

## Literature Review

# Gabapentinoid prescription in Oral Medicine and Oral Surgery practice. Part II — a systematic scoping review of the literature

Arek Sulukdjian, Richard L'Homme, Audrey Chanlon, Nathan Moreau\*

Orofacial Pain Clinic, Department of Oral Medicine and Oral Surgery, Bretonneau Hospital, AP-HP, Paris, France

(Received: 13 March 2020, accepted: 17 July 2020)

**Keywords:**  
gabapentin /  
pregabalin /  
orofacial pain

**Abstract – Introduction:** Gabapentinoids, pregabalin and gabapentin, neuronal voltage-gated calcium channel inhibitors are first-line treatments for painful neuropathic conditions (and several non-neuropathic painful conditions). Nevertheless, their efficacy and prescription in Oral Medicine and Oral Surgery practice has received little attention so far. A previous article, the first of a two-part series, presented the experience of a French tertiary orofacial pain clinic regarding the prescription of gabapentinoids in orofacial conditions. This second article aimed to explore the scientific literature on the subject. **Material and methods:** A systematic scoping review was conducted on multiple relevant databases (MEDLINE®, Cochrane®, Agence Nationale de Sécurité du Médicament et des produits de santé, Haute Autorité de Santé) and journal archives (JOMOS, JSOMFS) to assess the indications, non-indications and contraindications of gabapentinoids in an Oral Medicine/Oral Surgery context. **Results:** Out of 131 records selected during the initial screening, 34 matched the inclusion criteria and were used for subsequent analyses. Gabapentinoids were prescribed in three clinical contexts: orofacial pain management (32 studies), anxiolysis (1 study) and prevention of postoperative nausea/vomiting (1 study), with variable quality of evidence: high (6 studies), moderate (3 studies), low (5 studies) and very low (20 studies) quality studies (GRADE scale). Untoward effects of gabapentinoids were reported in 16 studies, mainly neurological (vertigo, drowsiness, sedation) and gastro-intestinal (nausea, vomiting, diarrhea, constipation). Gabapentinoids were ineffective in preemptive and postoperative analgesia and for the management of mucositis-related pain. **Discussion:** There is some evidence supporting the use of gabapentinoids in Oral Medicine/Oral Surgery in adherence with current practices observed in France and other countries (practices often extrapolated from their use in other non-orofacial painful conditions). The methodological quality of the studies included in this scoping review is often poor and publication bias is most probable in this field. Therefore, any conclusion drawn from such studies must be subject to circumspection. **Conclusion:** Data obtained from the present scoping review suggests the potential use of gabapentinoids as second-line treatments for anxiolysis, prevention of postoperative nausea/vomiting and the management of trigeminal neuralgia and masticatory myalgia. Other potential indications of gabapentinoids in Oral Medicine/Oral Surgery practice include cranial neuralgias, post-traumatic trigeminal neuropathies, first bite syndrome, burning mouth syndrome and migraine prophylaxis, when other treatment options are inefficient or unavailable.

## Introduction

Gabapentinoids, pregabalin and gabapentin, a recent class of neuronal voltage-gated calcium channel inhibitors mainly used for the treatment of partial epilepsy and neuropathic pain have been increasingly prescribed these past few years [1,2], despite growing concerns regarding potential misuse of such drugs and increased mortality risk when associated with opioids [3]. Although they are part of the recommended pharmacolog-

ical armamentarium for the treatment of neuropathic pain [4], no specific guidelines have been edicted so far regarding their use in orofacial conditions [5].

In a previous article [6], the first of a two-part series, we presented our experience of the use of gabapentinoids within a tertiary orofacial pain clinic for the management of several orofacial pain conditions that fall within the scope of the oral surgeon's practice, namely:

- painful neuropathies (painful post-traumatic trigeminal neuropathy, trigeminal neuralgia, chemotherapy-induced neuropathic pain, central post-stroke pain, post-traumatic neuroma, cervico-brachial neuralgia, idiopathic small fiber neuropathy, post-herpetic neuralgia);

\* Correspondence: [nthmoreau@gmail.com](mailto:nthmoreau@gmail.com)

- headaches (tension-type headache, paroxysmal hemicrania);
- ENT/jaw diseases (hamular bursitis, pharyngeal dystonia);
- mucosal diseases (inflammatory anemia-related glossitis);
- and myalgias (chronic myofascial pain syndrome).

Such indications are empirical, based mainly on extrapolations made from treatment recommendations for similar conditions and the authors' experience. Indeed, quite unfortunately, systematic reviews of current evidence –required for the elaboration of relevant treatment guidelines– are lacking.

The aim of this article, the second of a two-part series, was thus to systematically review the scientific literature on gabapentinoid prescription in an Oral Medicine/Oral Surgery clinical context.

## Material and methods

A systematic review of the available scientific literature on the indications, non-indications and contraindications of gabapentinoids in Oral Medicine/Oral Surgery practice was performed using a scoping review methodology, according to the Preferred Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [7]. Such methodology was chosen as no literature reviews have been conducted on the subject so far.

### Scientific question

The review was conducted to answer the following scientific question: *What are the indications, non-indications and contraindications of gabapentinoids in Oral Medicine and Oral Surgery practice?*

Database search strategy and relevant keywords were chosen after detailing the scientific question using the PICOS methodology:

- *Population (P)* = All patients referred to oral medicine/oral surgery practices regardless of age, sex or health status;
- *Intervention (I)* = Prescription of pregabalin or gabapentin;
- *Comparison (C)* = Standard of care (when existing), placebo or lack of treatment;
- *Outcome (O)* = Effectiveness (=indication), ineffectiveness (=non-indication) or harm (=contraindication);
- *Study types (S)* = All study types: meta-analyses, randomized controlled trials (RCTs), prospective/retrospective cohort studies, case-control studies, case series, case reports and editorials/letters.

### Databases and keywords

Data search was conducted in MEDLINE<sup>®</sup> and Cochrane<sup>®</sup> databases, on the websites of the Haute Autorité de Santé and of the Agence Nationale de Sécurité du Médicament et des produits de santé and in the online archives of the Journal of Oral Medicine and Oral Surgery and of the Journal of Stomatology Oral and Maxillofacial Surgery.

The following keywords were used to query the various databases: *gabapentinoid; pregabalin; gabapentin; oral medicine; oral surgery; facial surgery; oral and maxillofacial surgery; orofacial pain; facial pain.*

For the MEDLINE<sup>®</sup> search, the following query was used: *((gabapentin) OR (pregabalin) OR (gabapentinoids)) AND (“orofacial pain” OR “facial pain” OR “oral medicine” OR “oral surgery” OR “facial surgery” OR “oral and maxillofacial surgery”)*

Only studies in French or English were considered in this study, without any restrictions in terms of date of publication.

### Inclusion criteria

Studies were included in the analysis when they met the following criteria:

- Study pertaining to a disease or treatment relevant to Oral Medicine/Oral Surgery practice (within the scope of practice as currently defined by French regulatory laws);
- Type and dosage of gabapentinoid is mentioned;
- Indication of gabapentinoid prescription is mentioned;
- Report of efficacy (e.g. pain relief, sleep quality, increase in quality of life...);
- Report of untoward effects (drug side-effects, disease aggravation...).

