




INVITED REVIEW

## Pharmacological management of orofacial pain – a clinician's guide

M.V. Clark<sup>1,2</sup> , C.C. Donnell<sup>2</sup> , J. Durham<sup>1,2</sup>  & R. Balasubramaniam<sup>3</sup>

<sup>1</sup>School of Dental Sciences, Newcastle University, Newcastle upon Tyne, UK

<sup>2</sup>Newcastle Dental Hospital, Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, UK

<sup>3</sup>UWA Dental School, The University of Western Australia, Perth, WA, Australia

**Key words:**

indications, medical management, medications, orofacial pain

**Correspondence to:**

MV Clark  
School of Dental Sciences  
Framlington Place  
Newcastle upon Tyne NE2 4BW  
UK  
Tel.: +44 191 282 0603

email: megan.clark12@nhs.net

**Accepted:** 6 July 2020

doi:10.1111/ors.12542

[Correction added on 14 September 2020 after first online publication: The author affiliation details for R. Balasubramaniam has been amended from Newcastle upon Tyne, UK to Perth, Australia.]

### Abstract

Managing orofacial pain can be a daunting prospect for the dentally qualified clinician. This article aims to alleviate some of these concerns by providing guidance when pharmacological intervention may be recommended, alongside their dosing regimens and contraindications. The medications discussed include amitriptyline, nortriptyline, gabapentin, pregabalin, duloxetine, carbamazepine, oxcarbazepine, clonazepam, capsaicin, baclofen, lamotrigine, alpha-lipoic acid, lidocaine hydrochloride and benzydamine hydrochloride. Management of orofacial pain is complex and, hence, often requires the input of specialists in secondary care. While the scope of this guide is aimed chiefly at pharmacological management by secondary care dental prescribers, a holistic approach encompassing all biopsychosocial factors is encouraged. The main take home points have been summarised in a table, aimed for use as a 'quick reference guide' during clinic sessions. Other contemporaneous prescribing guides and guidelines should always be used in conjunction with this article as licensing and dosing regimens of medications can be different around the world.

### Introduction

The International Association for the Study of Pain (IASP) describe pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.<sup>1</sup> There are different mechanisms for pain and within the orofacial region the most common include: (i) nociceptive pain which is typically odontogenic and musculoskeletal in origin, (ii) neuropathic pain such as trigeminal neuralgia and painful trigeminal neuropathy and (iii) nociplastic or centralised pain (fibromyalgia being the classic example of a centralised pain state) that presents as a continuum and can mimic both nociceptive and neuropathic pain.<sup>2</sup>

'Acute' pain is short term and likely to be associated with a *potential* for tissue damage. Following an

ankle sprain, for example, you are more likely to feel pain associated with the swelling and bruising. This is 'acute' and tends to dissipate over the next few weeks to months. Following the healing process, the affected region no longer requires protecting. 'Chronic' or 'persistent' pain are interchangeable terms with the same meaning. Persistent pain tends to last longer than would be expected for pain of an acute nature. Unlike acute pain, however, it refers more to the changing elements of an individual's nervous system rather than actual tissue damage. Persistent pain is as if a volume control on our 'pain system' had been turned up, like a television stuck on 'loud'. It is important to note that the volume *can* be turned down but will require time and effort and, most importantly, patience.<sup>3</sup>

A patient experiencing orofacial pain is more like an athlete rehabilitating from injury than an ill

patient waiting for a cure. Athletes get back to their sport little by little, following a carefully calculated plan, to ensure they don't overdo it at the start. Family and work commitments mean that like athletes, patients can't wait until they feel entirely better to get 'back in the game'. The goal, as with pharmacological management in orofacial pain, is to restore function to a level that means they can resume their normal, everyday activities.<sup>4</sup>

Nociceptive pain is due to the activation of nociceptors from actual or threatened damage to non-neural tissue.<sup>1</sup> This is in contrast to neuropathic pain where there is an abnormally functioning somatosensory nervous system.<sup>1</sup> Musculoskeletal pain in the orofacial region is the most common origin of orofacial pain following odontogenic pain and, hence, temporomandibular disorders (TMD) are the most common cause of this pain after dental pain.<sup>5</sup>

