

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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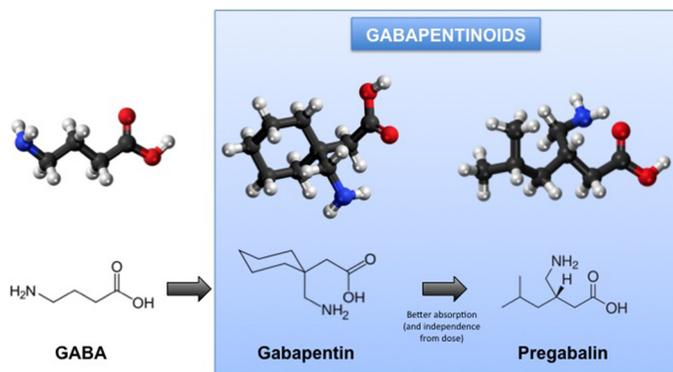


Figure 1. Chemical structure of gabapentinoids. The evolution of their chemical structure from GABA is shown (black arrows). (All images are of public domain or under creative commons license CC BY-SA 4.0.)

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)	

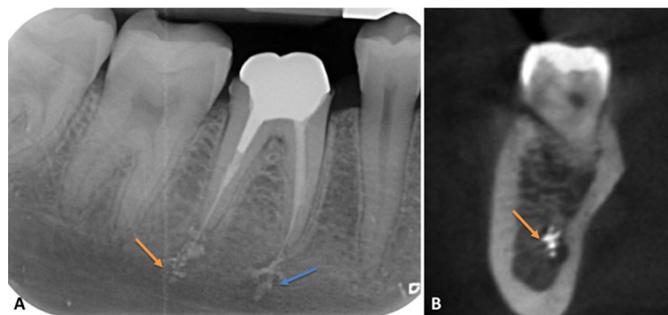


Figure 3. A. Periapical radiograph of tooth 46 showing the overfilling on the mesial and distal roots near the mandibular canal (blue and orange arrows respectively). B. Coronal CBCT slice centered on the distal root of tooth 46 showing the overfilling extending into the mandibular canal (same orange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

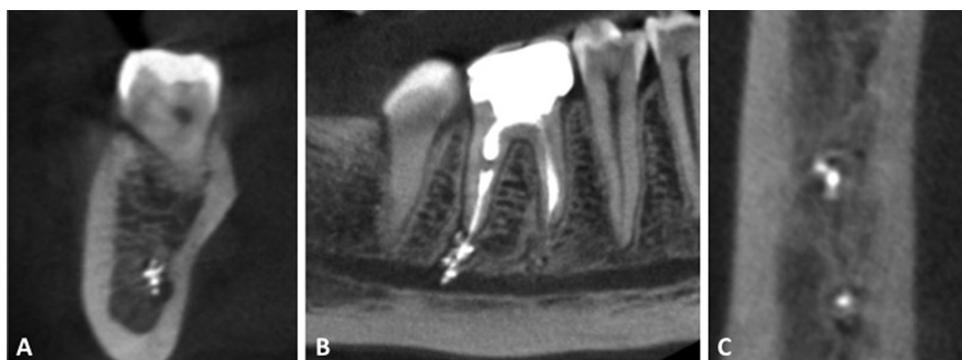


Figure 4. CBCT images at 1-year follow-up. Bone sclerosis can be observed on coronal (A), sagittal (B) and axial (C) slices.

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 analgesic 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.

