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Les gabapentinoïdes en médecine et chirurgie orale

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THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN CHIRURGIE DENTAIRE

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Par

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Les gabapentinoïdes en médecine médecine et chirurgie orale

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À Sutra, lorem ipsum dolor sit amet, consectetur adipiscing elit. Sed non risus et plus encore.

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Introduction

Le geste médical faisant disparaître instantanément la douleur reste la principale attente du patient quand il consulte un chirurgien-dentiste. Bien que cela puisse être une réalité pour certaines pathologies courantes, cela reste malheureusement un mythe dans de nombreuses douleurs chroniques, de traitement souvent difficile, voire parfois impossible.

Cette douleur permanente ou paroxystique qui perturbe son quotidien et sa qualité de vie devient souvent insupportable de par son caractère persistant sans perspective de fin ou d'amélioration en l'absence d'une prise en charge adaptée, s'appuyant sur la compréhension de ses mécanismes physiopathologiques sous-jacents et des perspectives thérapeutiques associées.

Le praticien est alors confronté à la difficulté d'expliquer au patient l'étiologie de ces douleurs -qui reste en partie mal connue- puis de proposer et mettre en place des traitements médicamenteux inhabituels dans le contexte d'une pratique de ville.

Le chirurgien-dentiste est prescripteur de nombreux médicaments et certaines pathologies de la sphère orofaciale peuvent nécessiter des traitements spécifiques peu connus de tels praticiens. Dans le cas de douleurs chroniques endo- ou exobuccales, le diagnostic peut non seulement être complexe, mais la mise en place du traitement adéquat peut l'être encore plus sans formation spécifique.

Depuis le 1er septembre 2016, l'équipe du Dr Moreau de l'hôpital Bretonneau à Paris reçoit des patients adressés pour des douleurs chroniques oro-faciales inexplicables. Parmi ces douleurs, un nombre important concerne des douleurs neuropathiques pour lesquelles des traitements médicamenteux efficaces existent, notamment les gabapentinoïdes.

Les gabapentinoïdes, la prégabaline et la gabapentine, sont des inhibiteurs neuronaux des canaux calciques voltage-dépendants principalement prescrits pour le traitement de l'épilepsie partielle et des douleurs neuropathiques. Bien que leur efficacité en tant que traitements de première ligne pour les neuropathies douloureuses (et plusieurs pathologies douloureuses non neuropathiques) soit bien établie dans la pratique médicale générale, leur efficacité et leur prescription en médecine et chirurgie orale ont jusqu'à présent reçu peu d'attention.

L'objectif de ce travail était d'étudier la place et l'usage des gabapentinoïdes en médecine et chirurgie orale en s'appuyant sur l'expérience développée au sein de la consultation spécifique de l'hôpital Bretonneau (susmentionnée) et d'une revue systématique de la littérature scientifique (selon une méthodologie de *scoping review*).

Les données ainsi colligées ont été synthétisées au sein de deux publications scientifiques dans le *Journal of oral medicine and oral surgery*, reproduites ci-après.

1 : Expérience des gabapentinoïdes au sein de la consultation « douleurs chroniques oro-faciales » de l'hôpital bretonneau à Paris

Cette partie est constituée entièrement par la reproduction autorisée de notre publication parue en avril 2020 et intitulée « Gabapentinoid prescription in oral medicine and oral surgery practice. Part I, Experience from a french orofacial pain clinic ». ¹

¹ Sulukdjian et al., « Gabapentinoid prescription in oral medicine and oral surgery practice. Part I, Experience from a french orofacial pain clinic ».

Educational Article

Gabapentinoid prescription in oral medicine and oral surgery practice. Part I — Experience from a French Orofacial pain clinic

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Abstract – Gabapentinoids, pregabalin and gabapentin, are neuronal voltage-gated calcium channel inhibitors mainly prescribed for the treatment of partial epilepsy and neuropathic pain. Although their efficacy as first-line treatments for painful neuropathic conditions (and several non-neuropathic painful conditions) has been well established in general medical practice, their efficacy and prescription in Oral Medicine and Oral Surgery practice has received little attention so far. This didactic article, the first of a two-part series, aims to present the experience of a French tertiary orofacial pain clinic regarding the prescription of gabapentinoids in Orofacial pain conditions that fall within the scope of the oral surgeon's practice.

Introduction

Gabapentinoids, pregabalin and gabapentin, are a recent class of neuronal voltage-gated calcium channel inhibitors, mainly prescribed for the treatment of partial epilepsy and neuropathic pain. Owing to their efficacy, limited major side effects and lack of pharmacological interactions, their prescription has significantly increased these past few years [1,2]. In parallel, there is an increasing concern regarding potential misuse of such drugs and increased mortality risk when associated with opioids [3]. Reasonable rational prescription of gabapentinoids is quintessential to mitigate such risks, *inter alia* by following the relevant scientific recommendations.

In 2010, the European Federation of Neurological Societies published guidelines regarding the pharmacological treatment of neuropathic pain and addressing the respective role of gabapentinoids in the pharmacological armamentarium [4]. Unfortunately, no specific guidelines have been edicted regarding orofacial neuropathic pain conditions (with the exception of trigeminal neuralgia). Such conditions are thus treated by extrapolating the prescription pattern from other similar painful neuropathies [5]. Furthermore, considering the preventive effect of gabapentinoids on the development of central sensitization

(leading to pain chronification), their prescription has been extended to other non-neuropathic painful conditions such as headache [6] or myalgias [7].

This didactic article, the first of a two-part series, aims to present the experience of a French orofacial clinic regarding the prescription and efficacy of gabapentinoids for the management of orofacial pain conditions that fall within the scope of the oral surgeon's practice.

Gabapentinoid pharmacology

Gabapentinoids are alkylated analogs of γ -amino-butyric acid (GABA), the main inhibitory neurotransmitter of the peripheral and central nervous system. As such, the two main gabapentinoids, gabapentin and pregabalin, were developed initially as anti-epileptic drugs and then as treatments for painful neuropathic conditions (Fig. 1).

Their pharmacological effect is non-GABAergic, as gabapentinoids are high affinity ligands for the $\alpha_2\delta$ sub-unit of neuronal voltage-gated calcium channels, blocking the (calcium-mediated) release of excitatory neurotransmitters (such as glutamate, noradrenaline or substance P), resulting in decreased neuronal excitability and in an anti-hyperalgesic effect [8].

These drugs are thus effective treatments to decrease peripheral and central sensitization, in painful conditions such as painful neuropathies [4], myalgias [7] or headaches [6].