Nociplastic, a term derived from 'nociceptive plasticity', was introduced to reflect a change in our understanding of the *function* of nociceptive pathways.<sup>6</sup> Nociplastic pain occurs when there is no evidence of actual or threatened tissue damage, such as that seen in nociceptive pain, yet peripheral nociceptors are still activated resulting in perceived pain. The somatosensory system shows no evidence of either a lesion or disease which could otherwise explain activation of these nociceptors.<sup>1</sup> Patients can therefore suffer from a combination of both nociceptive and nociplastic pain.<sup>1,7</sup> Studies have highlighted changes in cerebral activation and an alteration in pain transmission with hyperresponsiveness of the

central nervous system (CNS) in conditions such as fibromyalgia.<sup>8</sup> This sensitisation of the CNS and changes in cerebral connectivity are also highlighted in other chronic pain conditions such as chronic back pain and osteoarthritis.<sup>7,9</sup>

Neuropathic pain is defined as pain 'caused by a lesion or disease of the somatosensory nervous system', by the IASP.<sup>1</sup> Broadly speaking, neuropathic pain can be managed with either a tricyclic antidepressant (TCA) or antiepileptic medication.<sup>10</sup> Neuropathic pain differs from odontogenic pain in that odontogenic pain is often acute and inflammatory in nature, whereas neuropathic pain is thought to involve some form of sensitisation of the CNS; activity in C-fibres is thought to be necessary to evoke the central sensitisation mechanisms.<sup>11,12</sup> Peripheral and central mechanisms of orofacial pain transmission exist via small-diameter Aδ-fibres and unmyelinated C-fibres which process orofacial nociception across orofacial skin, mucous membrane and muscles as well as the teeth, tongue and temporomandibular joint (Figs 1 and 2).<sup>13</sup> Common neuropathic orofacial pain conditions include burning mouth syndrome (BMS), trigeminal neuralgia and persistent idiopathic dentoalveolar pain.<sup>14</sup>

All neuropathic pain, with the exception of trigeminal neuralgia, may be initially managed with amitriptyline, duloxetine, gabapentin or pregabalin.<sup>15</sup> If the initial drug chosen is neither tolerated nor effective, it may then be changed to one of the others and so forth. Tramadol may be considered as an acute rescue remedy in specialist settings for

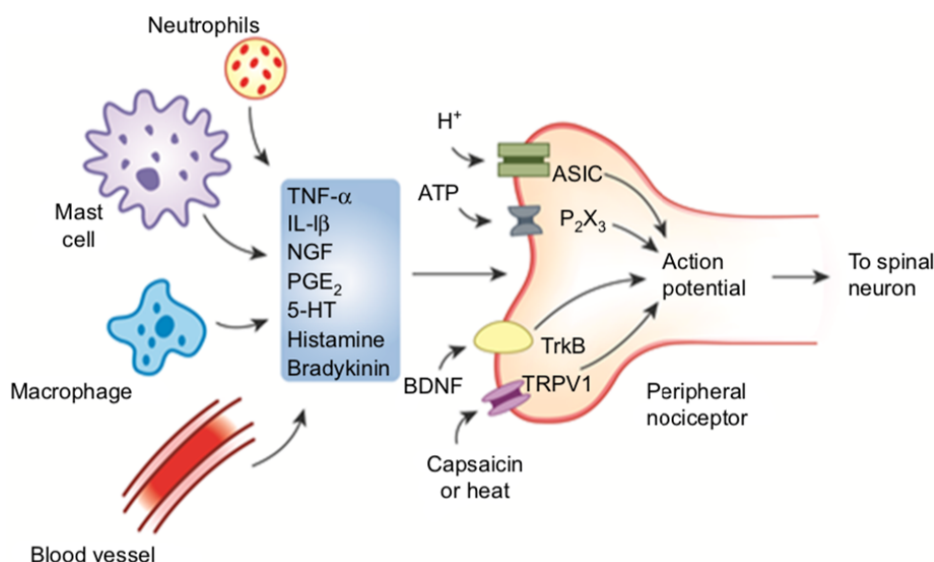
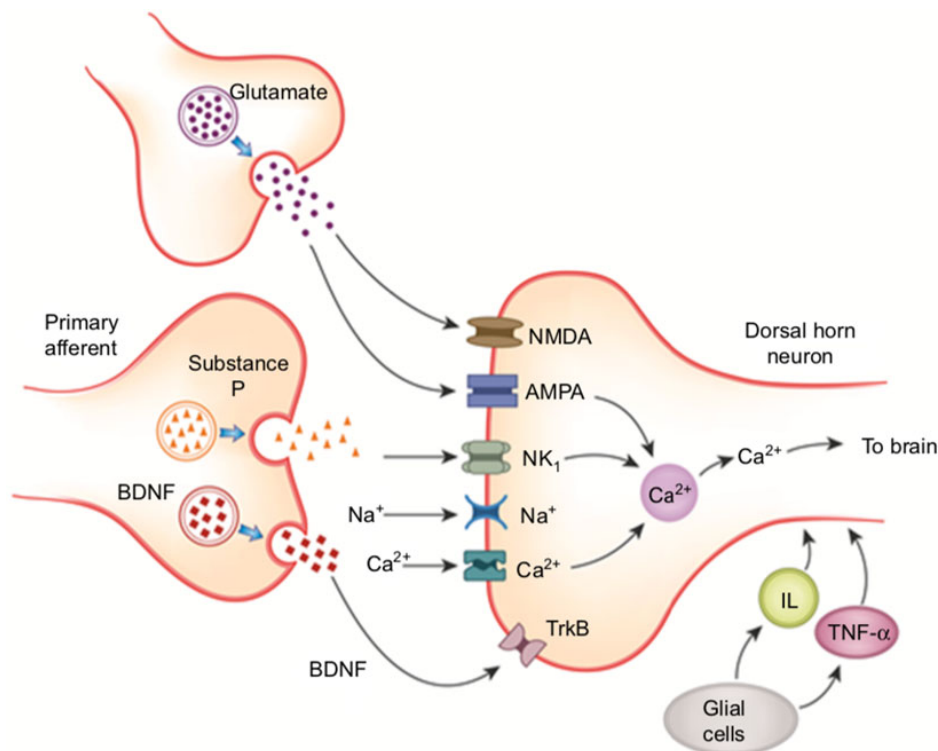


