting the specified recommendations.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the identified published literature, treatments for patients with AFP are varied and include a range of surgical techniques, as well as non-surgical non-drug interventions and drug therapies. Patient outcomes relating to pain relief and adverse events or complications following surgical intervention are generally poor among this patient population; in addition, the rate of pain recurrence is of significant concern. The effectiveness of non-surgical interventions (drug and non-drug) in alleviating pain and minimizing treatment-related complications in patients with AFP was limited. Furthermore, the identified evidence-based guideline recommends the use of conservative pharmacologic intervention as first-line therapy, followed by minimally-invasive surgical intervention for patients refractory to drug treatment. These recommendations were based on a small number of low-quality studies.

Collectively, findings from clinical studies warrant careful interpretation owing to a number of limitations, including the large number of non-randomized studies with no control group, use of a retrospective study design, and reliance on small samples of patients and non-validated outcome measures for the analysis of treatment effectiveness. Moreover, high-quality evidence-based guidelines for the management of AFP are needed before conclusions on best clinical practices can be drawn.

In brief, the available evidence suggests that well-designed studies regarding the clinical effectiveness of interventions for AFP are currently lacking; as a result, large, prospective studies with appropriate randomization procedures and adapted for the Canadian setting are required to address this evidence gap.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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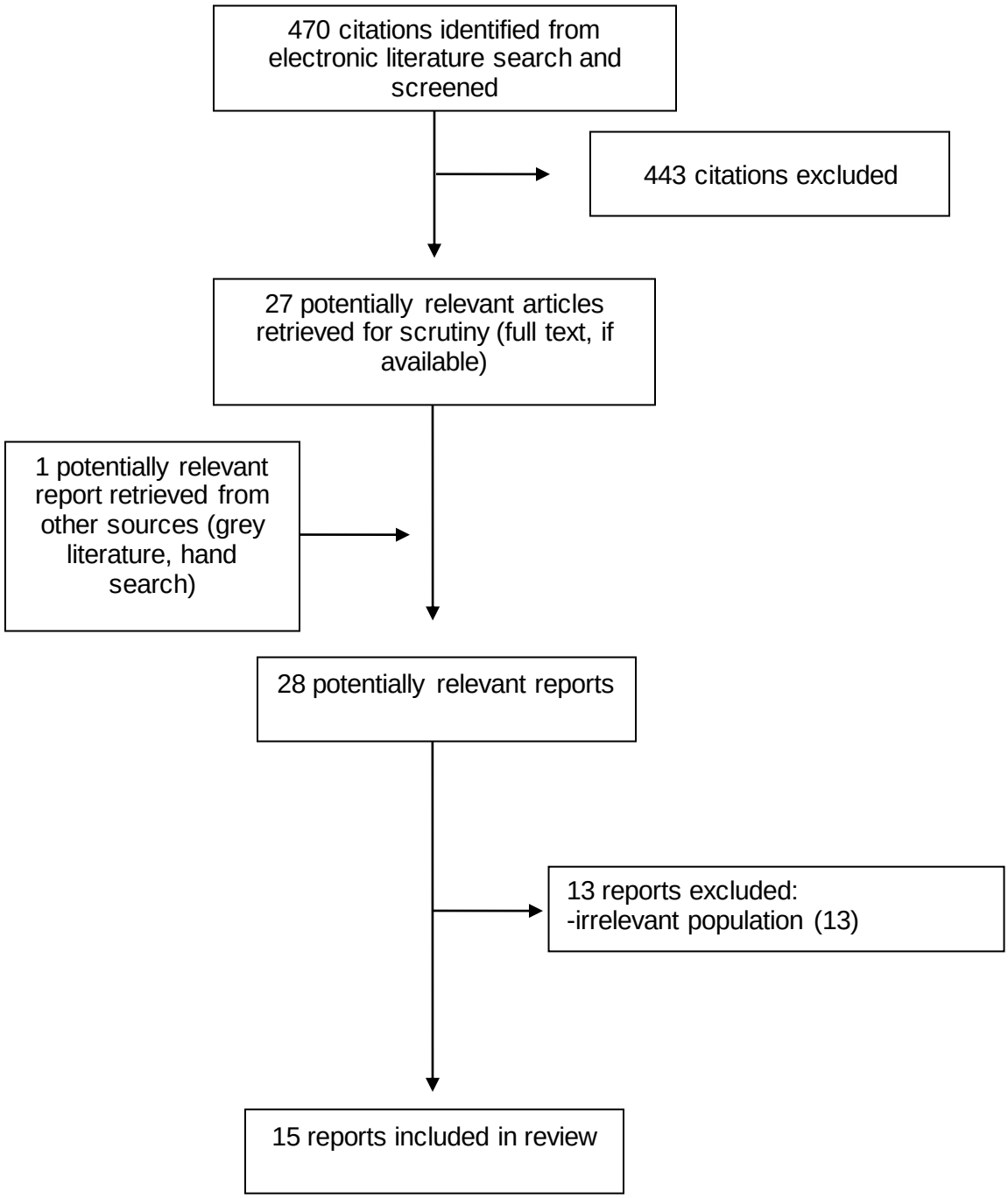
APPENDIX 1: SELECTION OF INCLUDED STUDIES