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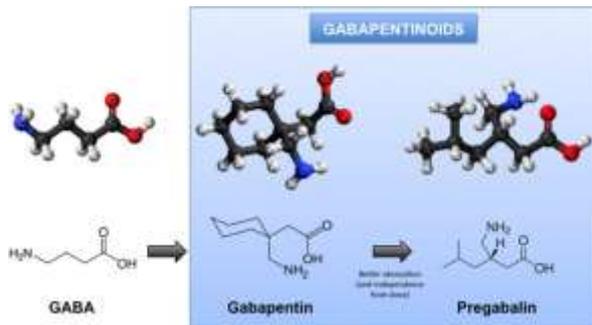


Figure 1. Chemical structure of gabapentinoids. The evolution of their chemical structure from GABA is shown (black arrows). (All images are of public domain or under creative commons license CC BY-SA 4.0.)

Principles of gabapentinoid prescription in orofacial conditions

Choice of gabapentinoid

Both gabapentinoids (gabapentin and pregabalin) have similar pharmacology and there is little evidence to favor one gabapentinoid over the other. Pregabalin appears to be better tolerated than gabapentin (and was developed as an improvement of gabapentin for that reason) and can be considered the first line gabapentinoid of choice. In case of pregabalin intolerance or inefficacy, gabapentin can be considered as a second line treatment [5].

The French Pain Society recommends that gabapentinoids be prescribed at low doses and gradually titrated until a significant clinical effect is obtained [9].

Pregabalin can be started at 150 mg daily (50 mg t.i.d) or lower (if the patient is known to have many or severe drug-related untoward effects). Gabapentin can be started at 300 mg daily (100 mg t.i.d) or lower [9].

Reevaluation

A reevaluation must systematically be performed between day 15 and day 30, with special focus on pharmacological effect and untoward effects. It is noteworthy that such untoward effects usually appear at initiation of treatment and/or dose increases. Most of them are temporary.

Four main situations can be encountered (from worse to best case scenario), summarized in Figure 2:

1. *The treatment has worsened the symptomatology and/or untoward effects are not tolerated*

The treatment must be stopped, and another drug prescribed.

2. *The treatment has no effect and/or untoward effects are tolerable*

Treatment is maintained for one month (as a therapeutic trial) then reevaluated (as drug effect is dose-dependent and time-dependent). After reevaluation the dose can be increased if necessary.

Pharmacological effect	++ TOTAL	+ PARTIAL	- NONE	-- AGGRAVATION
Secondary and untoward effects	--- BENEFICIAL EFFECT	- NONE	+ MODERATE UNTOWARD EFFECTS	++ SEVERE UNTOWARD EFFECTS
Suggested conduct	Dose maintenance then tapering	Dose increase (titration)	Therapeutic trial (1 month drug maintenance) and reevaluation	Drug switch

Figure 2. Suggested conduct upon reevaluation between day 15 and day 30.

3. *The treatment has a partially beneficial effect and/or is without any significant untoward effect*

Treatment is titrated, i.e. drug posology is gradually increased until total pharmacological effect or until severe untoward effects appear.

4. *The treatment is totally beneficial and/or is accompanied by positive side effects (e.g. increased sleep quality)*

Treatment is maintained at the same dose for a variable amount of time (based on disease and pain duration), before progressive drug tapering. A minimum of 6 months efficient treatment is usually necessary (see Tapering section).

Tapering

Complete drug tapering is the final objective of all gabapentinoid treatments when prescribed for the management of oral painful conditions. Whereas it can be expected in acute painful conditions and recent chronic painful conditions, it is near impossible (or impossible) to obtain in established chronic painful conditions (i.e. that have been present for several years).

The treatment will have to be maintained for several months before tapering can be considered, and the patient will have to be informed accordingly. The French Pain Society recommends a minimum of 6 months effective treatment (i.e. of total pain relief) duration before starting any tapering [9].

No formal rules of tapering have been edicted but several principles must be followed:

- The tapering must be slow and gradual to avoid the occurrence of withdrawal symptoms (such as brutal pain increase).
- Frequent reevaluations must be performed, focusing on both physical and psychological symptomatology.
- The tapering will be stopped immediately if pain recurs, even slightly.

Indications of gabapentinoid prescription in a French tertiary orofacial pain clinic

Presentation of the orofacial pain clinic and patient cohort

A tertiary orofacial pain clinic was opened in the dental medicine department of an academic hospital in Paris (France)

Table I. Indications of gabapentinoid prescription in the tertiary orofacial pain clinic patient cohort (n=49 patients). PPTN = Painful Post-Traumatic Trigeminal Neuropathy; CIPN = Chemotherapy-Induced Peripheral Neuropathy; CPSP = Central Post-Stroke Pain; CBN = Cervico-Brachial Neuralgia; SFN = Small Fiber Neuropathy; TTH = Tension-Type Headache; PH = Paroxysmal Hemicrania.

INDICATIONS OF GABAPENTINOID PRESCRIPTION					
Painful neuropathies (41)	Headaches (4)	Jaw diseases (1)	ENT diseases (1)	Oral diseases (1)	Myalgias (1)
PPTN (28) Trigeminal neuralgia (5) CIPN (2) CPSP (2) Post-traumatic neuroma (1) CBN (1) Idiopathic SFN (1) Post-herpetic neuralgia (1)	TTH (3) PH (1)	Hamular bursitis (1)	Pharyngeal dystonia (1)	Inflammatory anemia glossitis (1)	Chronic myofascial pain syndrome (1)

Table II. Efficacy of gabapentinoid prescriptions in the patient cohort (n = 33 patients, after 13 patients were lost to follow-up and 3 were excluded from the analysis: 1 patient had a co-treatment with amitriptyline and 2 ceased treatment early because of severe untoward effects). PPTN = Painful Post-Traumatic Trigeminal Neuropathy; SFN = Small Fiber Neuropathy; CIPN = Chemotherapy-Induced Peripheral Neuropathy.

Total efficacy (n=10)	Partial efficacy (n=12)	No efficacy (n=10)	Aggravation (n=1)
PPTN (6) Cervico-brachial neuralgia (1) Paroxysmal hemicrania (1) Tension-type headache (1) Central Post-Stroke Pain (1)	PPTN (5) Trigeminal neuralgia (2) Post-traumatic neuroma (1) Central Post-Stroke Pain (1) Inflammatory glossitis (1) Tension-type headache (1) Pharyngeal dystonia (1)	PPTN (3) Trigeminal neuralgia (3) Myofascial pain syndrome (1) Tension-type headache (1) Idiopathic SFN (1) CIPN (1)	PPTN (1)

in September 2016. Since then, out of 249 patients treated for numerous painful orofacial conditions, 49 have received a gabapentinoid prescription. Of these 49 patients, there were 31 women and 18 men (F/M sex-ratio = 1.7, as compared to the overall sex ratio of 2.3). All patients were examined by the same practitioner, following a standardized interview and clinical examination, the results of which were transcribed verbatim on a specific case report form.