Figure 1 Peripheral sensitisation. Adapted from ref.<sup>116</sup> [Colour figure can be viewed at wileyonlinelibrary.com]



**Figure 2** Central sensitisation. Adapted from ref.<sup>116</sup> [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

short-term periods only due to the potential for dependency if, for example, waiting for a referral to specialist care, however, there is some continuing debate over its role.<sup>16</sup> Trigeminal neuralgia is primarily medically managed with carbamazepine, the only drug currently licensed in the United Kingdom (UK) for this condition, or neurosurgically.<sup>15,17</sup>

A Cochrane systematic review found multiple poor-quality studies regarding pharmacological management of orofacial pain conditions such as TMDs and BMS.<sup>5,18</sup> Traditionally, before a medication can be marketed within the UK, it has to be licensed for a particular condition. Therefore, prescribing for orofacial pain will often involve a medication which is unlicensed or 'off-label', that is, being prescribed to treat a condition for which it was not originally intended. In the UK, for instance, the Medicines and Healthcare products Regulatory Agency (MHRA) are responsible for regulating the licensing of medications and will issue a license if: clinical trials prove efficacy for that medication to be used in that particular condition; the adverse effects are acceptable; the medication meets safety and quality standards.<sup>19</sup>

While this article will describe dosing regimens and some of the important contraindications to pharmacological agents used to manage orofacial pain, it

should be noted that it is not a substitute for checking reference guides such as the British National Formulary (BNF) in the UK, or an appropriate alternative such as the Monthly Index of Medical Specialties (MIMS) as well as the appropriate manufacturer's instructions. Liaising with the patient's family physician or general medical practitioner (GP) is also recommended, as simply listing the full extent of contraindications, dosing guidance or potential interactions with other medications is outside the remit of this article.

Of the medications discussed in this article, in the UK, a National Health Service (NHS) prescription will only permit general dental practitioners to prescribe ibuprofen, paracetamol and carbamazepine, as per the Dental Practitioners Formulary on a FP10D form (GP14 in Scotland and WP10D in Wales).<sup>20</sup> Medications such as carbamazepine, for example, when prescribed for the management of orofacial pain, are being prescribed off-label and the patient needs to be informed of such. Clinicians prescribing off-label should be satisfied that when doing so, it is in the best interests of the patient's needs.<sup>21</sup> This should be noted in the clinical records, along with evidence of providing information on the risks and benefits of use, alternatives and possible adverse

effects. Medication information leaflets could be provided in the copy of the letter sent to the patient and adverse effects need to be noted at each review appointment. Prescribers in both primary and secondary care need to consider a number of factors when prescribing dental therapeutics, such as remaining mindful of other medications in a patient's history which may interact with the proposed therapy, as well as having an awareness of the side-effect profile of a medication they are prescribing. The large side-effect profile of some medications, including those prescribed 'off-label' for chronic pain, can lead to adverse effects which may interfere with patient acceptability and/or tolerability of a medication.<sup>22</sup> Medication tolerance, that is, the patient's diminished response to a medication following repeated use, should not be confused with medication tolerability, that is, the degree to which overt adverse effects can be tolerated by a patient.<sup>23</sup>