APPENDIX 2: CHARACTERISTICS OF INCLUDED PUBLICATIONS

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Surgical interventions					
Kastler, 2014[11] France	**NRS:** Retrospective chart review	Patients with unilateral acute or chronic facial pain who had undergone CT-guided sphenopalatine absolute alcohol neurolysis; all patients were previously treated with pharmacologic therapy (including oxygeotherapy, triptans, intranasal lidocaine dihydroergotamine, verapamil, and lithium). **n = 42;** 14 patients with cluster headache; **10 patients with PIFP;** 18 patients with "other" types of facial pain Mean age: 51.5 years (range 28 - 87) Male/Female (n): 25/17 Pre-procedure pain duration for PIFP patients (months): 63.6 ± 70.5	Alcohol neurolysis of the sphenopalatine ganglion under CT guidance (n = 58).	None.	Mean pain relief period following procedure (up to 48 months follow-up). Effectiveness rate, defined as pain relief ≥ 50% pain reduction (as measured by VAS) lasting for ≥ 1 month (> 90% reduction = excellent; 50 – 89% reduction = good); < 50% pain reduction was considered a failure. Recurrence rate, defined as percentage of recurring pain following 'successful procedure' (i.e. > 50% pain reduction).
Oomen, 2012[12] The Netherlands	**NRS:** Retrospective chart review	Adult patients who had previously been diagnosed with facial pain or headache. **n = 15;** **10 patients with AFP** 3 patients with cluster headache	Radiofrequency thermocoagulation of the sphenopalatine ganglion.	None.	Pain relief, as measured by VAS (post-procedure VAS score of 3 = "adequate" pain relief; 1 – 3 = "almost complete"; 0 = "complete"; no change in VAS score = "none");

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		1 patient with post-herpetic neuralgia 1 patient with unsure diagnosis (TN or cluster headache) Mean age (AFP): 58.5 years (range 39 - 68) Male/Female (AFP; n): 3/7			diagnosis after retrospective evaluation.
Degn, 2010[13] Denmark	**NRS:** Retrospective chart review	Adult patients with TN1 and TN2, according to ICHD criteria; 30% of patients treated with MVD/rhizotomy had previously been treated with glycerol injection. **n = 70;** 48 patients (69%) with TN1 (brief lancinating pain); **22 patients (31%) with TN2 (continuous pain);** 2 patients with bilateral TN (each side treated separately) Mean age (TN1): 57 years Male/Female (TN1): 28/20 Mean age (TN2): 53 years Male/Female (TN2; n): 5/17	Percutaneous glycerol injection (110 procedures), MVD (40 procedures), rhizotomy (10 procedures) 32/70 patients (46%) underwent a single procedure.	None.	Clinically significant pain relief as measured by VNRS (A – E groups on vector-based pain diagram); outcome groups based on pain intensity and frequency: A (cured): completely free of pain; B (remnant): VNRS score < 5 and presentation < 7 days/month; C (rare attacks): less or no reduction in pain, presentation < 3 days/month; D (some effect): some pain reduction; E (background pain): reduction in intensity with less or no reduction in frequency (low-grade chronic dull pain); F (minimal effect): limited reduction in pain intensity and frequency;

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
					G (no effect): no positive effect of treatment Complications
Miller, 2009[21] United States	**NRS:** Analytic cross-sectional	Adult patients with TN1 and TN2 who had undergone a retromastoid craniectomy and MVD procedure and did not have a history of multiple sclerosis or prior MVD procedure; 50 patients (53%) had previously responded to anticonvulsant therapy. **n = 95;** 67 patients (71%) with TN1 pain (electric, shock-like, lancinating); **28 patients (29%) with TN2 pain** (aching, burning, throbbing, stinging); Mean age: 54.3 years Male/Female (n): 36/59	MVD	None.	Self-reported pain relief (no instrument): (1) pain relief without medication (excellent); (2) mild or intermittent pain controlled with low-dose medication (good); and (3) severe persistent pain or need for additional surgical treatment (poor).
Amador, 2008[17] United States	**NRS:** Uncontrolled before-and-after study	Adult patients with idiopathic persistent (recurrent) TN who had previously undergone posterior fossa exploration; patients had undergone a mean of 3.2 operations (range 1 – 6) at the time of their repeat posterior fossa exploration (MVD, n = 28; radiosurgery, n = 20; glycerol rhizotomy, n = 15; balloon microcompression, n = 15; radiofrequency rhizotomy, n = 10; partial nerve section, n = 3;	Repeat posterior fossa exploration	None.	Pain relief (no instrument) defined as: (1) no pain and not receiving medications (excellent outcome); (2) no pain and taking medications at reduced dose compared with before surgery (good outcome); and (3) pain despite receiving medications (poor outcome).

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		peripheral neurectomy, n = 2) **n = 29;** 24 patients with Burchiel TN1 **5 patients with Burchiel TN2** Mean age: 61.1 years (range 32 - 81) Male/Female (n): 14/15 Mean duration of pain before procedure: 11.2 years (range 4 – 29 years)			Complications
Kanpolat, 2008[22] Turkey	**NRS:** Analytic cross-sectional	Patients with craniofacial pain. **n = 65;** **21 patients with AFP;** 17 patients with vasoglossopharyngeal neuralgia; 13 patients with craniofacial malignancies; 5 patients with failed TN; 4 patients with geniculate neuralgia; 3 patients with postherpetic neuralgia; 1 patient with cluster headache; 1 patient with anesthesia dolorosa. Mean age: NR Male/Female (n): 8/13 (AFP group only; NR for other patients)	Trigeminal tractotomy-nucleotomy under CT guidance (73 procedures)	None.	Long-term pain relief (mean follow up of 5.3 years), as measured by the following grading system: (I) no pain; (II) partial satisfactory pain relief; (III) partial non-satisfactory pain relief; and (IV) no change in pain. A VAS was used to score the severity of pain, and the Karnofsky Performance Scale to determine the Day 1 post-operative performance status. Complications
Teixeira, 2006[14] Brazil	**NRS:** Retrospective	Adult patients with facial pain (diagnosed according to IASP	Radiofrequency percutaneous	None.	Pain relief (according to 7 degrees of pain defined by