Letters and/or editorials were included in the review when they met the following criteria:

- Content of the letter/editorial pertains to use or misuse of gabapentinoids;
- Context of the letter/editorial relates to Oral Medicine/Oral Surgery practice.

### Non-inclusion criteria

Studies were not included in the review in case of multiple pharmacological treatments, as it would preclude any imputability analysis.

Letters and/or editorials were not included if insufficient details were given regarding the type and dosage of gabapentinoid prescribed, the indication for prescription and the prescription outcomes (efficacy, inefficacy, harm...).

### Methodological quality assessment

The methodological quality of selected studies was assessed systematically using a 15-point methodological score as defined by Martin & Fourouzanfar and used for a previous systematic review on a similar topic [8]. Such score (ranging from 0 to 100) allowed an evaluation of the methodological quality of all study types (including case reports) and was thus perfectly suited for assessing study quality in this scoping review.

As recommended by Martin & Fourouzanfar, a study scoring higher than 50 out of 100 was considered of high methodological quality [8].

Study quality was also assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system (classifying evidence as high, moderate, low or very low quality), when appropriate [9].

### Data analysis

In cases of gabapentinoid prescription for the management of a painful orofacial condition, treatment effectiveness was graded as follows:

- Significant effect = more than 50% pain reduction;
- Partial effect = more than 30% pain reduction;
- No effect = less than 30% pain reduction.

The 30% cutoff was chosen in adherence with the seminal study from Farrar *et al.* [10] that showed that 30% pain reduction was associated with measurable improvement in overall quality of life.

In other indications of gabapentinoid prescriptions, treatment effectiveness was evaluated based on study conclusions and relevant comparisons (comparison with placebo or standard of care).

Clinical recommendations regarding gabapentinoid prescription were proposed based on the following arbitrary criteria:

- *Primary indication* (= first-line treatment option):
  - o Preexisting guidelines;
  - o One or more high quality randomized controlled trials (RCTs);
- *Secondary indication* (= second or third-line treatment option):
  - o One or more randomized controlled trials (RCTs);
  - o Well-conducted observational studies;
- *Potential indication* (= prescription possible with caution when no other treatment option or prescription guideline is available):
  - o Case series or case reports of sufficient methodological quality.

### Review conduct

**1-Data collection:** Relevant databases were queried by two authors in parallel (AS and NM) using the preselected keywords and papers fitting the inclusion criteria (without any non-inclusion criteria) were retrieved. References of each retrieved paper were assessed for other relevant papers which were included (if adhering to the inclusion/non-inclusion criteria) and duplicates were eliminated. Data collection was stopped on January 1, 2020.

**2-Data extraction:** Relevant data was retrieved and collected using a standardized Microsoft EXCEL® spreadsheet (Microsoft Corporation, Redmond, WA, USA) shared between authors. The following data was systematically collected:

- Authors;
- Study type;
- Population studied;
- Type of gabapentinoid;

- Dosage;
- Duration of treatment;
- Indication for prescription;
- Control condition (when applicable);
- Outcome(s) measured;
- Efficacy;
- Untoward effects.

Each paper retrieved was given a methodological score (see Methodological quality assessment chapter for details) on a separate standardized Microsoft EXCEL® spreadsheet (Microsoft Corporation, Redmond, WA, USA) shared between authors, with simple macros allowing automatic score calculations. Two authors (AS and NM) calculated the methodological scores separately.

**3-Data analysis:** Results from steps 1 and 2 were pooled between authors and a consensus was reached regarding the inclusion of each paper and the methodological score. In case of a lack of consensus, a third author (AC) reviewed the conflicting material and gave the final decision regarding inclusion and methodological score. Data was synthesized and qualitative analysis was performed to answer the scientific question in three parts: indications, non-indications and contraindications of gabapentinoids in Oral Medicine/Oral Surgery.

**4-Data reporting:** Two authors (AS and NM) drafted the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

## Results

The scoping review identified 131 articles of which 34 fit the inclusion criteria. The study flowchart is presented in [Figure 1](#). Of the 34 selected studies, there were 9 randomized controlled trials (RCTs), 5 observational studies, 2 retrospective studies and 18 case reports/case series. Based on the GRADE scale [9], 6 studies were of high evidence quality, 3 of moderate quality, 5 of low and 20 of very low quality. The methodological quality of the retrieved studies was quite poor, with only 9 studies (the 9 RCTs) considered of significant methodological quality (methodological score higher than 50 out of 100). The distribution of retrieved studies by study type is presented in [Figure 2](#).

### General indications of gabapentinoids in Oral Medicine and Oral Surgery

Overall, three types of indications were found in the analyzed literature, namely: anxiolytic premedication, anti-emetic premedication and orofacial pain management, detailed in [Figure 3](#).

### Gabapentinoids in the management of dental anxiety

A double-blind cross RCT of good quality (methodological score = 62/100) on 21 patients suggested that a single dose