The article will discuss the main medications used in the management of orofacial pain, describing the pharmacology, relative and absolute contraindications along with the dosing regimens. These are then summarised in a two page quick reference guide (Table 1). While chiefly aimed at secondary care clinicians, it may also better inform primary care clinicians, enabling them to take home salient points about the medical management of orofacial pain conditions. Discussion will be limited to management of adult patients, as there are often different prescribing regimens for paediatric patients. While the dosing regimens discussed are based on UK prescribing guidelines, the aim is to provide a reference point for prescribing from the relevant guidelines in other countries, if outside the UK. From this point forward, all medications listed including description, dosing regimen, along with the relative and absolute contraindications are all based on the BNF, unless otherwise indicated.

### Simple analgesia for acute inflammation

The UK's National Institute for Health and Care Excellence's (NICE) guidelines for managing mild-to-moderate pain in adults states the first choice for managing acute pain should be paracetamol, stepping up the maximum dose of 1 g per day in four divided doses.<sup>24</sup> Following this, consideration could be given to a non-steroid anti-inflammatory analgesic drug (NSAID) such as ibuprofen, 400 mg three times a day up to a maximum of 2400 mg per day before then considering a combination of the two. In cases where a patient may be unable to take NSAIDs

then a weak opioid may be used such as codeine phosphate (60 mg every 4–6 h, with a maximum dose of 240 mg daily). It is worth noting that codeine phosphate in some countries such as the UK is a controlled drug: a Class B controlled drug under the Misuse of Drugs Act 1971 and a Schedule 2/5 under the Misuse of Drugs Regulations 2001.<sup>25</sup>

A 2013 Cochrane review suggests that a combination of analgesics may be more effective than either analgesic alone, at the same dose compared to placebo.<sup>26</sup> The example given was ibuprofen 200 with 500 mg paracetamol, or 400 mg ibuprofen with 1000 mg paracetamol – ensuring longer lasting analgesia and fewer adverse events compared to the placebo, and may therefore be worth considering combining the ingestion of both medications to increase analgesic efficacy.

It is important to ensure the full therapeutic and tolerated dose of a prescribed analgesic has been reached prior to switching or introducing a different medication; this aids assessment of the efficacy of the original medication used, and therefore assessment of its true effect.<sup>27</sup> Pain is a 'biologically complex phenomenon' and a rationale exists for combining medications with different mechanisms of action; cross-tapering of medications can be employed where the dose of the first medication is gradually decreased at the same time of the increase in the dose of the new medication.<sup>28,29</sup> Patients who present with persistent orofacial pain who do not respond to simple analgesics could then be considered for a trial of another class of medication such as TCA or antiepileptic medications.<sup>30</sup>

It would be worth enquiring as to the patient's current medication regimen, especially with regard to paracetamol, NSAIDs and codeine phosphate, as regular use of these acute pain relief medications can cause 'medication-overuse headache' and may be contributing to the overall pain picture (Table 2).<sup>31,32</sup> In addition to this, it may be noteworthy to record the patient's daily caffeine consumption, as caffeine has been shown to have a bidirectional relationship with acute pain. While medication-overuse headache and caffeine-associated headaches are diagnostically separate, excessive caffeine consumption, that is, more than 400 mg of caffeine per day for more than 2 weeks, can induce 'caffeine overuse headache', whereas a Cochrane Review in 2014 found that the addition of caffeine  $\geq 100$  mg (i.e. equivalent to a mug of coffee) to a standard dose of commonly used analgesics provided a better level of pain relief than simple analgesia alone.<sup>33</sup>