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
	chart review	criteria) who had undergone surgical treatment as a result of prior treatment inefficacy and/or adverse effects. **n = 367;** 290 patients with idiopathic TN; 52 patients with symptomatic TN; **16 patients with AFP;** 9 patients with post-herpetic neuralgia. Mean age: 62.5 years (range 17 - 88) Mean age (AFP) 55.6 years (range 29 - 79) Male/Female (n): 201/166 Male/Female (AFP; n): 8/8	rhizotomy (n = 354); neurovascular decompression (n = 21). 16 patients with AFP were treated with radiofrequency percutaneous rhizotomy; 2 had also neurovascular decompression due to pain recurrence.		the authors); facial sensitivity deficit; neurological dysfunction; hypoesthesia; facial late deafferentation; clinical complications; pain recurrence. Outcomes measured at 1 month and 4 months post-procedure, and every 6 months after.
Non-surgical interventions (Non-drug)					
Hodaj, 2015[18] France	**NRS:** Uncontrolled before-and-after study	Adult patients with chronic facial pain (according to ICHD, 3rd edition) refractory to conventional therapy or associated with poor drug tolerance. **n = 55;** 19 patients with CH; **15 patients with AFP** (7 related to unclear pathophysiology in the context of dental surgery, 1 related to therapy for meningioma, 1 stroke-related, and 6 undetermined cause)	Repetitive transcranial magnetic stimulation of the motor cortex contralateral to pain.	None.	Pain relief, as measured on a visual numeric scale (0 - 10).

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		10 patients with traumatic TNP; 11 patients with inflammatory TNP Mean age (CH): 45.6 ± 13.4 years Mean age (TNP/AFP): 66.1 ± 11.8 years Male/Female (n): 30/25			
Lucas, 2014[15] United States	**NRS:** Retrospective chart review	Patients with facial pain who had a clinical diagnosis of TN; all patients had previously received pharmacologic treatment, and 30.9% of patients had undergone a prior procedure. **n = 446;** 385 patients with Burchiel TN1 **61 patients with Burchiel TN2** 32/446 (7.2%) patients with AFP (defined as facial pain resulting from a somatoform cause) Median age: 67.5 years (IQR 56.5-75.8) Male/Female (n): 173/273	Stereotactic radiation surgery: Gamma Knife radiation surgery.	None.	Pain relief (pre- and post-treatment), as measured at 3 months post-procedure by the BNI pain intensity score (scale); BNI score 1 to 3 considered success, BNI score 4 or 5 considered treatment failure.
Boras, 2013[19] Croatia	**NRS:** Design not described	Patients with PIFP (according to ICHD criteria) or traumatic trigeminal neuropathy **n = 21;** 11 patients with traumatic trigeminal neuropathy; **10 patients with PIFP** Mean age (PIFP): NR (range 52 –	Low level laser therapy with a gallium-aluminum arsenide laser (wavelength 830 nm); one 3 minute session every workday for two weeks (10 sessions).	None.	Pain relief, as measured by the following scale: 0 = no improvement; 1 = partial improvement; 2 = complete improvement.

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		72 years) Male/Female (PIFP; n): 2/8			
Jurgens, 2012[16] Germany	**NRS:** Retrospective chart review	Adult patients with facial pain or cranial neuralgias (according to ICHD criteria) treated with occipital nerve block due to impairment by acute exacerbations of pain. **n = 20;** 8 patients with TN; 6 patients with TNP; **5 patients with PIFP** 1 patient with occipital neuralgia. Mean age: 58.2 ± 20.4 years (range 21 - 89) Male/Female (n): 7/13	Occipital nerve block using lidocaine and dexamethasone (25 procedures).	None.	Pain relief, as measured by percentage reduction of original pain; positive response to occipital nerve block defined as ≥ 50% improvement in the patient's global rating (verbal rating scale) at first contact after the procedure. Adverse effects.
Yang, 2011[20] Taiwan	**NRS:** Uncontrolled before-and-after study	Patients with PIFP (according to ICHD criteria). **n = 16** Mean age: 46.8 years (range 30 - 72) Male/Female (n): 4/12	Low-level energy diode laser (800-nm wavelength diode laser).	None.	Pain and discomfort before and after treatment, as measured by a 10-cm VAS.
Non-surgical interventions (Drug)					
Baad-Hansen, 2007[23] Denmark	**RCT :** double-blinded, cross-over trial	Patients with spontaneous AO pain (n = 10) and healthy adult volunteers without orofacial pain (n = 10). **n = 20;**	*S*-ketamine (IV, 25 mg/mL); Fentanyl (IV, 50 mcg/mL)	Placebo (isotonic NaCl solution, 9 g/L)	Ongoing AO pain, as measured by a 0 - 10 electronic VAS; capsaicin-evoked pain (as measured by area under the VAS curve, maximum pain