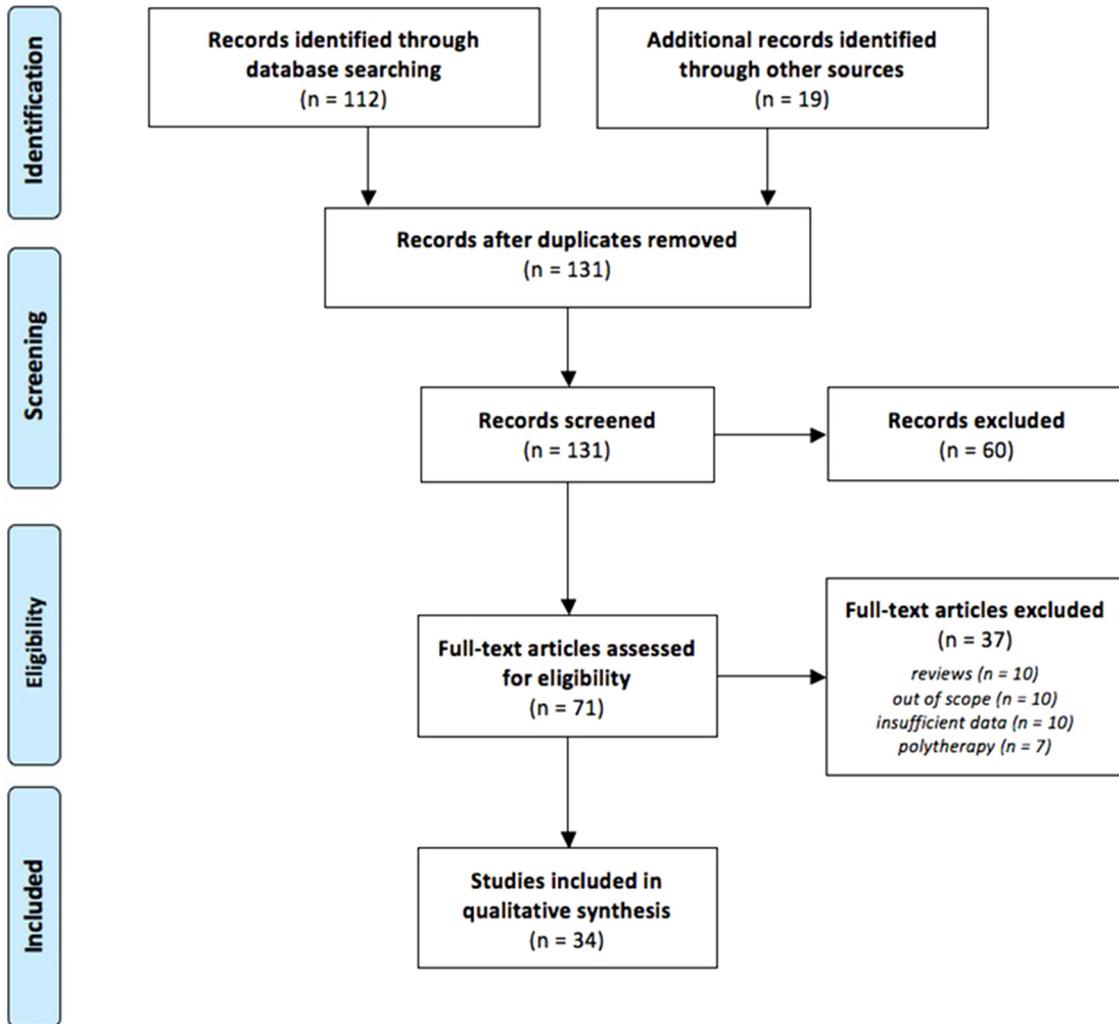


Fig. 1. Study flowchart (following PRISMA-ScR guidelines).

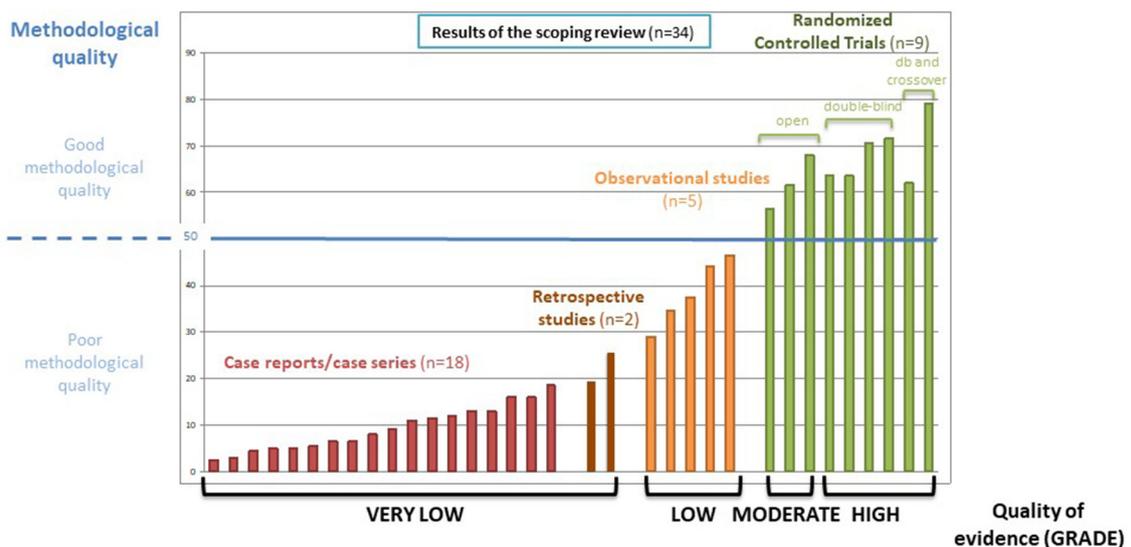
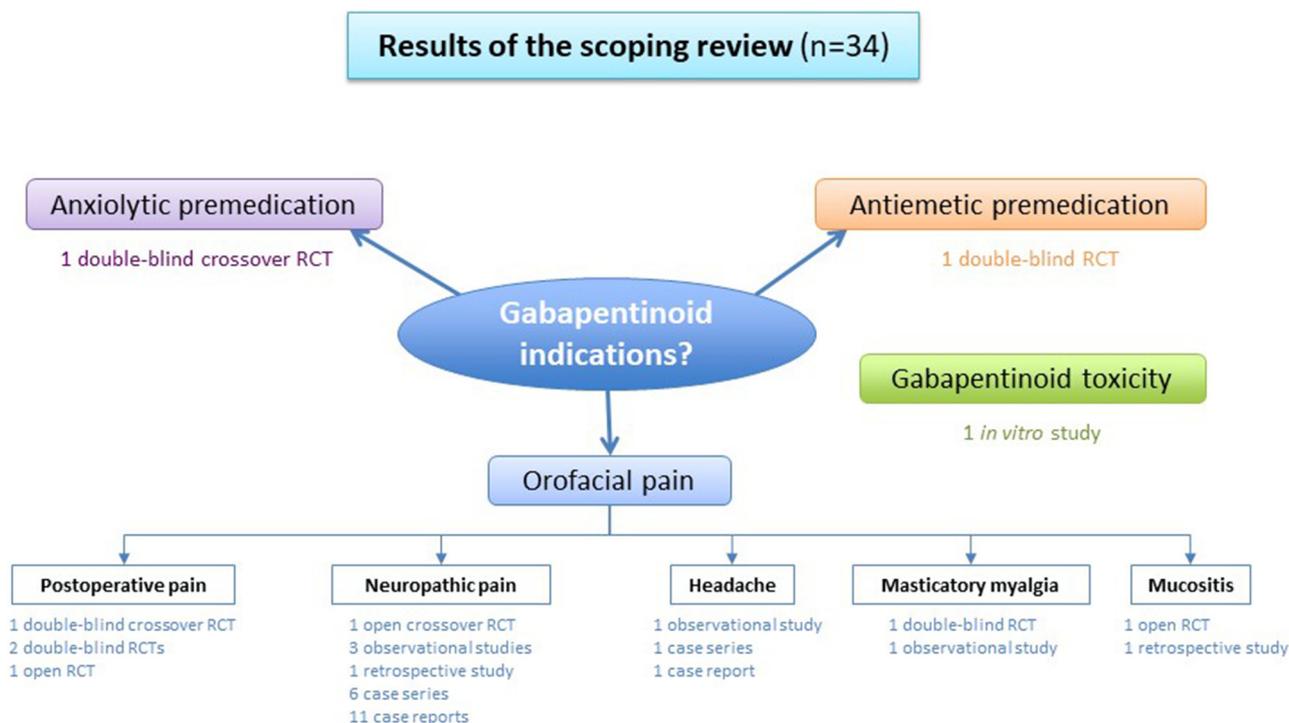


Fig. 2. Distribution of selected studies following the scoping review (db = double-blind).



**Fig. 3.** Distribution of selected studies sorted by indication (N.B: 1 case series in common for both neuropathic pain and headache).

**Table I.** Scoping review results – Gabapentinoids in the management of dental anxiety.

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
Eskandarian <i>et al.</i> 2015 [11]	Double-blind crossover RCT	62/100	21	Anxiolytic premedication of children with dental anxiety	Single dose 75 mg pregabalin 2 h prior dental procedure	Rapid anxiolytic and sedative effect seen from 2 hour after oral administration No significant improvement in childrens’ behavior ratings More effective behavior-guidance techniques in pregabalin group Higher number of “successful” treatment visits in pregabalin group

RCT = Randomized Controlled Trial.

of 75 mg pregabalin 2 hours prior to a dental procedure provided a significant rapid anxiolytic and sedative effect in children (as compared to placebo), without any serious side effects [11]. Although the children’s behavior ratings were not significantly different between the groups, the number of “successful” treatment visits was higher in the pregabalin group compared to the placebo group. Furthermore, the behavior-guidance techniques were more effective in the pregabalin group than in the placebo group, suggesting another interesting effect of pregabalin premedication [11].