Patient diagnoses

Gabapentinoids were prescribed to prevent or mitigate peripheral and/or central sensitization in various (often painful) orofacial conditions.

The diagnoses that led to the prescription of gabapentinoids were painful neuropathies (41 patients), headaches (4 patients), jaw diseases (1 patient), ENT diseases (1 patient), oral diseases (1 patient) and myalgias (1 patient).

The different diagnoses are summarized in [Table I](#).

Treatment efficacy

Of the 49 patients who received from a gabapentinoid prescription, 13 were lost to follow-up and 3 were excluded from analysis (1 had a co-treatment with amitriptyline and 2 had severe untoward effects requiring early treatment discontinuation). Within the 33 remaining patients, the treatment was total effective in 10 patients, partially effective in 12 patients, ineffective in 10 patients, or worsened the symptomatology in 1 patient.

The efficacy data is summarized in [Table II](#).

Untoward effects

Various untoward effects were observed in 9 patients out of the 39 patients of the cohort that were followed-up (some patients had more than one untoward effect). One patient had a positive side effect, namely an improvement in sleep quality. Although the exact prevalence of untoward effects in the whole

Table III. Side effects of gabapentinoids in the patient cohort (n=10 patients out the 39 patients that were followed up).

GABAPENTINOID SIDE EFFECTS (n=10)	
Untoward effects (n=9)	Positive side effects (n=1)
Vertigo (3)	Improved sleep quality (1)
Drowsiness (3)	
Tremor (1)	
Heaviness in the legs (1)	
Burning sensations (1)	
Visual disturbances (1)	
Nausea (1)	
Tingling (1)	
Edema (1)	
Fatigue (1)	



Figure 3. A. Periapical radiograph of tooth 46 showing the overfilling on the mesial and distal roots near the mandibular canal (blue and orange arrows respectively). B. Coronal CBCT slice centered on the distal root of tooth 46 showing the overfilling extending into the mandibular canal (same orange arrow as in A.).

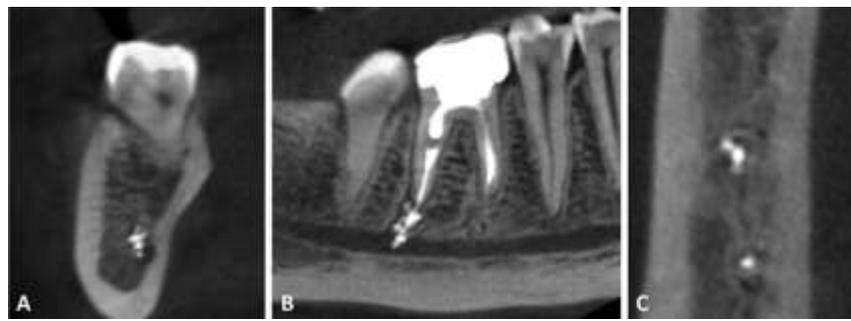


Figure 4. CBCT images at 1-year follow-up. Bone sclerosis can be observed on coronal (A), sagittal (B) and axial (C) slices.

patient cohort could not be properly assessed (as several patients were lost to follow-up, possibly because of such negative effects), at least 30 patients out of the 49 (61%) did not report any side effects at all.

The treatment untoward effects are summarized in Table III.

Clinical illustration

A 23-year-old healthy female patient was referred to the orofacial pain clinic for the diagnosis and management of severe facial pain following the endodontic retreatment of tooth 46.

Upon clinical interview she reported excruciating paroxysmal pain attacks (10 out of 10 pain intensity, lasting a few seconds, around 20 times a day) on the right hemiface, without any remission despite numerous opioid analgic drugs and antibiotic treatments.

Clinical examination revealed severe static and dynamic mechanical allodynia of the right mandibular nerve region. Periapical radiograph objectified an overfilling of both the mesial and distal roots of tooth 46 impinging on the superior

aspect of the mandibular canal (Fig. 3A). A three-dimensional CBCT imaging confirmed the extrusion of the filling material within the mandibular canal (Fig. 3B), thus leading to the diagnosis of Painful Post-Traumatic Trigeminal Neuropathy (PPTN) (based on the criteria of Benoliel *et al.* [10]) secondary to inferior alveolar nerve axonotmesis resulting from the chemical and mechanical irritation of the filling material [11].

Considering the hyperalgesic painful neuropathy and the location of the overfilling, surgical removal of the filling material was ruled out and pregabalin was prescribed at a dose of 150 mg/day (50 mg t.i.d) for pharmacological management of the painful neuropathy. The treatment was well tolerated, and the dose was titrated up to 450 mg/day, allowing complete pain relief (and an important patient-reported increase in quality of life).

Complete tapering of the drug was obtained after 6 months and prosthodontic rehabilitation of tooth 46 was pursued. The 1-year control CBCT (Fig. 4) shows complete bone healing with residual bone sclerosis (a common finding after inferior alveolar nerve injury, see reference [12] for details).

Discussion

Gabapentinoids for neuropathic pain treatment

There is ample evidence to recommend the use of gabapentin and pregabalin for the management of neuropathic pain in many painful neuropathic conditions, as confirmed by relevant Cochrane systematic reviews (in 2017 [13] and 2019 [14] respectively). In the 2010 European Federation of Neurological Societies guidelines on the pharmacological treatment of neuropathic pain, both gabapentinoids had level A evidence of their efficacy for diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain, recommending their prescription as first line treatments in all these conditions [4]. Concerning post-surgery/post-traumatic neuropathic pain, there is less data available but gabapentinoids are still recommended in association or in place of tricyclic antidepressants (such as amitriptyline) as first line treatments [4]. More recently, the transparency committee of the French Health Authority (Haute Autorité de Santé) has reaffirmed the important added medical value of pregabalin (in 2017 [1]) and gabapentin (in 2018 [2]) in these indications.

Toxicity and potential harmfulness of gabapentinoids

In 2016, the French National Drug Safety Agency issued a safety notice regarding the prescription of pregabalin, especially in patients with a history of drug abuse. Indeed, since 2010, there have been reports in France of cases of abuse and dependence to pregabalin, which led to the instauration in 2013 of a national surveillance [15].

In the United States, there have been numerous reports of opioid overdose-related deaths that could have been favored by co-prescription of a gabapentinoid [16]. In 2017, Gomes *et al.* showed in a population-based nested case-control study that concomitant gabapentin and opioid exposure was associated with a 49% higher risk of dying from an opioid overdose [3]. This risk is likely linked to cumulative depressing effects on the central respiratory centers.

All in all, there is reason for concern and caution when co-prescribing gabapentinoids and opioids [3,16], but one should keep in mind that the analgesic and anti-hyperalgesic effects of gabapentinoids will preclude the need for opioids as means of pain relief, and thus mitigate such increased risk of mortality.