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		10 patients with spontaneous AO Mean age (AO): 48.1 ± 11.7 years Mean age (controls): 40.6±11.9 years Male/Female (AO; n): 3/7 Male/Female (controls; n): 4/6 Mean pain intensity in the last 4 weeks of baseline on VAS (AO): 5.1 ± 1.3			[peak VAS], and time from beginning of VAS recording); adverse effects.
List, 2006[24] Sweden	**RCT :** Multicentre, double-blinded, cross-over trial	Patients suffering from pain in the jaw and diagnosed with AO. **n = 35;** Mean age: 55.8 years (range 31 - 81) Male/Female (n): 4/31	Lidocaine (IV, 20 mg/mL) and adrenaline (IV, 12.5 mcg/mL)	Placebo (9 mg/mL NaCl solution)	Pain relief and "unpleasantness", as measured by 0-10 cm VAS; response defined as > 50% pain reduction from baseline within 30 mins of injection. Number-needed-to-treat (NNT) value, defined as the number of patients who had to be treated in order to obtain one patient with at least 50% pain reduction. Adverse events.

AFP = atypical facial pain; AO = atypical odontalgia; BNI = Barrow Neurologic Institute; cm = centimetre; CT = computed tomography; g = gram; IASP = International Association for the Study of Pain; ICHD = International Classification of Headache Disorders; IQR = interquartile range; IV = intravenous administration; L = litre; mcg = microgram; mg = milligram; mL = millilitre; MVD = microvascular decompression; n = number; NaCl = sodium chloride; ND = neurovascular decompression; nm = nanometre; NR = not reported; NRS = non-randomized study; PIFP = persistent idiopathic facial pain; RCT = randomized controlled trial; RPR = radiofrequency percutaneous rhizotomy; TN = trigeminal neuralgia; TN1 = type 1 trigeminal neuralgia; TN2 = type 2 trigeminal neuralgia; TNP = trigeminal neuropathic pain; VAS = visual analogue scale; VNRS = verbal numerical rating scale.

Table A2: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Cornelissen, 2009[8] – World Institute of Pain						
Pain specialists who have the responsibility of confirming a PIFP diagnosis of a referring physician before initiating an interventional pain management technique; physicians with interest in pain management.	Conservative management and interventional pain management techniques for PIFP patients.	Diagnosis; Therapeutic options; Practice algorithm; Recommendations.	High-quality review articles for disease and diagnosis-related information; in-depth literature searches were performed for information on efficacy, side effects and complications. Only articles published in peer reviewed journals were included.	Available evidence on interventional pain management techniques was weighted using a scoring methods adapted from those proposed by Guyatt et al. (2006): "Grading strength of recommendations and quality of evidence in clinical guidelines".[25]	Evidence scores were based on the following: i. Determining if possible benefit outweighs risk and burden: score of "**1**" assigned if benefit associated with treatment effectiveness is greater than risk and burden of potential complications; score of "**2**" assigned if benefit of effect closely balances risk and burden of potential complications. ii. Grade of the evidence: "**A**" stands for the highest level of evidence (various good-quality RCTs); "**B**" stands for RCTs with methodological limitations or large observational studies; and, "**C**" stands for observational studies or case series. An indication of "**0**" was given for interventions only described in case series reports or for which insufficient evidence was available ("study-related"). iii. Intervention outcome: a "**+**" was assigned for positive outcome, and a negative outcome was indicated by a "**–**" sing; when studies with conflicting outcome were used, a "**±**" was assigned.	No evidence of guideline validation was reported.

Score	Implication
1 A +	Positive recommendation
1 B +	
2 B +	
2 B ±	Considered, preferably study-related
2 C +	
0	Only study-related
2 C -	Negative recommendation
2 B -	
2 A -	

PIFP = persistent idiopathic facial pain; RCT = randomized controlled trial

APPENDIX 3: CRITICAL APPRAISAL OF INCLUDED PUBLICATIONS

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
Surgical Interventions	
Kastler, 2014[11]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported	• Study was retrospective • No control group • Small sample size (patients with PIFP were a small subgroup of total study sample) • Some patients benefited from several procedures, which may lead to selection bias • Risk of recall bias was high among surveyed participants at follow-up • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of all patients with chronic facial pain), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not appear to adjust for study subjects' different lengths of follow-up • Validity and reliability of outcome measures used is unclear • Inter-observer variability was not assessed • No power calculation for determining adequate sample size
Oomen, 2012[12]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported	• Study was retrospective • No control group • Small sample size • Risk of recall bias was high among surveyed participants at follow-up • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with facial pain who did not undergo intervention of interest), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not appear to adjust for study subjects' different lengths of follow-up • Effect of therapy on pain relief could not be statistically analyzed because pain relief data were based on semi-quantitative measurements at the time of study, limiting the ability to make firm conclusions about pain relief • Validity and reliability of outcome measures

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
	used is unclear • No power calculation for determining adequate sample size
Degn, 2010[13]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported • Analysis was based on an unselected sample of consecutive patients, strengthening the representativeness of findings	• Study was retrospective • No control group • Small sample size (patients with type 2 TN pain were a small subgroup of total study sample) • Many patients underwent multiple interventions, and it was difficult to separate outcomes of different interventions • Risk of recall bias was high among surveyed participants at follow-up • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Miller, 2009[21]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Treatment staff, setting, and facilities were representative of that in use in the source population	• No control group • Small sample size (patients with type 2 TN pain were a small subgroup of total study sample) • Risk of recall bias was high among surveyed participants at follow-up • Treatment-related adverse events were not reported • Unclear whether included participants were representative of the entire population from which they were recruited, limiting generalizability • No evidence of validity or reliability of outcome measures used • No power calculation for determining adequate sample size
Amador, 2008[17]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported • Treatment staff, setting, and facilities were representative of that in use in the source population	• No control group • Small sample size • Unclear whether included participants were representative of the entire population from which they were recruited, limiting generalizability • No evidence of validity or reliability of outcome measures used • No power calculation for determining adequate sample size