The literature data related to gabapentinoids in the management of dental anxiety is summarized in Table I.

**Gabapentinoids in the prevention of postoperative nausea and vomiting**

A double-blind RCT of good quality (methodological score=63.5/100) on 30 patients evaluated the effect of a single dose of 300 mg gabapentin (among other treatment options separately evaluated) 1 hour prior to general

**Table II.** Scoping review results – Gabapentinoids in the prevention of postoperative nausea and vomiting.

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
Jahromi <i>et al.</i> [12]	Double-blind RCT	63.5/100	30	<i>Prevention of postoperative nausea and vomiting in maxillofacial trauma surgery</i>	Single dose 300 mg gabapentin 1 hour prior to anesthesia	Significant reduction in early (<24 hours) nausea and vomiting following maxillofacial trauma surgery Treatment safe and cost effective

RCT=Randomized Controlled Trial.

anesthesia as means of preventing postoperative nausea and vomiting following maxillofacial trauma surgery [12]. Such treatment resulted in significant reduction in early (less than 24 hours) nausea and vomiting following maxillofacial trauma surgery. The authors conclude that single dose gabapentin could be a safe and cost-effective treatment option for the prevention of postoperative nausea and vomiting [12].

The literature data related to gabapentinoids in the prevention of postoperative nausea and vomiting is summarized in Table II.

### Gabapentinoids in the management of orofacial pain

Of the 34 retrieved studies, 32 pertained to the management of painful orofacial conditions, that could be subdivided in the following categories: postoperative pain, neuropathic pain, headaches, masticatory myalgias and mucositis.

#### Postoperative pain

Four RCTs of good methodological quality (61.5 to 79/100) assessed the usefulness of pregabalin in preemptive analgesia and/or postoperative analgesia before or following third molar surgery [13–15] or orthognathic surgery [16]. One double-blind RCT showed that a single postoperative 300 mg dose of pregabalin was superior to ibuprofen or placebo for pain relief following third molar surgery [13]. Two other RCTs did not show any significant effect of 75 mg pregabalin 1 hour prior and/or after third molar surgery [14,15]. Finally, one double-blind RCT on 40 patients showed that 75 mg pregabalin 1 hour prior to general anesthesia induction allowed a significant decrease in pain and postoperative opioid consumption following orthognathic surgery [16].

#### Neuropathic pain – trigeminal neuralgias

Both gabapentin and pregabalin have been evaluated in the management of trigeminal neuralgias (idiopathic and secondary) with overall partial or total effectiveness in one open

crossover RCT [17], two prospective observational studies [18,19], one retrospective cohort study [20], two case series [21,22] and one case report [23].

One prospective observational study on 35 patients with trigeminal neuralgia suggested that pregabalin at doses of  $196 \pm 105$  mg/day allowed clinically and statistically significant reduction of pain, anxiety, depression and improvement of sleep quality [19].

#### Neuropathic pain – Glossopharyngeal neuralgias

Three case reports (of poor methodological quality) have suggested the use of gabapentin [24] or pregabalin [25,26] at various doses for the successful management of glossopharyngeal neuralgias (complete pain relief). The lack of proper randomized trials can be explained by the rarity of this painful condition.

#### Neuropathic pain – painful post-traumatic trigeminal neuropathies

One prospective observational study [27], three case reports [28–30] and two case series [31,32] have reported the successful use of pregabalin or gabapentin in the management of painful posttraumatic trigeminal neuropathies of various origins (rhizotomy, implant placement, endoscopy...). In the case series of Rozen [31] on post-traumatic external nasal pain syndrome, two patients out of the four reported had no effect of pregabalin at a dose of 675 mg/day.

#### Neuropathic pain – other painful neuropathies

Four case reports (of varying methodological quality) reported the successful management of trigeminal trophic syndrome [33], chemotherapy-induced painful glossopharyngeal neuropathy [34] or first-bite syndrome secondary to schwannoma surgery [35] or to bilateral total temporomandibular joint replacement [36] with pregabalin or gabapentin.

Two case series have reported the use of pregabalin for the successful management of burning mouth syndrome [37] or atypical facial pain [38].

## Headaches

One prospective observational study of poor methodological quality evaluated the use of pregabalin (300 mg/day) for migraine prophylaxis on 47 patients [39] with mitigated results: 26% of cases had a significant decrease in number of days with migraine ( $\geq 50\%$  reduction); 34% of cases had a moderate decrease (49–25% reduction) and 40% of cases had less than 25% reduction in number of days with migraine.

In a recent case series [38], pregabalin was effective in managing a transformed migraine (i.e. chronic migraine) in five patients, whereas gabapentin (300 mg three times a day) allowed a rapid and dramatic decrease in number of attacks in a case of post-traumatic Short-lasting Unilateral Neuralgiform headache with cranial Autonomic symptoms (SUNA) [40].

## Masticatory myalgias

A double-blind RCT of good methodological quality (methodological score=63.5/100) on 50 patients evaluated gabapentin (at doses between 300 and 4200 mg/day) for the management of chronic (i.e. more than 6 months) masticatory myalgias [41]. Overall, a 51% pain reduction was observed, with a decrease in the number of painful trigger points and a 52% increase in masticatory efficacy.

A prospective observational study of moderate methodological quality (methodological score=44/100) on 19 patients suffering from persistent myofascial pain showed that gabapentin (at doses between 900 and 1800 mg/day) as second line treatment led to a higher than 50% reduction in pain scores in 38.6% of cases [42].

## Mucositis

An open RCT of good methodological quality (methodological score=56.5/100) assessed the analgesic effect of gabapentin (900 mg/day) on 22 patients with radiation-induced mucositis (in a context of upper aerodigestive tract cancer) but did not show any difference compared to a standard analgesic regimen [43].

Conversely, a retrospective cohort analysis of 42 patients suffering from chemotherapy- and radiation-induced mucositis (also in a context of upper aerodigestive tract cancer) showed that gabapentin (2700 mg/day) allowed significant pain relief in 50% of cases (resulting in decreased opioid use) [44].

The literature data related to gabapentinoids in the management of orofacial pain is summarized in Table III.

## Untoward effects and toxicity of gabapentinoids

Of the 34 selected studies, 16 studies reported untoward effects, 3 reported effects similar to those of the control group, 4 reported no untoward effects at all and 11 did not evaluate the untoward effects. Untoward effects were mostly neurological (21 cases), gastro-intestinal (7 cases), dermatological (5 cases) or systemic (8 cases) as presented in Figure 4.

One study specifically assessed sexual dysfunction in patients taking pregabalin for various conditions: sciatica, atypical facial pain, chronic tension headache, transformed migraine, fibromyalgia and generalized anxiety disorder [38]. In this case series, sexual dysfunction was not an infrequent untoward effect and could present as erectile dysfunction, anorgasmia or loss of libido. Such effect was not dose dependent and often occurred at low dosages [38].