Specificities of the orofacial region

Painful conditions affecting the cephalic region (and more importantly the orofacial region) differ from their somatic counterparts from pathophysiological, clinical, therapeutic and prognostic standpoints. This is mostly due to the specificities of trigeminal nociception, the neurophysiological substrate of orofacial pain [5,17]. For instance, significant differences in peripheral nerve ultrastructure have been shown between trigeminal and spinal nerves in animal models

[18,19] that translate to differences in neuropathic pain phenotype and treatment efficacy in humans [20]. Consequently, and quite unfortunately, there is little focus on trigeminal neuropathies in the relevant clinical guidelines [4,9,21] with the exception of trigeminal neuralgia. Furthermore, there is still much debate on the precise diagnostic criteria of many neuropathic or nociceptive orofacial painful conditions. Hopefully, the advent of the International Classification of Orofacial Pain (ICOP) will help clarify this issue [22].

Gabapentinoids in oral surgery and oral medicine practice

Oral surgeons are the prime oral cavity specialists, trained to treat both dental and medical diseases affecting this region. The focus and expertise in Oral Medicine is quintessential, especially considering the unfortunate lack of significant focus on oral diseases in other relevant medical specialties [23]. Painful orofacial conditions typically fall within the scope of the Oral surgeon, both in terms of diagnosis and treatment, usually in collaboration with other medical specialists (ENT surgeons, neurologists, neurosurgeons...). As in the cohort presented herein, painful neuropathies represent the vast majority of cases (84% of patients treated with gabapentinoids [41 cases out of 49] and 25% of all patients from the orofacial pain clinic) and are a frequent occurrence in Oral Surgery practice. For instance, painful post-traumatic trigeminal neuropathies can result from third molar removal [10], cystic enucleations [10] or implant placement [24] and will require early efficient treatment to provide adequate pain relief (as in the previously presented illustrative case report) and prevent pain chronification (secondary to central sensitization). To this end, gabapentinoids are very useful and efficient drugs, of easy manipulation, that every Oral surgeon should know how to prescribe and follow-up. These drugs can be integrated in a global treatment algorithm (based on the relevant literature [4,9] and our personal experience) that is summarized in Figure 5.

Conclusion

Gabapentinoids are potent-often well-tolerated-drugs, of interest for the management of oral painful neuropathies and other painful conditions (such as headaches or myalgias) that fall within the scope of Oral Surgery and Oral Medicine practice. Although there is reason for concern and caution when co-prescribing gabapentinoids with opioids, when used adequately these drugs are still a safe and sound tool in the pharmacological armamentarium of the Oral Surgeon.

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

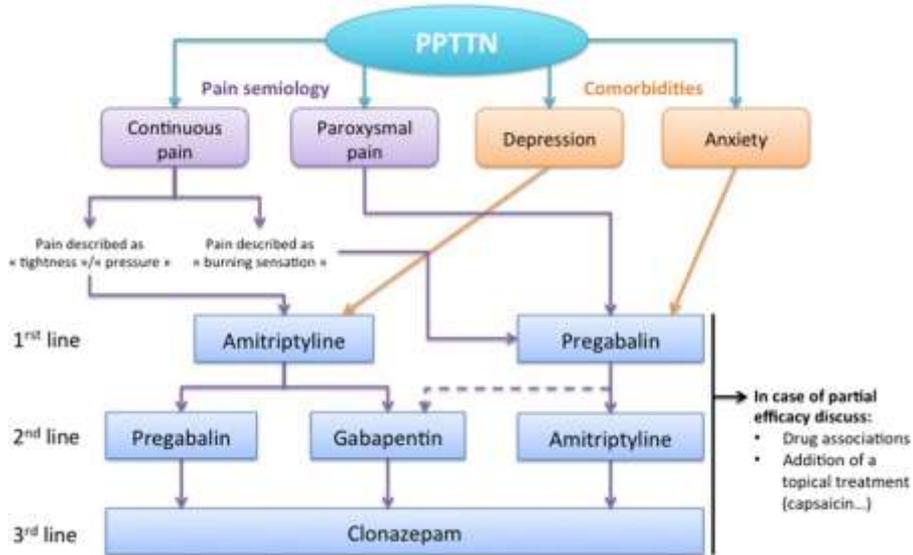


Figure 5. Therapeutic algorithm for the pharmacological treatment of Painful Post-Traumatic Trigeminal Neuropathy (PPTN). Algorithm developed according to the patient cohort and to French [9] and European guidelines [4].

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2 : Revue systématique de la littérature scientifique

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² Sulukdjian et al., « Gabapentinoid prescription in oral medicine and oral surgery practice. Part II, A systematic scoping review of the literature ».

Literature Review

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

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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), anxiety (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 anxiety, 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);

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- 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® and Cochrane® 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® 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

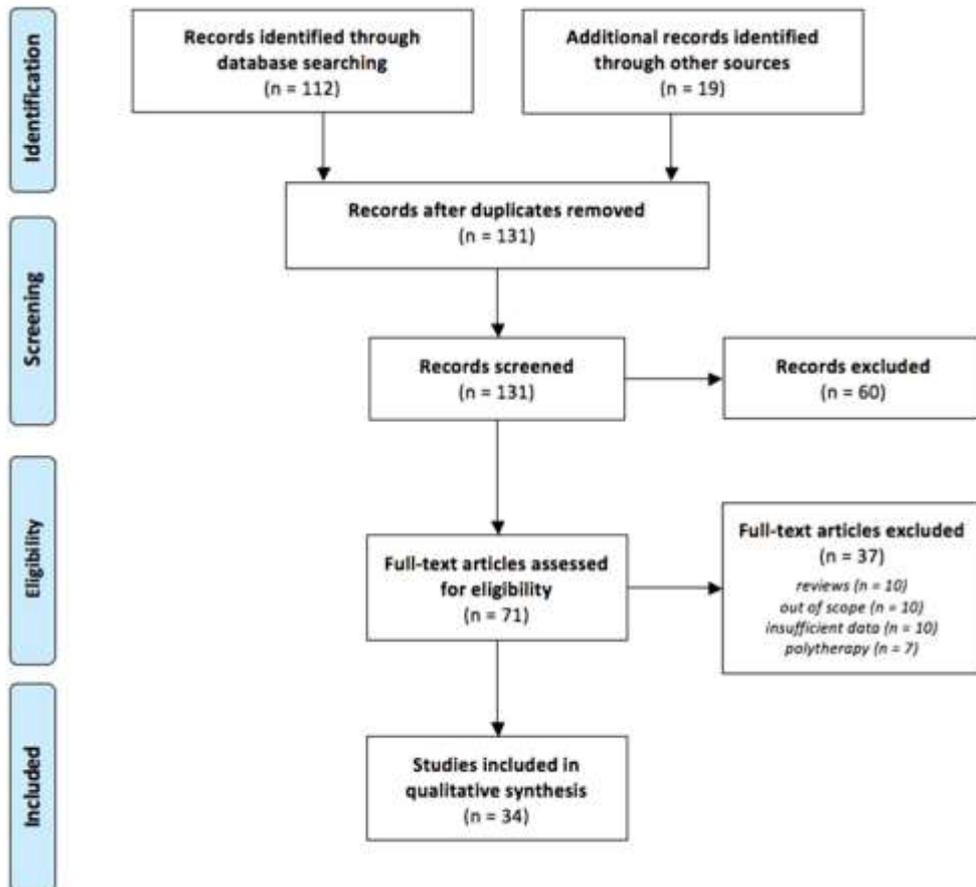


Fig. 1. Study flowchart (following PRISMA-ScR guidelines).