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
Kanpolat, 2008[22]	
• Intervention of interest was described in considerable detail • Adverse events that may have been a consequence of the intervention were measured and reported	• No control group • Small sample size (patients with AFP were a subgroup of total study sample) • Study objective was not clearly described • Characteristics of patients included in study were not clearly described • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with craniofacial pain who did not undergo specified therapy), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not appear to adjust for study subjects' different lengths of follow-up • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Teixeira, 2006[14]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported	• No control group • Study was retrospective • Small sample of patients with AFP among larger study sample • Risk of recall bias was high among surveyed participants at follow-up • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with facial pain who did not undergo surgical intervention), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not appear to adjust for study subjects' different lengths of follow-up • No evidence of validity or reliability of outcome measures used • No power calculation for determining adequate sample size
Non-surgical interventions (Non-drug)	
Hodaj, 2015[18]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail	• No control group • Study was retrospective • Small sample size (patients with AFP were a small subgroup of total study sample) • Treatment-related adverse events were not

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
	reported • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with chronic facial pain who did not undergo specified procedure), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Lucas, 2014[15]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail	• No control group • Study was retrospective • Small sample of patients with type 2 TN pain among larger study sample • Risk of recall bias was high among surveyed participants at follow-up • Treatment-related adverse events were not reported • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with facial pain who did not undergo specified therapy), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Boras, 2013[19]	
• Study objective and main outcomes were clearly described • PIFP case definitions and exclusion criteria were provided • Intervention of interest was described in sufficient detail	• No control group • Patient selection methods not clearly described • Small sample size • Treatment-related adverse events were not reported • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with facial pain who did not undergo specified therapy), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Validity and reliability of outcome measures

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]

Strengths	Limitations
	used is unclear • No estimates of variability in the data reported • No power calculation for determining adequate sample size
Jurgens, 2012[16]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events that may have been a consequence of the intervention were measured and reported	• No control group • Study was retrospective • Small sample size (patients with PIFP were a small subgroup of total study sample) • Risk of selection bias was high as only patients with complete datasets were included • Risk of recall bias was high among surveyed participants at follow-up • Unclear whether study subjects were representative of the population from which they were recruited (i.e. representative of patients with facial pain or cranial neuralgias who did not undergo specified therapy), limiting generalizability • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not adjust for study subjects' different lengths of follow-up • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Yang, 2011[20]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Study participants comprised the entire source population, increasing generalizability of findings	• No control group • Small sample size • Treatment-related adverse events were not reported • Unclear whether the treatment staff, setting, and facilities were representative of that in use in the source population • Analysis did not adjust for study subjects' different lengths of follow-up • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size
Non-surgical interventions (Drug)	
Baad-Hansen, 2007[23]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Adverse events and losses to follow-up	• Small sample size • Unclear whether included participants were representative of the entire population from which they were recruited, limiting generalizability • Validity and reliability of outcome measures

Table A3: Strengths and Limitations of Included Clinical Studies using the Downs and Black Checklist[9]	
Strengths	**Limitations**
described • Patients and outcome assessors blinded • Adequate method of randomization	used is unclear • No power calculation for determining adequate sample size
List, 2006[24]	
• Study objective was clearly described • Patient characteristics, including selection criteria, were clearly described • Intervention of interest was described in sufficient detail • Blinding of patients was applied • Adequate method of randomization	• Small sample size • Treatment-related adverse events were not reported • Unclear whether included participants were representative of the entire population from which they were recruited, limiting generalizability • Unclear if outcome assessors were blinded to treatment status • Validity and reliability of outcome measures used is unclear • No power calculation for determining adequate sample size

Table A4: Strengths and Limitations of Guidelines using AGREE II[10]	
Strengths	**Limitations**
Cornelissen, 2009[8]	
• The overall objective of the guideline is specifically described in a related document separate from the PIFP-specific guideline.[26] • The population to whom the guideline is meant to apply is specifically described • The target users of the guideline are clearly described • Methods for formulating recommendations are clearly described • Health benefits, side effects, and risks have been considered in formulating the recommendations • There is an explicit link between the recommendations and the supporting evidence (sources were referenced) • Recommendations are specific and unambiguous • Different options for management of the condition are clearly presented (albeit limited) • Key recommendations are easily identifiable • Guideline provides guidance on how the recommendations can be put into practice (i.e. clinical practice algorithm described)	• The health questions covered by the guideline are not specifically described • Development of the guideline did not appear to include individuals from all relevant professional groups (expert opinion and the published literature were consulted) • The views and preferences of the patient population were not sought • Unclear whether systematic methods were used to search for evidence (literature review process is not described in sufficient detail) • Strengths and limitations of the body of evidence was not adequately described • Unclear whether the guideline has been externally reviewed by experts prior to its publication. • Guideline does not describe facilitators and barriers to its application • Guideline does not present monitoring and/or auditing criteria • Potential conflicts of interest are not reported