Although not part of the included studies per se, an interesting *in vitro* study retrieved during the review evaluated the effects of topical gabapentin (as part of other drugs tested) on oral and skin keratinocytes in a monolayer tissular model. Gabapentin (at doses varying between 0.002 and 0.09% equivalent clinical concentration) was applied in orobase for 30 minutes and did not produce any local toxicity [45].

The literature data related to gabapentinoid toxicity is summarized in Table IV.

Finally, although out of the scope of the review (because not related to the orofacial region), a recent population-based nested case-control study found that concomitant gabapentin and opioid exposure was associated with a 49% high risk of dying from an opioid overdose (because of cumulative central depressor effects), an important factor to take into consideration when prescribing such drugs [3]. Furthermore, significant risk of abuse of gabapentinoids exists, especially in patients with a history of drug abuse [46]. Other potential risks also merit mention: dizziness/drowsiness that can lead to falls (especially in elderly patients), emergence of withdrawal symptoms when stopping the treatment and possible development and/or amplification of suicidal ideations in some patients [1,2].

## Indications, non-indications and contraindications of gabapentinoids in Oral Medicine and Oral Surgery

In sum, analysis of the collected data (as defined in the Materials and Methods section) suggests the following indications, non-indications and contraindications of gabapentinoids in Oral Medicine and Oral Surgery (Fig. 5):

- *Indications* (= effectiveness of gabapentinoid use):
  - o as second line treatments in anxiety, antiemetic premedication, trigeminal neuralgia or masticatory myalgias;
  - o as potential treatment options for cranial neuralgias, post-traumatic trigeminal neuropathies, first bite syndrome, burning mouth syndrome or migraine prophylaxis, when other treatment options aren't efficient or available;
- *Non-indications* (= ineffectiveness of gabapentinoid use):
  - o Preemptive analgesia;
  - o Postoperative analgesia;
  - o Mucositis;
- *Contraindications* (= harm of gabapentinoid use):
  - o Absolute contraindications: hypersensitivity to pregabalin or gabapentin;
  - o Relative contraindications: toxicomania, preexistent sexual dysfunction, concomitant opioid use.

**Table III.** Scoping review results – Gabapentinoids in the management of orofacial pain.

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
<b>Postoperative pain</b>						
Hill <i>et al.</i> [13]	Double-blind RCT	70.5/100	50	<i>Postoperative analgesia following third molar surgery</i>	Single postoperative dose of 300 mg pregabalin	300 mg pregabalin superior to ibuprofen and to placebo
Cheung <i>et al.</i> [14]	Double-blind crossover RCT	79/100	34	<i>Preemptive or postoperative analgesia following third molar surgery</i>	Single dose 75 mg pregabalin 1 hour prior or after surgery	No usefulness of preemptive analgesia
Ahiskalioglu <i>et al.</i> [16]	Double-blind RCT	71.5/100	40	<i>Preemptive analgesia before orthognathic surgery</i>	75 mg pregabalin 1 hour prior to general anesthesia	Significant decrease in pain and in postoperative opioid consumption
Olmedo-Gaya <i>et al.</i> [15]	Open RCT	61.5/100	60	<i>Postoperative analgesia following third molar surgery</i>	75 mg pregabalin 1 hour prior and 1 hour after surgery	No difference compared to standard analgesic regimen
<b>Neuropathic pain – Trigeminal neuralgias</b>						
Cheshire [20]	Retrospective cohort analysis	25.5/100	92	<i>Trigeminal neuralgia</i>	Gabapentin 700-1200 mg/day	Effective in 47% of cases with total effect in 17% of cases
Obermann <i>et al.</i> [18]	Prospective observational study	37.5/100	53	<i>Idiopathic (47) or secondary (6) trigeminal neuralgia</i>	Pregabalin 600 mg/day	Total effect (25%) Partial effect (>50% relief) (49%) No effect (26%)
Perez <i>et al.</i> [19]	Prospective observational study	46.5/100	35	<i>Trigeminal neuralgia</i>	Pregabalin 196 ± 105 mg/day	"Clinically and statistically significant" reduction of pain, anxiety, depression and improvement of sleep quality
Ordas <i>et al.</i> [23]	Case report	6.5/100	1	<i>Trigeminal neuralgia secondary to Wallenberg syndrome</i>	Gabapentin 600 mg x3/day	Total pain relief
Rustagi <i>et al.</i> [17]	Open crossover RCT	68/100	22	<i>Refractory trigeminal neuralgia</i>	Pregabalin 300 mg x2/day	Total effect (36%) Partial effect (>50% pain relief) (54%) i daily activities
Pareja & Cuadrado [21]	Case series	5/100	2	<i>Lacrymal neuralgia</i>	Pregabalin 100–400 mg/day	Partial (1) or total (1) effect
Ruiz <i>et al.</i> [22]	Case series	4.5/100	3	<i>Auriculo-temporal neuralgia</i>	Gabapentin 800-2400 mg/day	Total (2) or no (1) effect
<b>Neuropathic pain – Glossopharyngeal neuralgias</b>						
Moretti <i>et al.</i> [24]	Case report	11.5/100	1	<i>Glossopharyngeal neuralgia</i>	Gabapentin 400 mg x6/day	Total effect and weaning (4 year follow-up : 1 recurrence, treated and new drug weaning)
Kitchener [25]	Case report	11/100	1	<i>Glossopharyngeal neuralgia</i>	Pregabalin 75 mg x2/day	Total effect
Vecchi <i>et al.</i> [26]	Case report	8/100	1	<i>Glossopharyngeal neuralgia</i>	Pregabalin 300 mg/day	Total effect
<b>Neuropathic pain – Painful post-traumatic trigeminal neuropathies</b>						
Rozen [28]	Case report	5/100	1	<i>Anesthesia dolorosa (after trigeminal rhizotomy in a CH case)</i>	Gabapentin 1200 mg/day	Total effect
Fischhoff & Sirois [29]	Case report	16/100	1	<i>Compression neuropathy of inferior alveolar nerve in systemic sclerosis</i>	Gabapentin 2700 mg/day (titrated)	Total effect (2 year follow-up)
Rozen [31]	Case series	6.5/100	4	<i>Post-traumatic external nasal pain syndrome</i>	Pregabalin 675 mg/day	Subtotal (1) or no (2) effect Effect unreported (1)
Park <i>et al.</i> [27]	Prospective observational study	29/100	6	<i>Post-implant trigeminal neuropathic pain</i>	Gabapentin 1800–2400 mg/day	45.8% pain reduction
Seto <i>et al.</i> [32]	Case series	9/100	12	<i>Orofacial painful neuropathies (lingual, cervical, gingival, glossopharyngeal)</i>	Gabapentin 200–600 mg/day	>50% pain reduction in all patients