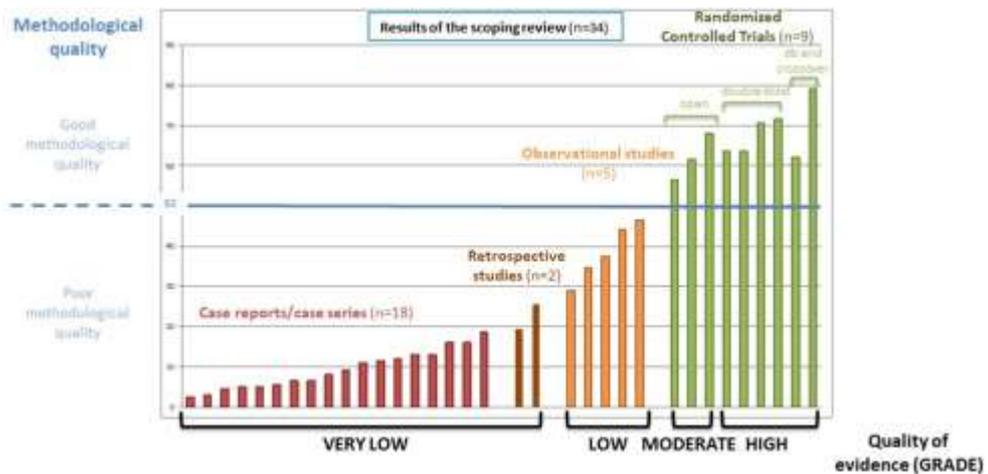


Fig. 2. Distribution of selected studies following the scoping review (db = double-blind).

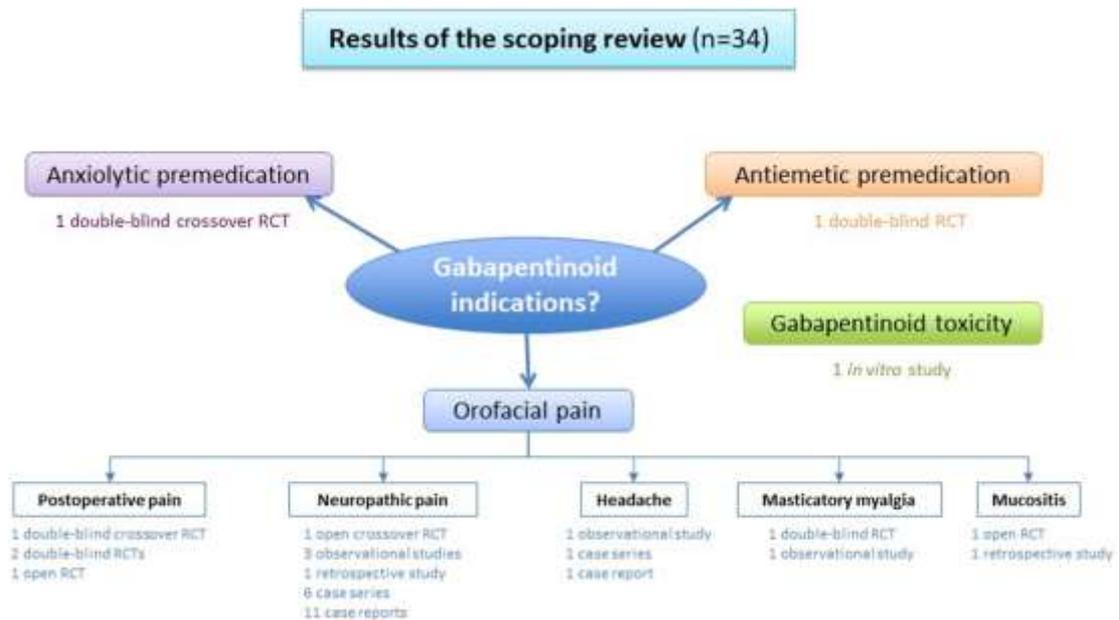


Fig. 3. Distribution of selected studies sorted by indication (N.B: 1 case series in common for both neuropathic pain and headache).

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 ± 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
Postoperative pain						
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
Neuropathic pain – Trigeminal neuralgias						
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
Neuropathic pain – Glossopharyngeal neuralgias						
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
Neuropathic pain – Painful post-traumatic trigeminal neuropathies						
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
Neuropathic pain – Other painful neuropathies						
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)
Headaches						
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
Masticatory myalgias						
Kimos <i>et al.</i> [41]	Double-blind RCT	63.5/100	50	<i>Chronic (>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)
Mucositis						
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.

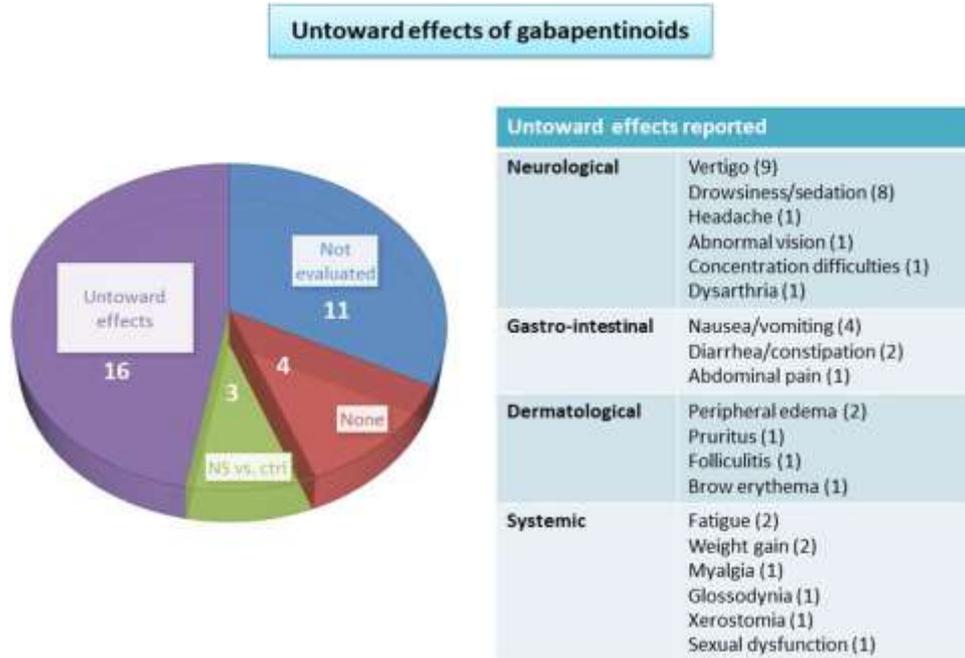


Fig. 4. Untoward effects of gabapentinoids reported in the scoping review.