APPENDIX 4: MAIN STUDY FINDINGS AND AUTHOR'S CONCLUSIONS

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Surgical Interventions	
Kastler, 2014[11]	
PIFP group (n = 10; 21 procedures): Effectiveness rate: 85.70% (18/21 procedures) Recurrence rate: 89% (16/18 successful procedures recurred) Complications for whole cohort (58 procedures): **Short-term complications** (15/58 procedures, 25.6%): 4 local hematomas, 4 transient hemipalate anesthesia, 3 pain increase after procedure. **Long-term complications** (4/58 procedures, 6.9%): 2 cases of persisting hemipalate paresthesia, 2 cases of persisting hemipalate anasthesia.	• "Alcohol [sphenopalatine ganglion neurolysis]under CT guidance appears as a safe and effective treatment of refractory facial pain… and should be considered as a possible alternative to existing techniques […]. The best indications with higher success rates appear to be cluster headache and persistent idiopathic facial pain" (p.595)
Oomen, 2012[12]	
AFP group: • 4/10 patients (40%) initially diagnosed with AFP were correctly diagnosed (after reassessment based on the ICHD) • 2/4 patients diagnosed with AFP (after reassessment) had almost complete pain reduction (1 RFT procedure); 1 patient had adequate pain reduction secondary to infection (2 RFT procedures); and 1 patient had no pain reduction (1 RFT procedure).	• "Headache and facial pain patients may frequently be misdiagnosed […]" (p.63) • "Effects of RFT on the SPG varied within pain diagnosis; RFT seemed effective in patients with AFP." (p.63)
Degn, 2010[13]	
TN type 2 pain patients (n = 22; number of patients per procedure not specified): Proportion of patients (%) with clinically significant positive effect following MVD after: 1 year: 73% 3 years: 28% Median duration of positive effect ($t_{1/2}$): 2 years Proportion of patients (%) with significant positive effect following rhizotomy after: 1 year: 33% 3 years: 0% Median duration of positive effect ($t_{1/2}$): 8 months Proportion of patients (%) with significant positive effect following glycerol injection after: 1 year: 30% 3 years: 14% Median duration of positive effect ($t_{1/2}$): 3 months Complications (n = 70; unclear number of TN type	• In patients with "medically treatment-resistant type 1 TN, MVD and [rhizotomy] are reasonably safe and effective interventions. The surgical results with type 2 TN are still very poor." (p.2125) • "The long-term effect of MVD appear to be superior to any of the ablative therapies [in patients with type 1 and type 2 TN]" (p.2131)

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
2 patients with each complication) *MVD-related:* postoperative liquoree (16%; MVD/rhizotomy); cerebellar hematoma, infarction, and edema (4%; one patient per cerebellar event); chemical meningitis (1%). *rhizotomy-related:* postoperative facial hypoesthesia (89%). *glycerol injection-related:* postoperative facial hypoesthesia (20%); transient facial paresis (3%), pneumonia (3%); pneumonia (3%); corneal anesthesia (2%); stinging tongue sensation (1%); transient peroperative asystolia (1%).	
Miller, 2009[21]	
MVD outcome for TN type 2 pain patients (n = 28) after ≥ 36 months: • 7 patients (25%) pain-free without medications (excellent outcome) • 11 patients (39%) with mild or intermittent pain controlled with low-dose medication (good outcome) • 10 patients (36%) with severe persistent pain or need for additional surgical treatment (poor outcome) Outcome was excellent, good, and poor for Type 1 versus Type 2 TN patients in 60 versus 25%, 24 versus 39%, and 16 versus 36%, respectively.	• "[…] patients with Type 1 TN pain are more than twice as likely as those with Type 2 pain to have long-term pain relief after MVD. Moreover, type of TN pain is more predictive of [good long-term] outcome [after MVD] than any other feature of TN." (p.623)
Amador, 2008[17]	

Burchiel Type 2 TN pain patients (n = 5):
 	
Proportion of patients that were pain-free without medications (excellent outcome) after:
• 1 year: 27%
• 3 years: 27%
 	
Complications (unclear number of Type 2 TN patients with each complication)
• New or increased:
  ○ facial numbness (n = 15; 52%)
  ○ trigeminal deficits (post-partial nerve section: n = 10, 91%; post-MVD: n = 5, 28%)
• anesthesia dolorosa (post-partial nerve section: n = 2; 7%)
• hearing loss (n = 2)
• temporary ataxia (n = 2)
• cerebrospinal fluid leak (n = 1)
• aseptic meningitis (n = 1)
• wound infection (n = 1)
	• "Repeat [posterior fossa exploration]for patients with persistent or recurrent TN after prior [posterior fossa exploration] is a safe and effective option with results comparable with other destructive procedures." (p.920)
	• "[…] patients with Burchiel Type 2 TN clearly did poorly when compared with patients with Burchiel Type 1 TN. […] Unfortunately, these patients also seem to benefit less from destructive procedures, so it remains unclear what the best surgical procedure is for this difficult-to-treat patient group." (p.919)