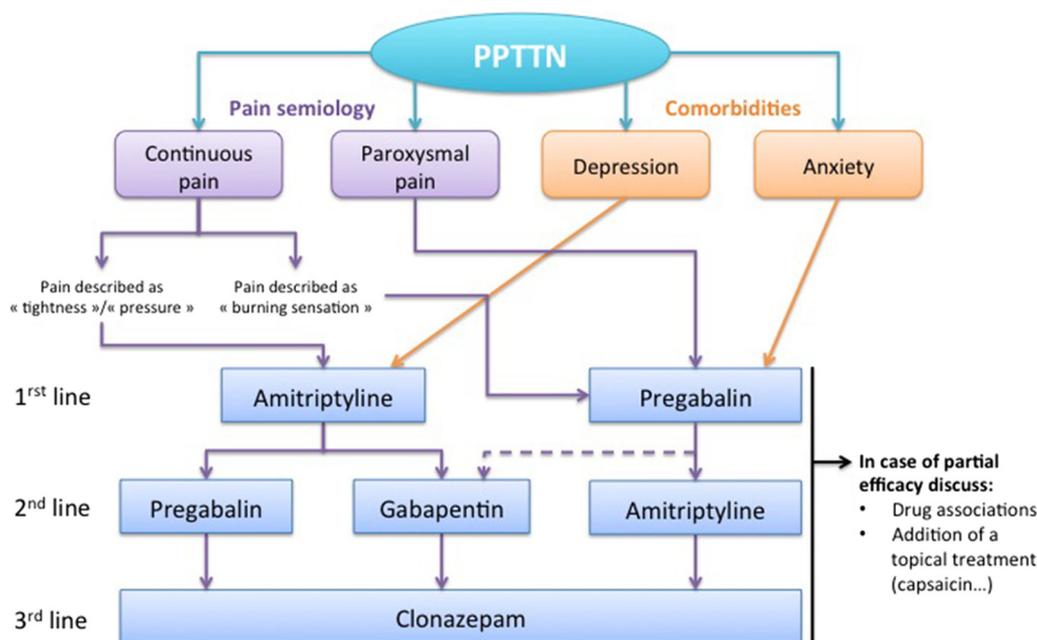


Figure 5. Therapeutic algorithm for the pharmacological treatment of Painful Post-Traumatic Trigeminal Neuropathy (PPTN). Algorithm developed according to the patient cohort and to French [9] and European guidelines [4].

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
- Haute Autorité de Santé – Commission de Transparence – Avis du 18 avril 2018–gabapentine. Available at: https://has-sante.fr/jcms/c_2848081/fr/neurontin
- 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 [Article 28-290-C-10].
- 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.
- 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.
- Kremer M, Salvat E, Muller A, *et al.* Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. *Neuroscience* 2016;338:183–206.
- Martinez V, Attal N, Bouhassira D, *et al.* Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecine ambulatoire. *Recommandations de pratique clinique de la SFETD. Douleurs* 2010;11:3–21.
- Benoliel R, Kahn J, Eliav E. Peripheral painful traumatic trigeminal neuropathies. *Oral Dis* 2012;18:317–332.
- Alonso-Ezpeleta O, Martin PJ, Lopez-Lopez J, *et al.* Pregabalin in the treatment of inferior alveolar nerve paraesthesias following overfilling of endodontic sealer. *J Clin Exp Dent* 2014;6:e197–e202.
- Ido-Yonemochi H, Yamada Y, Yoshikawa H, Seo K. Locally produced BDNF promotes sclerotic change in alveolar bone after nerve injury. *PLoS ONE* 2017;12:e0169201.
- Wiffen PJ, Derry S, Bell RF, *et al.* Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2017;6:CD007938.
- Derry S, Bell RF, Straube S, *et al.* Pregabalin for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2019;1:CD007076.
- 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) – Point d’Information 30/06/2016. Available at: <https://www.anm.sante.fr/S-informer/points-d-information-Points-d-information/Risques-d-abus-de-mesusage-et-de-pharmacodependance-lies-a-l-utilisation-de-la-pregabaline-Lyrica-et-generiques-Point-d-Information>
- Peckham AM, Evoy KE, Oschs L, Covvey JR. Gabapentin for off-label use: Evidence-based or cause for concern? *Substance Abuse: Research and Treatment* 2018;12:1–8.
- Dallel R, Villanueva L, Woda A, *et al.* Neurobiologie de la douleur trigéminal. *Médecine/Sciences* 2003;19:567–574.
- Tal M, Devor M. Ectopic discharge in injured nerves: comparison of trigeminal and somatic afferents. *Brain Res.* 1992;579:148–151.
- Moreau N, Dieb W, Mauborgne A, *et al.* Hedgehog pathway-mediated vascular alterations following trigeminal nerve injury. *J Dent Res.* 2017;96:450–457.

20. Hargreaves KM. Orofacial pain. *Pain* 2011;152(3):S25–S32.
21. Finnerup NB, Haroutounian S, Kamerman P, *et al.* Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 2016;157:1599–1606.
22. International Classification of Orofacial Pain version 1 beta. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=2ahUKewjVyICI7cvnAhUhyIUKHfYDFgQFjAAegQIARAB&url=https%3A%2F%2Fwww.ihf-headache.org%2Fbinary_data%2F3468_the-international-oro-facial-pain-classification-committee-icop-1-beta-for-review.pdf&usq=A0vVaw2raaYKKDsfl6wQA73Pg422
23. Moreau N. Rethinking the scope of oral medicine/oral surgery practice: 7 unusual must-know conditions for the oral surgeon. *J Oral Med Oral Surg.* 2019;25:24.
24. Sulukdjian A, Nguyen D, Chanlon A, *et al.* Neuropathies post-implantaires : diagnostic et prise en charge. *Implant* 2019;25:1–8.