Table IV. Scoping review results – Gabapentinoid toxicity.

Study	Study type	Methodological score	Number of patients	Indication	Gabapentinoid	Conclusion
Al-Musawi et al. [45]	In vitro study	N/A	N/A	Effect of topical gabapentin on oral and skin keratinocytes (monolayer models)	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].

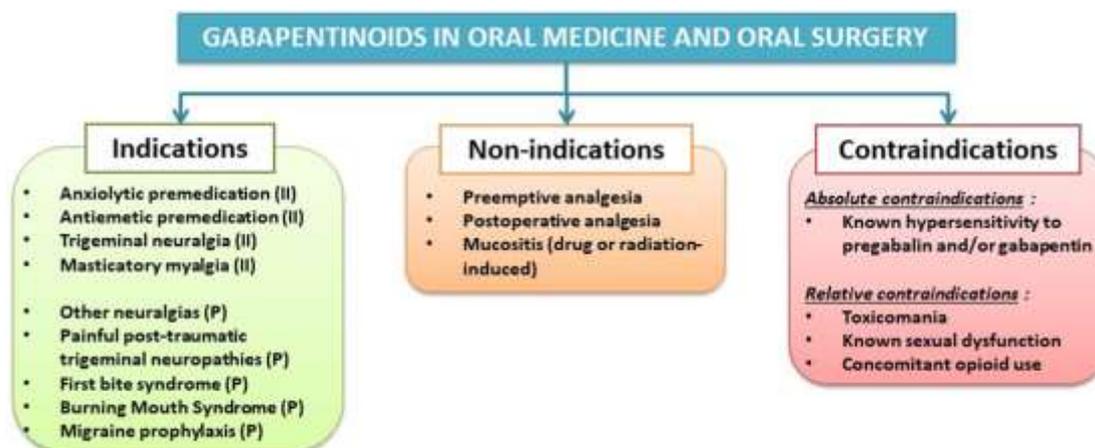


Fig. 5. Conclusions of the scoping review: indications, non-indications and contraindications of gabapentinoids in Oral Medicine and Oral Surgery (II = secondary indication, P = potential indication).

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 orabase 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.

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3 : Discussion

Le recours aux gabapentinoïdes comme traitements spécifiques des douleurs neuropathiques est scientifiquement reconnue et documentée, notamment par deux revues systématiques Cochrane (en 2017 et 2019).^{3 4} Cet arsenal thérapeutique que les spécialistes de la douleur connaissent bien, n'a cependant reçu à ce jour qu'une attention faible quant à son application à la médecine et chirurgie orale, vraisemblablement par manque de formation et d'expérience pratique dans ce contexte.

3.1 Rappels historiques

Les gabapentinoïdes constituent un groupe de médicaments dont les chefs de file, la gabapentine puis la prégabaline, ont reçu une Autorisation de mise sur le marché en France (AMM), respectivement le 12/10/1994 sous le nom commercial Neurontin et le 06/07/2004 sous le nom commercial Lyrica.

La gabapentine a été décrite pour la première fois en 1975 par le laboratoire Parke-Davis (devenu Pfizer depuis) et approuvée en 1993 comme traitement anti-épileptique au Royaume-Uni. La prégabaline a été synthétisée par l'équipe du chimiste R.B. Silverman à la Northwestern University d'Evanston dans l'Illinois en 1990. Tout d'abord testé comme anti-épileptique chez Parke-Davis, son indication s'est ensuite étendue aux douleurs neuropathiques diabétiques, puis à la névralgie post-herpétique. En 2005, l'Europe a approuvé son utilisation dans le traitement du trouble anxieux généralisé.

3.2 Pharmacologie

3.2.1 Structure chimique

La gabapentine tout comme la prégabaline, sont des 3-substitués, dérivés de l'Acide γ -aminobutyrique (GABA). La première est un dérivé de GABA avec un cyclohexane en position 3 : 3-cyclohexyl-GABA ; alors que la prégabaline est un dérivé avec un isobutyl en position 3 : (S)-(+)-3-isobutyl-GABA. De par leurs structures chimiques respectives, elles sont donc toutes deux analogues structurels du GABA.

³ Wiffen et al., « Gabapentin for chronic neuropathic pain in adults ».

⁴ Derry et al., « Pregabalin for neuropathic pain in adults ».

3.2.2 Pharmacocinétique

La forte proximité structurale sur le plan chimique avec certains acides aminés comme la L-leucine et la L-isoleucine leur permet d'être absorbée au niveau intestinal et au niveau de la barrière hémato-encéphalique par le même transporteur d'acides aminés.

La biodisponibilité par voie orale de la gabapentine est d'environ 80 % et celle de la prégabaline de 90 %.

Que ce soit la gabapentine ou la prégabaline, aucune des deux molécules ne subit de métabolisme majeur (expliquant l'absence d'interactions médicamenteuses) et toutes deux sont éliminées par voie rénale.

Leurs demi-vies sont de 5 à 7 heures pour la gabapentine et de 6,3 heures pour la prégabaline. Il est intéressant de noter que dans le résumé des caractéristiques de produit dans le eVIDAL® il est proposé une prescription en 2 prises par jour, insuffisante d'après notre expérience, certains patients ayant des recrudescences douloureuses dans l'intervalle entre les 2 prises (disparaissant lors du passage à 3 prises par jour sans augmentation de la dose totale).

3.2.3 Pharmacodynamie

Bien que très proches du GABA, ces analogues ont un effet pharmacologique indépendant des récepteurs GABAergiques. En effet, ils sont des ligands de haute affinité des sous-unités $\alpha_2\delta$ des canaux calciques voltage-dépendants neuronaux. Cette liaison entraîne un blocage de la libération (calcium-dépendante) des neurotransmetteurs excitateurs (glutamate, noradrénaline, substance P...). Il en résulte une diminution de l'excitabilité neuronale et un effet anti-hyperalgésique central.