**Table III.** (continued).

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
Kalladka <i>et al.</i> [30]	Case report	16/100	1	<i>Post-endoscopy neuropathic pain</i>	Gabapentin 300 mg x3/d	75% pain reduction
<b>Neuropathic pain – Other painful neuropathies</b>						
Garza [33]	Case report	3/100	1	<i>Trigeminal trophic syndrome</i>	Gabapentin 2400 mg/d	Partial effect
Ito <i>et al.</i> [37]	Case series	13/100	5	<i>Burning mouth syndrome</i>	Pregabalin 50 mg/day (3) or 150 mg/day (2)	Total (3) or subtotal (2) effect
Heir & Materson [34]	Case report	12/100	1	<i>Chemotherapy-induced painful glossopharyngeal neuropathy</i>	Pregabalin 100 mg x3/day	Total effect (initially 6-9/10 pain)
Hamed [38]	Case series	13/100	8	<i>Atypical facial pain</i>	Pregabalin 50–100 mg/day	Total effect
Casserly <i>et al.</i> [35]	Case report	5.5/100	1	<i>First bite syndrome secondary to schwannoma surgery</i>	Pregabalin 75 mg x2/day	Total effect (at 18 months)
Alwanni <i>et al.</i> [36]	Case report	18.5/100	1	<i>First bite syndrome secondary to bilateral total TMJ replacement</i>	Gabapentin 300 mg x3/day	Progressive significant pain reduction (9/10 to 3/10)
<b>Headaches</b>						
Jacob <i>et al.</i> [40]	Case report	2.5/100	1	<i>Post-traumatic SUNA</i>	Gabapentin 300 mg x3/day	“Rapid and dramatic response” (from 5–10 daily attacks to 1 attack per week)
Pizzolato <i>et al.</i> [39]	Prospective observational study	34.5/100	47	<i>Migraine prophylaxis</i>	Pregabalin 300 mg/day	≥50% reduction in days with migraine (in 26% of cases) 49–25% reduction (in 34% of cases) <25% reduction (in 40% of cases)
Hamed [38]	Case series	13/100	5	<i>Transformed migraine</i>	Pregabalin 50–100 mg/d	Total effect
<b>Masticatory myalgias</b>						
Kimos <i>et al.</i> [41]	Double-blind RCT	63.5/100	50	<i>Chronic (&gt;6 months) masticatory myalgias</i>	Gabapentin 300–4200 mg/day	51% pain reduction Decrease in number of painful trigger points (mean = 6 fewer) 52% increase in masticatory efficacy
Haviv <i>et al.</i> [42]	Prospective observational study	44/100	19	<i>Persistent myofascial pain</i>	Gabapentin 900–1800 mg/day (second line treatment after TCAs)	≥50% reduction in pain scores (in 38.6% of cases)
<b>Mucositis</b>						
Bar Ad <i>et al.</i> [44]	Retrospective cohort analysis	19.5/100	42	<i>Chemotherapy- and radiation-induced mucositis (UADT cancers)</i>	Gabapentin 2700 mg/day	Pain relief in 50% of cases (resulting in decreased opioid use)
Kataoka <i>et al.</i> [43]	Open RCT	56.5/100	22	<i>Radiation-induced mucositis (UADT cancers)</i>	Gabapentin 900 mg/day	No difference compared to standard analgesic regimen

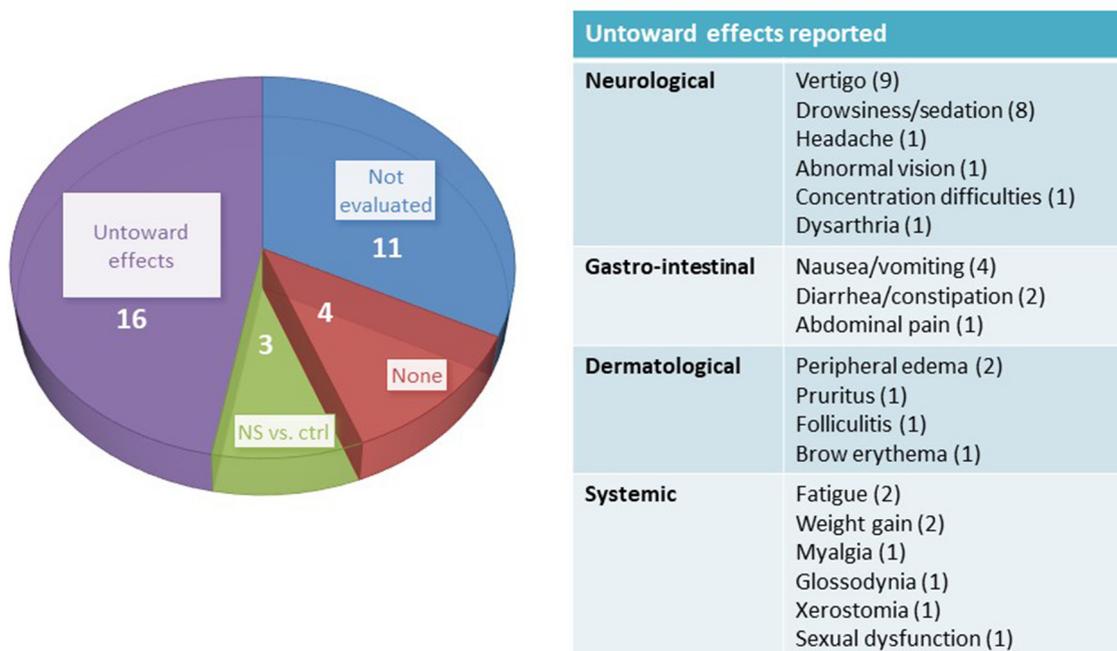
CH = Cluster Headache; RCT = Randomized Controlled Trial; SUNA = Short-lasting Unilateral Neuralgiform headache with cranial Autonomic symptoms; TCA = TriCyclic Antidepressants; TMJ = Temporo-Mandibular Joint; UADT = Upper Aero-Digestive Tract.

## Discussion

This systematic scoping review explored the available literature on the use of gabapentinoids in an Oral Medicine/ Oral Surgery clinical context. Although quite heterogenous in methodological quality, the majority of the studies fitting the inclusion criteria suggested a partial, subtotal or total effect of gabapentinoids in various clinical situations such as anxiolytic premedication for dental procedure,

antiemetic premedication for the prevention of postoperative nausea and vomiting following maxillofacial trauma surgery and management of numerous orofacial painful conditions such as trigeminal and other cranial neuralgias, painful post-traumatic trigeminal neuropathies, headaches and myalgias. Obviously, a publication bias is highly probable, as clinicians are more likely to publish positive effects of gabapentinoids on unusual conditions rather than lack of effect.

**Untoward effects of gabapentinoids**



**Fig. 4.** Untoward effects of gabapentinoids reported in the scoping review.

**Table IV.** Scoping review results – *Gabapentinoid toxicity*.

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
Al-Musawi et al. [45]	<i>In vitro</i> study	N/A	N/A	<i>Effect of topical gabapentin on oral and skin keratinocytes (monolayer models)</i>	Gabapentin 0.002–0.09% (equivalent clinical concentration) topical application (in orabase) for 30 minutes	No local toxicity of gabapentin