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Kanpolat, 2008[22]	
AFP patient outcome following trigeminal tractotomy-nucleotomy procedure (n = 21; mean follow up time for AFP patients not specified): • 15 patients (71%) with no pain (Grade I pain score); • 4 patients (19%) with partial satisfactory pain relief (Grade II pain score); • 1 patient (5%) with partial non-satisfactory pain relief (Grade III pain score); • 1 patient (5%) with no change in pain (Grade IV pain score). Complications (n = 65; unclear number of AFP patients with each event) • no mortality • transient ataxia (n = 4; 6%) • transient motor complications (n = 2; 3%)	• "CT-guided trigeminal tractotomy-nucleotomy […] can be considered as a first-step procedure in patient management in view of its high efficacy, low complication rate, and minimal invasiveness." (p.5152)
Teixeira, 2006[14]	
AFP patient outcome following radiofrequency percutaneous rhizotomy (n = 16): • 5 patients with Degree 1 pain score: pain relief, hypalgesia or analgesia, tactile sensitivity deficit at the trigeminal branch affected, no neurological complications ; • 1 patient with Degree 3 pain score: pain relief, anaesthesia at any facial area or corneal, transient functional deficit or ocular motor nerves or other nerves, paresthesia with need of medication, lesion of encephalic structures ; • 4 patients with Degree 0 pain score: failure of treatment (no pain alleviation); • 6 patients with Degree M pain score: partial improvement in pain or residual pain treated with medication. AFP patient outcome following neurovascular decompression (n = 2): • 2 patients with Degree 3 pain score. **Post-operative complications** occurred in 5 AFP patients (31.3%) who received radiofrequency percutaneous rhizotomy (i.e. 1 corneal hyporeflex, 1 keratitis, 2 central pain, 1 other) and 1 patient (50%) who underwent ND (i.e. 1 compromise of extrinsic motility of the eye) **Number of recurrences in AFP patients:** 4 (3 with radiofrequency percutaneous rhizotomy, mean duration of recurrence = 12 months; 1 with neurovascular decompression, mean duration of recurrence = 6 months)	• "[Radiofrequency percutaneous rhizotomy] was also efficient to treat symptomatic facial pain and post-herpetic facial pain, but not [a good technique for] atypical facial pain and inflammatory pain (sinusitis)." (p.989)

Table A5: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">Non-surgical interventions (Non-drug)</td></tr>
<tr><td colspan="2">Hodaj, 2015[18]</td></tr>
<tr><td>Number of patients with AFP, idiopathic or of central cause, according to level of pain reduction at 15-180 days after the initiation of rTMS therapy (n = 15):

<table>
<tr><th rowspan="2">Day</th><th colspan="6">Category of response</th></tr>
<tr><th>A</th><th>B</th><th>C</th><th>D</th><th>E</th><th>F</th></tr>
<tr><td>15</td><td>4</td><td>6</td><td>3</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>30</td><td>4</td><td>2</td><td>6</td><td>1</td><td>2</td><td>0</td></tr>
<tr><td>90</td><td>2</td><td>4</td><td>5</td><td>1</td><td>3</td><td>0</td></tr>
<tr><td>180</td><td>2</td><td>3</td><td>3</td><td>2</td><td>4</td><td>1</td></tr>
</table>
A: Very good response (≥70% pain reduction)
B: Good response (50-69% pain reduction)
C: Moderate response (30-49% pain reduction)
D: Poor or no response (<30% pain reduction)
E: Withdrawn from rTMS
F: Lost to follow-up

• 8/15 AFP patients who were responders to rTMS (pain reduction ≥ 30% compared to baseline) completed the "maintenance phase" of the protocol (up to day 180).</td><td>• The "long-term maintenance rTMS protocol can be [efficacious to control pain for several months] in the clinical management of patients with chronic refractory facial pain, […]. However, only a part of the patients respond to this technique and session duration should not be reduced." (p.801)</td></tr>
<tr><td colspan="2">Lucas, 2014[15]</td></tr>
<tr><td><u>Burchiel TN2 pain patients (n = 61):</u>
• Median time to pain relapse: 20.75 months
• Pain relapse at time of last follow-up: 55.7% of patients
• Proportion of patients achieving BNI 1 (complete pain relief without medications) to BNI 3 (some pain but adequately controlled with medications) pain relief:
  • 1 year: 79.3%
  • 3 years: 46.2%
  • 5 years: 29.3%
• Proportion of patients achieving BNI 1 pain relief:
  • 1 year: 47.5%
  • 3 years: 25.2%
  • 5 years: 9.2%

<u>AFP patients (n = 32; may overlap with TN2 group)</u>
• Median time to pain relapse: 7.89 months
• Pain relapse at time of last follow-up: 62% of patients
• Proportion of patients achieving BNI 1 to BNI 3 pain relief:
  • 1 year: 62.7%
  • 3 years: 50.2%
  • 5 years: 25%</td><td>• "The durability of [Gamma Knife radiation surgery] for TN depends predominantly on Burchiel type presentation, posttreatment BNI score, and development of facial numbness after [Gamma Knife radiation surgery]. […] We found that patients with a history of procedures for TN were as likely to have durable relief as those who had not undergone [Gamma Knife radiation surgery]." (p.7)
• "Pain relief in higher-risk populations, such as those with type 2 TN, recurrent TN, or atypical facial pain may be less dependent on treatment technique and more dependent on an unidentified underlying pathology." (p.6)</td></tr>
</table>

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
• 13% of patients achieved BNI1 response	
Boras, 2013[19]	
PIFP patients (n = 10): • Total resolution of symptoms in 7 patients (70%) • Partial resolution of symptoms in 2 patients (20%) • No improvement in 1 patient (10%)	• "The results of our study show that [low level laser therapy] could have beneficial effect on patients with orofacial pain as total resolution of symptoms was achieved in 70% of patients with PIFP…" (p.4)
Jurgens, 2012[16]	