3.3 Toxicité des gabapentinoïdes

Bien que les gabapentinoïdes constituent une famille thérapeutique très sûre, avec un service médical rendu important, des cas de mésusage ont été rapportés à partir de 2010 et ont conduit l'ANSM à surveiller ces médicaments dès 2013, puis à publier une notice de sécurité en 2016.⁷

Aux Etats-Unis, la prise concomitante d'opiacés et de gabapentinoïdes a fait l'objet en 2017 d'un article de Gomes et al. décrivant une augmentation de près de 50 % du risque d'overdose et de mort par détresse respiratoire en cas d'association.⁸

⁷ Agence nationale de sécurité du médicament et des produits de santé, « Risques d'abus, de mésusage et de pharmacodépendance liés à l'utilisation de la prégabaline (Lyrica et génériques) ».

⁸ Gomes et al., « Gabapentin, opioids, and the risk of opioid-related death : a population-based nested case-control study ».

Le mésusage des gabapentinoïdes et leur détournement à des fins récréatives est en effet une problématique nouvelle et grandissante. Un bulletin de l'Association de Centres d'addictovigilance du 11 septembre 2019 mentionne une augmentation de 6,8 % du nombre d'ordonnances falsifiées mentionnant la prégabaline.¹⁰ Une revue systématique de 2015¹² rapporte que la prévalence d'un mésusage de gabapentine est de 1 % dans la population générale. Cependant, il passe à 40-65 % chez les individus présentant une prescription et entre 15 et 22 % chez les consommateurs abusifs d'opioïdes. Ces mésusages de gabapentine ont été principalement à but récréatif, puis d'automédication, ou de tentative de suicide et ce, avec une consommation seule, ou associée à des opioïdes, des benzodiazépines et/ou de l'alcool. Dans la plupart des cas, les mésusages étaient rapportés chez des individus ayant des antécédents de consommation de stupéfiants.

Une analyse de 2016 de la base de données de l'European Medicines Agency's EudraVigilance (base de données des effets indésirables suspectés des médicaments), rapporte que la prégabaline et la gabapentine auraient respectivement été associées avec 7639 et 4301 signalements de réactions indésirables de mésusage, abus et dépendance et que la fréquence de signalisations augmente avec le temps. Il y est également mentionné que la plupart des individus concernés étaient des femmes adultes.¹⁴

Dans une revue systématique plus récente de 2017, les auteurs rapportent une prévalence de mésusages des gabapentinoïdes dans la population générale de 1,6 % et de 3 à 68 % chez les consommateurs abusifs d'opioïdes.¹⁷ 11 940 cas d'abus de gabapentinoïdes ont été rapportés entre 2004 et 2015, avec une augmentation de plus de 75 % depuis 2012.

La Food and Drug Administration (FDA) des Etats-Unis a émis en décembre 2019 un bulletin d'alerte de sécurité concernant de sérieux problèmes respiratoires liés à des prises de gabapentinoïdes concomitantes avec des dépresseurs respiratoires ou chez des patients ayant des pathologies pulmonaires, notamment chez les patients atteints de bronchopneumopathie chronique obstructive (BPCO).¹⁸ Selon ce bulletin d'alerte, sur les 49 cas de difficultés respiratoires liées au gabapentinoïdes rapportés à la FDA entre 2012 et 2017, 12 sont décédés de dépression respiratoire, en ayant tous au moins un facteur de risque respiratoire. La FDA reprend également les résultats de plusieurs études cliniques randomisées en double aveugle contre placebo. Parmi elles, une a montré que la prise de

¹⁰ Centre d'addictovigilance de Toulouse, « Une crise des gabapentinoïdes ? »

¹² Smith, Havens, et Walsh, « Gabapentin misuse, abuse and diversion: a systematic review : gabapentin misuse and diversion review ».

¹⁴ Chiappini et Schifano, « A decade of gabapentinoid misuse: an analysis of the european medicines agency's 'suspected adverse drug reactions' database ».

¹⁷ Evoy, Morrison, et Saklad, « Abuse and misuse of pregabalin and gabapentin ».

¹⁸ Food and drug administration, « FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica cr) ».

prégabaline seule ou associée à un opioïde peut avoir une action dépressive sur la fonction respiratoire.²⁰ Une autre a démontré que la gabapentine seule augmente l'index d'apnée-hypopnée du sommeil chez les patients âgés.²² Trois études observationnelles ont montré une relation entre l'administration de gabapentinoïdes avant chirurgie et dépression respiratoire.²³

En avril 2019, le *BMJ* publiait un article mettant en relation la prise de gabapentinoïdes et l'augmentation du risque de comportement suicidaire, d'overdose et d'accident de la route ; tout en précisant que ce risque était plus important chez les jeunes de 15 à 24 ans du fait des surconsommations d'alcool ou de drogues²⁴. Les dossiers médicaux de 191 973 personnes traitées par de la prégabaline ou de la gabapentine ont été analysés. Cette analyse a montré que durant les périodes de traitement, les patients présentaient un risque augmenté de 26 % de décès par suicide, de 24 % d'overdose, de 22 % de blessure que ce soit à la tête ou au corps et de 13 % d'infraction au code de la route. En effet, 10 026 patients (5,2 %) ont eu un comportement suicidaire ou sont décédés par autolyse, 17 144 (8,9 %) ont fait une overdose, 12 070 (6,3 %) ont commis une infraction routière ou ont été victimes d'un accident de la route, 70 522 (36,7 %) ont été blessés. La prégabaline serait associée à un plus grand risque de survenue que la gabapentine. Il est cependant à noter que les potentielles interactions des gabapentinoïdes avec l'alcool ou les drogues n'ont pas été prises en compte dans cette analyse.

Les propriétés pharmacocinétiques légèrement différentes de la gabapentine et de la prégabaline pourraient expliquer un potentiel d'abus supérieur de la prégabaline par rapport à celui de la gabapentine.²⁵ En effet, l'absorption par voie orale de la prégabaline est plus rapide et les concentrations maximales sont atteintes en 1h, contre 3-4h pour la gabapentine, avec une meilleure biodisponibilité pour la prégabaline. De plus, l'absorption linéaire avec des concentrations plasmatiques proportionnelles à la dose administrée de la prégabaline ne connaît pas l'effet plateau de la gabapentine.

²⁰ Myhre, Diep, et Stubhaug, « Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanyl ».

²² Piovezan et al., « Gabapentin acutely increases the apnea-hypopnea index in older men : data from a randomized, double-blind, placebo-controlled study ».

²³ Weingarten et al., « Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty »; Cavalcante et al., « Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression »; Deljou et al., « Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration ».

²⁴ Molero et al., « Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime : population based cohort study in Sweden ».