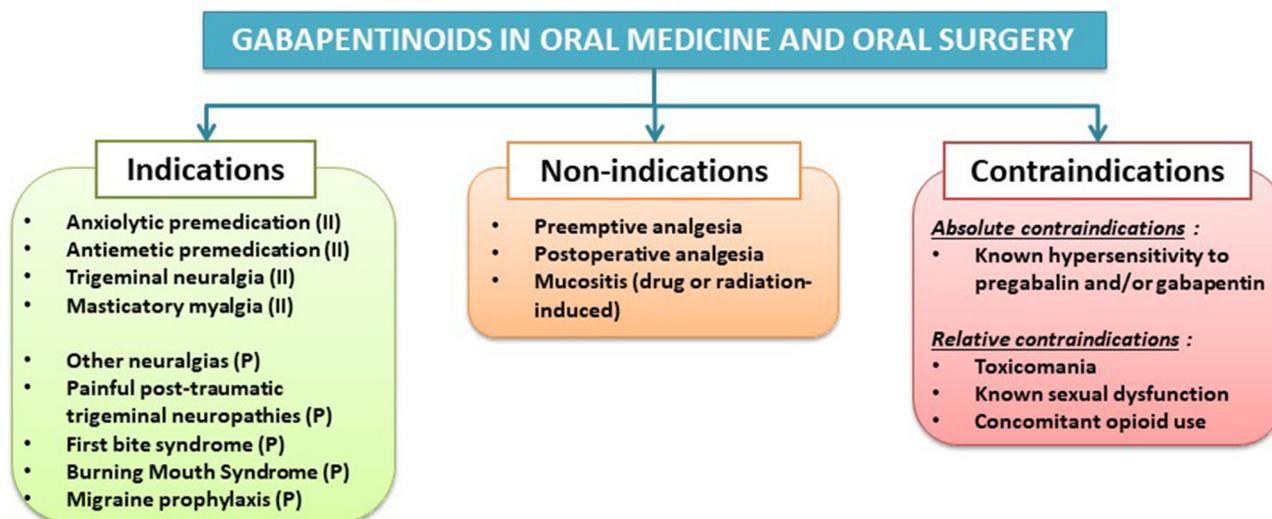
N/A = Not Applicable.

Effectiveness of gabapentinoids (i.e. indications) is suggested for the anxiolysis before dental procedures [11], prevention of postoperative nausea/vomiting [12] and the management of trigeminal neuralgia [17,19] and masticatory myalgia [41,42]. This is in adherence with known pharmacological effects of gabapentinoids on anxiety (pregabalin is approved for the management of generalized anxiety disorder [1]) and on the prevention of nausea/vomiting in other clinical contexts [47]. From a pathophysiological standpoint, it is thought that the anti-emetic effect of gabapentinoids could result from increased GABAergic tonus from the nucleus tractus solitarius on the dorsal motor nucleus of the vagus nerve, the main vagal nucleus responsible for emesis [48].

Ineffectiveness of gabapentinoids (i.e. non-indications) is suggested for preemptive and postoperative analgesia [14,15]

or radiation-induced mucositis analgesia [43]. A Cochrane review on the analgesic effect of gabapentin in 2010 concluded that although such an effect does exist (when compared to placebo) it is not clinically significant (as compared to standard analgesics) [49].

Harmfulness of gabapentinoids (i.e. contraindications) is mainly linked to possible untoward effects, mostly neurological (vertigo, sedation, drowsiness) linked to central depressor effect of these neuronal voltage-gated calcium channel inhibitors and potential for abuse [46]. This should warrant caution when prescribing such drugs (especially in patients with concurrent opioid treatments that have an increased risk of drug overdose [3]) but should not be considered absolute contraindications when necessary. Indeed, one should always keep in mind the fact that untreated pain also kills [50].



**Fig. 5.** Conclusions of the scoping review: indications, non-indications and contraindications of gabapentinoids in Oral Medicine and Oral Surgery (II = secondary indication, P = potential indication).

Interestingly, an *in vitro* study assessed potential local toxicity of gabapentin on both a skin and oral mucosa models at various concentrations (between 0.002 and 0.09% equivalent clinical concentration) in an orobase paste and concluded to the absence of local toxicity at such doses [45]. As primary afferent neurons express voltage-gated calcium channels [51], a local effect of gabapentinoids is pathophysiologically plausible and in adherence with what is observed in clinical practice. Indeed, topical gabapentin has been used successfully as an add-on treatment for the management of trigeminal neuralgia [52]. In our tertiary clinic, we have proposed mouthwashes with pregabalin as the sole (efficient) treatment option for management of inflammatory anemia-related glossitis [6] or for management of trigeminal neuropathy in a patient with severe bronchomalacia, who was deemed unfit for systemic administration (unpublished case report).

## Conclusion

Data obtained from the present scoping review suggests the potential use of gabapentinoids as second-line treatments for anxiolysis, prevention of postoperative nausea/vomiting and the management of trigeminal neuralgia and masticatory myalgia. Other potential indications of gabapentinoids in Oral Medicine/Oral Surgery practice include cranial neuralgias, post-traumatic trigeminal neuropathies, first bite syndrome, burning mouth syndrome and migraine prophylaxis, when other treatment options aren't efficient or available.

Additional studies and reviews are required to allow for the proper elaboration of gabapentinoid prescription guidelines in the Oral Medicine/Oral Surgery clinical context.

**Conflicts of interest:** All the authors of this article report no conflict of interest regarding this work.

No funding was received regarding this scoping review.

## References

- Haute Autorité de Santé – Commission de Transparence – Avis du 3 mai 2017–prégabaline. Available at: [https://has-sante.fr/upload/docs/evamed/CT-15083\\_LYRICA\\_PIS\\_RI\\_Avis2\\_CT9953&15083.pdf](https://has-sante.fr/upload/docs/evamed/CT-15083_LYRICA_PIS_RI_Avis2_CT9953&15083.pdf)
- Haute Autorité de Santé – Commission de Transparence – Avis du 18 avril 2018–gabapentine. Available at: <https://has-sante.fr/jcms/neurontin-18042018-avis-ct15567>
- Gomes T, Juurlink DN, Antoniou T, *et al.* Gabapentin, opioids, and the risk of opioid-related death: a population-based nest case-control study. *PLoS Med.* 2017;14:e1002396.
- Attal N, Cruccu G, Baron R, *et al.* EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17:1113–e88.
- Moreau N, Boucher Y. Encyclopédie Médico-Chirurgicale Médecine Buccale: Douleurs oro-faciales 2020:1–21 [Article 28-290-C-10].
- Sulukdjian A, L'Homme R, Chanlon A, Moreau N. Gabapentinoid prescription in Oral Medicine and Oral Surgery practice: Part I – Experience from a French Orofacial pain clinic. *J Oral Med Oral Surg.* 2020;26:13.
- Tricco AC, Lillie E, Zarin W, *et al.* PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* 2018;169:467–473.
- Martin WJ, Forouzanfar T. The efficacy of anticonvulsants on orofacial pain: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011;111:627–633.
- Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924–926.
- Farrar JT, Young Jr JP, LaMoreaux L, *et al.* Clinical importance of the changes in chronic pain intensity measured on an 11-point numerical rating scale. *Pain* 2001;94:149–158.
- Eskandarian T, Eftekharian H, Soleymanzade R. Efficacy and safety of premedication with single dose of oral pregabalin in children with dental anxiety: a randomized double-blind placebo-controlled crossover clinical trial. *Dent Res J* 2015;12:528–533.
- Jahromi HE, Gholami M, Rezaei F. A randomized double-blind placebo controlled study of four interventions for the prevention of postoperative nausea and vomiting in maxillofacial trauma surgery. *J Craniofac Surg.* 2013;24:e623–e627.