PIFP patients (n = 5):
• 1 patient (20%) responded to occipital nerve block
• 2 out of 9 nerve blocks (procedures) were considered effective (22%)
  • Mean pre-procedure pain (VAS): 6.3 ± 1.7
  • Mean post-procedure pain (VAS): 4.9 ± 1.9
  • t-test for post-procedure pain reduction $P = 0.140$
• Mean percent of baseline pain at 3 days post-procedure: 85.3 ± 23.5
• Adverse effects (n = 1): cranial flush, local tenderness over injection site (left occiput)
	• "Occipital nerve block seems to be more effective in trigeminal neuralgia than in trigeminal neuropathic pain and persistent idiopathic facial pain. […] Given that side effects are mild and that the procedure is minimally invasive, we suggest using this method before considering more invasive approaches such as thermocoagulation or vascular decompression." (p.212)

Yang, 2011[20]	
Outcome based on VAS pain scores (n = 16): • Mean pre-treatment pain score: 7.4 (range 3.5 - 10.0) • Mean post-treatment pain score: 4.1 (range 2.0 - 8.4) • Average percent pain reduction: 43.87% (range 5.6 - 74%)	• "Low-level energy diode laser may be an effective treatment for PIFP." (p.707)
Non-surgical interventions (Drug)	
Baad-Hansen, 2007[23]	
Ongoing AO pain (n = 10): No differences between treatments were found on the ongoing AO pain (Time 1 to 10 minutes) (Tukey: $P > 0.990$) [results presented graphically]	• "AO is unlikely to be primarily due to a persistent afferent barrage from the peripheral region. Furthermore, in contrast to studies on various neuropathic pain conditions, fentanyl and *S*-Ketamine in the present doses failed to attenuate AO pain." (p.53)
List, 2006[24]	
Treatment group (n = 35): • VAS pain scores at 15, 30, 45, 60, 90, 120, and 180 minutes after lidocaine injection were significantly lower than at baseline (Tukey: $P = 0.038$) • VAS unpleasantness scores at 15, 30, 45, 60, 90, 120, and 180 minutes after lidocaine injection were significantly lower than at baseline (Tukey: $P < 0.022$)	• "AO patients experienced a significant, but not complete, pain relief from administration of local anesthetics compared with placebo. This indicates that persistent peripheral afferent inputs alone cannot explain the spontaneous pain in AO patients and that sensitization and plasticity of higher order trigeminal neurons may contribute." (p.313)

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Placebo group (n = 35): • VAS pain scores at 15, 30, 45, 60, 90, and 180 minutes after saline injection were significantly lower than at baseline (Tukey: $P < 0.040$) • VAS unpleasantness scores at 15, 30, 45, 60, 90, 180 and 240 minutes after saline injection were significantly lower than at baseline (Tukey: $P < 0.045$) Comparisons: • VAS pain scores at 15, 30, 45, 60, 90, and 120 minutes after lidocaine injections were significantly lower compared with placebo injections (Tukey: $P < 0.008$) • VAS unpleasantness scores at 15, 30, 45, 60, 90, and 120 minutes after lidocaine injections were significantly lower compared with placebo injections (Tukey: $P < 0.028$) • VAS pain relief was significantly greater following lidocaine injections at 15, 30, 45, 60, 90, and 120 minutes compared with placebo injections (Tukey: $P < 0.05$) • Treatment responders were significantly more numerous in the lidocaine group (54%) than placebo (29%) Number-needed-to-treat value 30 minutes after injection: 3.3 patients (CI 2.0 - 9.8) Adverse events: • Hypoesthesia/hyperesthesia in 57% of patients • Brush-evoked allodynia was observed in the majority of patients • 29% of patients reported adverse events after lidocaine injection, including: headache, increased pain, heart palpitation. • 26% of patients reported adverse events after placebo injection, including: headache, increased pain, dizziness, tiredness, and paresthesia.	

AFP = atypical facial pain; AO = atypical odontalgia; BNI = Barrow Neurologic Institute; cm = centimetre; CT = computed tomography; ICHD = International Classification of Headache Disorders; MVD = microvascular decompression; n = number; PIFP = persistent idiopathic facial pain; RCT = randomized controlled trial; RFT = radiofrequency thermocoagulation; rTMS = repetitive transcranial magnetic stimulation of the motor cortex; SPG = sphenopalatine ganglion; TN = trigeminal neuralgia; TN1 = type 1 trigeminal neuralgia; TN2 = type 2 trigeminal neuralgia; TNP = trigeminal neuropathic pain; VAS = visual analogue scale.

Table A6: Summary of Guideline Recommendations	
Author, Year, Guideline Society or Institute	**Recommendations [recommendation grade, level of evidence]**
Cornelissen, 2009[8] World Institute of Pain	"Pharmacological treatment with tricyclic antidepressants and anti-epileptic drugs can be tried. The conservative pharmacological treatment with amitryptiline is the primary choice. Venlafaxine and fluoxetine can also be considered." (p.447) [evidence score not reported] "In patients with chronic atypical facial pain refractory to conservative therapy, [pulsed radiofreqency treatment] of the ganglion pterypalatinum can be considered. […] PRF current of 45 V with a maximal temperature of 42 [degrees Celsius] is applied one or more times during a period of 120 seconds." (p.446-7) [2 C+]