²⁵ Centre d'addictovigilance de Toulouse, « Une crise des gabapentinoïdes ? »

En médecine de la douleur, quelle que soit la région anatomique concernée, il n'est pas rare que les patients aient recours à des opiacés lors de crise algiques. Le prescripteur a donc une obligation de précaution lors de la prescription simultanée de ces deux familles thérapeutiques. Celle-ci est heureusement rare car le traitement par gabapentinoïdes rend le recours aux opioïdes souvent inutile. Il doit mettre en garde le patient quand aux éventuels effets indésirables de ces médicaments, ainsi qu'au risque potentiel de dépression respiratoire à évaluer avant toute prescription.

3.4 Les gabapentinoïdes dans la pratique de la médecine et chirurgie orale

Comme énoncé précédemment, du fait des spécificités de la nociception trigéminal, les douleurs de la région orofaciale diffèrent de celles des régions périphériques. Malheureusement, ces spécificités n'ont été que peu étudiées et mise à part des études sur les névralgies trigéminales, les autres neuropathies trigéminales et leurs traitements sont encore méconnus. La revue systématique de la littérature souligne les besoins, en termes d'études, des différentes pathologies douloureuses de la région oro-faciale.

Le chirurgien oral, en sa qualité de spécialiste de la cavité orale, est très largement sollicité pour des pathologies douloureuses de cette région. La prise en charge de ces pathologies se fait avec collaboration avec les autres spécialistes de la douleur (neurologues, neurochirurgien, etc.). De plus, les douleurs neuropathiques trigéminales peuvent survenir suite à un acte tout à fait banal de leur exercice, allant de l'avulsion des troisièmes molaires, aux chirurgies implantaires ou aux énucléations kystiques... Pourtant, a contrario de leurs collègues algologues, peu de chirurgiens oraux sont à l'aise avec l'utilisation des gabapentinoïdes, molécules de choix dans le traitement de ces douleurs. Nous avons donc suggéré dans le second article, l'utilisation d'un algorithme intégrant ces molécules comme outil de prise en charge dans la pratique de la chirurgie orale.

Bien que futurs prescripteurs de ces molécules, les étudiants en chirurgie dentaire ne reçoivent à ce jour qu'une initiation à ces molécules, sans en connaître les mécanismes, modalités de prescription ni de surveillance. Pourtant, il serait intéressant d'intégrer à ce cursus – et ce au cours du deuxième cycle ou à minima du troisième cycle – une formation approfondie des futurs chirurgiens dentistes, spécialistes ou non en chirurgie orale. La douleur, quelle que soit sa forme et sa localisation est le principal motif de consultation des patients en médecine bucco-dentaire. Très largement prescripteurs d'antalgiques, nous ne pouvons passer à côté de cet arsenal thérapeutique disponible

et connu, uniquement par manque de formation et d'information. Il en va du devoir du chirurgien-dentiste, qui voyant son champ de compétences s'élargir, se doit d'élargir en conséquence ses connaissances.

Les publications retenues dans la revue systématique ont montré un effet partiel, subtotal ou total des gabapentinoïdes, malgré une nette hétérogénéité en terme de méthodologie, en traitement de diverses affections, quelles soient non douloureuses (prémédication anti-émétique avant chirurgie maxillaire), ou douloureuses (névralgies, neuropathies douloureuses trigéminales d'origine post-traumatique, céphalées ou myalgies).

Il est cependant important de noter qu'il existe un important biais de sélection de ces publications de par le fait qu'il est bien plus probable qu'un clinicien publie les effets positifs des gabapentinoïdes chez leurs patients plutôt que leur manque d'effet.

Les principales failles méthodologiques rencontrées dans les articles publiés sont : la taille des populations étudiées, l'absence de randomisation, l'absence d'insu et l'existence de traitements concomitants. Afin de confirmer les résultats de cette revue systématique, des études de plus grande qualité méthodologique seront nécessaires pour chaque indication.

Concernant les effets indésirables, ceux-ci – bien que non négligeables – sont connus de par l'utilisation des gabapentinoïdes en médecine générale. Il est important que le prescripteur les connaisse, en informe les patients, mais sans hésiter pour autant à les prescrire. En effet, le traitement des douleurs ne doit absolument pas être considéré comme un traitement de confort, puisque celles-ci peuvent engendrer de graves conséquences tant sur le plan physique que psychologique, allant même jusqu'à l'autolyse (« La douleur tue. »). Le prescripteur pourra notamment rassurer le patient du fait que la majorité de ces effets indésirables sont passagers, d'où l'importance de l'augmentation progressive des doses (titration prudente). De plus, un sevrage progressif jusqu'à l'arrêt complet du traitement sera systématiquement envisagé et proposé au patient dès que possible.

Conclusion

Les données obtenues à partir de la revue systématique de la littérature, suggèrent l'utilisation de gabapentinoïdes (gabapentine et prégabaline) comme traitement de seconde intention comme prémédication sédatrice, en prévention des nausées et vomissements post-opératoires, ainsi que dans la prise en charge de la névralgie du trijumeau et des myalgies masticatoires. En médecine et chirurgie orale, les autres indications sont : les névralgies crâniennes, les neuropathies trigéminales d'origine post-traumatiques, le « First-Bite Syndrome », le « Burning Mouth Syndrome », ainsi que la prévention des migraines en l'absence d'alternative thérapeutique.

L'expérience que nous en avons au sein de la consultation de douleurs chroniques oro-faciales à l'hôpital Bretonneau à Paris est en adéquation avec les données de la littérature et souligne l'intérêt parfois majeur de ces molécules dans le traitement de pathologies douloureuses chroniques extrêmement invalidantes.

D'autres études et revues seront nécessaires pour permettre l'élaboration de recommandations formalisées de prescription des gabapentinoïdes en médecine et chirurgie orale. D'ici là, la prescription des gabapentinoïdes – dont l'intérêt est indubitable en médecine et chirurgie orale – devra s'appuyer sur les données et l'expérience existante, telles que rapportées dans les publications issues de ce travail.

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Le Doyen Louis MAMAN

Les gabapentinoïdes en médecine et chirurgie orale

Résumé :

Les gabapentinoïdes, la prégabaline et la gabapentine, sont des inhibiteurs neuronaux des canaux calciques voltage-dépendants principalement prescrits pour le traitement de l'épilepsie partielle et des douleurs neuropathiques. Bien que leur efficacité en tant que traitements de première ligne pour les neuropathies douloureuses (et plusieurs pathologies douloureuses non neuropathiques) soit bien établie dans la pratique médicale générale, leur efficacité et leur prescription en médecine et chirurgie orale ont jusqu'à présent reçu peu d'attention. Ce travail a eu pour objectif de présenter l'expérience de l'utilisation des gabapentinoïdes au sein d'une consultation « douleurs chroniques oro-faciales » dans un hôpital parisien puis, par une revue systématique de la littérature scientifique, de définir plus précisément les indications, non-indications et contre-indications de ces médicaments dans l'état actuel des connaissances scientifiques.

Discipline :

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Mots clés français (fMeSH et Rameau) :

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