13. Hill CM, Balkenohl M, Thomas DW, *et al.* Pregabalin in patients with postoperative dental pain. *Eur J Pain.* 2001;5:119–124.
14. Cheung CW, Choi WS, Leung YY, *et al.* A double-blind randomized crossover study to evaluate the timing of pregabalin for third molar surgery under local anesthesia. *J Oral Maxillofac Surg.* 2012;70:25–30.
15. Olmedo-Gaya MV, Manzano-Moreno FJ, Galvez-Mateos R, *et al.* Oral pregabalin for postoperative pain relief after third molar extraction: a randomized controlled clinical trial. *Clin Oral Invest.* 2016;20:1819–1826.
16. Ahiskalioglu A, Ince I, Aksoy M, *et al.* Effects of a single-dose of pre-emptive pregabalin on postoperative pain and opioid consumption after double-jaw surgery: a randomized controlled trial. *J Oral Maxillofac Surg.* 2016;74:53.e1–e7.
17. Rustagi A, Roychoudhury A, Bhutia O, *et al.* Lamotrigine versus pregabalin in the management of refractory trigeminal neuralgia: A randomized open label crossover trial. *J Maxillofac Oral Surg.* 2014;13:409–418.
18. Obermann M, Yoon MS, Sensen K, *et al.* Efficacy of pregabalin in the treatment of trigeminal neuralgia. *Cephalalgia* 2007;28:174–181.
19. Perez C, Navarro A, Saldana MT, *et al.* Patient-reported outcomes in subjects with painful trigeminal neuralgia receiving pregabalin: evidence from medical practice in primary care settings. *Cephalalgia* 2009;29:781–790.
20. Cheshire Jr WP. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. *J Pain* 2002;3:137–142.
21. Pareja JA, Cuadrado ML. Lacrimal neuralgia: so far, a missing cranial neuralgia. *Cephalalgia* 2013;33:1198–1202.
22. Ruiz M, Porta-Etessam J, Garcia-Ptacek S, *et al.* Auriculotemporal neuralgia: eight new cases report. *Pain Med.* 2016;17:1744–1748.
23. Ordas CM, Cuadrado ML, Simal P, *et al.* Wallenberg's syndrome and symptomatic trigeminal neuralgia. *J Headache Pain* 2011;12:377–380.
24. Moretti R, Torre P, Antonello RM, *et al.* Gabapentin treatment of glossopharyngeal neuralgia: a follow-up of four years of a single case. *Eur J Pain.* 2002;6:403–407.
25. Kitchener JM. Glossopharyngeal neuralgia responding to pregabalin. *Headache.* 2006;46:1307–1308.
26. Vecchi M, Mestre RP, Thiekalamuriyil SL, Cartolari R. A rare case of glossopharyngeal neuralgia due to neurovascular conflict. *Case Rep Neurol.* 2017;9:309–315.
27. Park JH, Lee SH, Kim ST. Pharmacological management of trigeminal nerve injury pain after dental implant surgery. *Int J Prosthodont.* 2010;23:342–346.
28. Rozen TD. Relief of anesthesia dolorosa with gabapentin. *Headache.* 1999;39:761–762.
29. Fischhoff DK, Sirois D. Painful trigeminal neuropathy caused by severe mandibular resorption and nerve compression in a patient with systemic sclerosis: case report and literature review. *Oral Med Oral Surg Oral Pathol Radiol Endod.* 2000;90:456–459.
30. Kalladka M, Nasri-Heir C, Eliav E, *et al.* Continuous neuropathic pain secondary to endoscopic procedures: report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Radiol.* 2016;122:e55–e59.
31. Rozen T. Post-traumatic external nasal pain syndrome (a trigeminal based pain disorder). *Headache.* 2009;49:1223–1228.
32. Seto M, Sakamoto Y, Furuta H, Kikuta T. Gabapentin therapy in patients with orofacial neuropathic pain: report of 12 cases. *Oral Sci Int.* 2011;8:17–19.
33. Garza I. The trigeminal trophic syndrome: an unusual cause of face pain, dysaesthesias, anaesthesia and skin/soft tissue lesions. *Cephalalgia.* 2008;28:980–985.
34. Heir GM, Masterson M. Bilateral glossopharyngeal neuropathy following chemo and radiation therapy for a primitive neuroectodermal tumour. *J Oral Rehab.* 2016;43:154–158.
35. Casserly P, Kiely P, Fenton JE. Cervical sympathetic chain schwannoma masquerading as a carotid body tumour with a postoperative complication of first-bite syndrome. *Eur Arch Otorhinolaryngol.* 2009;266:1659–1662.
36. Alwanni N, Altay MA, Baur DA, Quereshy FA. First bite syndrome after bilateral temporomandibular joint replacement: case report. *J Oral Maxillofac Surg.* 2016;74:480–488.
37. Ito M, Tokura T, Yoshida K, *et al.* Five patients with burning mouth syndrome in who an antidepressant (serotonin-noradrenaline reuptake inhibitor) was not effective, but pregabalin markedly relieved pain. *Clin Neuropharm.* 2015;38:158–161.
38. Hamed SA. Sexual dysfunction induced by pregabalin. *Clin Neuropharm.* 2018;41:116–22.
39. Pizzolato R, Villani V, Prosperini L, *et al.* Efficacy and tolerability of pregabalin as preventive treatment for migraine: a 3-month follow-up study. *J Headache Pain* 2011;12:521–525.
40. Jacob S, Saha AR, Rajabally YA. Post-traumatic short-lasting unilateral headache with cranial autonomic symptoms (SUNA). *Cephalalgia* 2008;28:991–993.
41. Kimos P, Biggs C, Mah J, *et al.* Analgesic action of gabapentin on chronic pain in the masticatory muscles: a randomized controlled trial. *Pain* 2007;127:151–160.
42. Haviv Y, Rettman A, Aframian D, *et al.* Myofascial pain: an open study on the pharmacotherapeutic response to stepped treatment with tricyclic antidepressants and gabapentin. *J Oral Facial Pain Headache.* 2015;29:144–151.
43. Kataoka T, Kiyota N, Shimada T, *et al.* Randomized trial of standard pain control with or without gabapentin for pain related to radiation-induced mucositis in head and neck cancer. *Aurus Nasus Larynx.* 2016;43:677–684.
44. Bar Ad V, Weinstein G, Dutta PR, *et al.* Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. *Cancer.* 2010;116:4206–4213.
45. Al-Musawi M, Durham J, Whitworth JM, *et al.* Effect of topical neuromodulatory medications on oral and skin keratinocytes. *J Oral Pathol Med.* 2017;46:134–141.
46. Evoy KE, Morrison MD, Sadklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs.* 2017;77:403–426.
47. Guttuso T Jr. Gabapentin's anti-nausea and anti-emetic effects: a review. *Exp Brain Res.* 2014;232:2535–2539.
48. Babic T, Browning KN. The role of vagal neurocircuits in the regulation of nausea and vomiting. *Eur J Pharmacol.* 2014;722:38–47.
49. Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2010, issue 5. Art. No.: CD008183.
50. MacDonald S. Leo died the other day. *CMAJ.* 2019;191:E49–E50.
51. Weon H, Kim TW, Youn DH. Postsynaptic N-type or P/Q-type calcium channels mediate long-term potentiation by group I metabotropic glutamate receptors in the trigeminal oralis. *Life Sci.* 2017;188:110–117.
52. Brid T, Sacristan De Lama MP, Gonza N, Baamonde A. Topical gabapentin as add-on therapy for trigeminal neuralgia. A case report. *Pain Med.* 2017;18:1824–1826.