**Table 1** Pharmacological medications—quick reference guide

Medication	Indications	Mechanism of action	Standard dose regimen	Slow tapering dosing regime	Adverse effects	Absolute contraindications	Relative contraindications
<i>Amitriptyline</i> (tricyclic antidepressant)	TMDs, neuropathic pain, headache disorders	Non-selective monoamine reuptake inhibitor. Antihistaminergic activity. Blocks Na <sup>+</sup> , K <sup>+</sup> and Ca <sup>2+</sup> ion channels. Enhances GABA and NMDA antagonist	10–25 mg OD (pm) Step up to 25–50 mg OD in steps of 10–25 mg every 3–7 days	10 mg nocte Increase by 10 mg every 1–2 weeks Target dose range 30–70 mg	Drowsiness, xerostomia, blurred vision, increased ocular pressure, urinary retention	Heart block, after a myocardial infarction, arrhythmias, manic phase of bipolar disorder, known hypersensitivity	Diabetes, epilepsy, bipolar disorder, liver disease, hyperthyroidism, glaucoma, patients at risk of suicide. Care in elderly or cardiovascular disease. Caution with patients on SSRI/SNRI's
<i>Nortriptyline</i> (tricyclic antidepressant)	TMDs, neuropathic pain	Inhibits reuptake of noradrenaline. Blocks Na <sup>+</sup> , K <sup>+</sup> and Ca <sup>2+</sup> ion channels. Blocks NMDA, muscarinic cholinergic, H1-histaminergic, alpha-adrenergic receptors	10 mg OD (pm), can be increased gradually up to 50 mg daily	Titrate by 10 mg every 1–2 weeks	Drowsiness (although less than amitriptyline), xerostomia, increased appetite	Heart block, after a myocardial infarction, arrhythmias, manic phase of bipolar disorder, known hypersensitivity	Cardiac disease, diabetes, glaucoma, hyperthyroidism, liver disease. Care in elderly patients
<i>Gabapentin</i> (anticonvulsant, Class C Schedule 3 drug)	Neuropathic pain	Interacts with $\alpha 2\delta$ Ca <sup>2+</sup> channels, increases GABA synthesis and release.	Initially 300 mg OD day 1, 300 mg BD day 2, 300 mg TDS day 3, increase in steps of 300 mg every 2–3 days in divided doses up to a maximum of 3600 mg/day	Initially, 100 mg daily. Slowly titrate up over weeks rather than days to accommodate for side effects	Confusion, weight gain, xerostomia, constipation, diarrhoea, visual impairment, hypertension. Risk of substance misuse	Known hypersensitivity	Diabetes, psychotic illness, substance dependence, seizures, low body weight, pregnancy, elderly, compromised respiratory function, neurological disease

**Table 1** (Continued)

Medication	Indications	Mechanism of action	Standard dose regimen	Slow tapering dosing regime	Adverse effects	Absolute contraindications	Relative contraindications
<i>Pregabalin</i> (anticonvulsant, Class C Schedule 3 drug)	Neuropathic pain	Binds to Ca <sup>2+</sup> channels reducing calcium influx, therefore, releasing neurotransmitters, e.g. glutamate, substance P and noradrenaline	15 daily in 2–3 divided doses, increased after 3–7 days up to 300 mg daily in 2–3 divided doses. Further increase after 3–7 days up to 600 mg daily in 2–3 divided doses	Consider asymmetric doses, lower doses or a slower taper over several weeks as many patients won't tolerate a rapid regime	Confusion, weight gain, xerostomia, constipation, diarrhoea, visual impairment, hypertension. Risk of substance misuse	Known hypersensitivity	Congestive heart failure, history of substance dependence, pre-existing conditions which may precipitate encephalopathy
<i>Duloxetine</i> (SNRI)	Neuropathic pain	Inhibits reuptake of serotonin and noradrenaline and dopamine to a lesser extent.	20–30 mg OD, titrate slowly up to 60–90 mg daily as 30 mg BD or 60 mg OD, increase slowly over 4–8 weeks between increments	Expert-based anecdotal practice often indicates titration up to 60 mg twice daily	Nausea and vomiting, cardiovascular effects, hypertension, sexual dysfunction, hepatic damage	Epilepsy, glaucoma, hepatic or renal conditions, psychiatric illness, uncontrolled hypertension, known hypersensitivity	Bleeding disorders, cardiac conditions, elderly patients, hypertension
<i>Carbamazepine</i> (anticonvulsant)	Trigeminal neuralgia (first line)	Na <sup>+</sup> and Ca <sup>2+</sup> channel blocker. Metabolite 10,11-epoxycarbamazepine limits repetitive firing across neurones.	100 mg OD-BD, increase gradually up to 1600 mg/day. Normal dose is 200 mg TDS/QDS	Tegretol Retard™ 100–200 mg in 2 divided doses, usually up to 600–800 mg daily in 2 divided doses, up to a maximum of 1600 mg daily in two divided doses – slow release preparation may be better tolerated	Weight gain, nausea and vomiting, dizziness, drowsiness, xerostomia, fatigue, blood abnormalities, SJS/TEN	Acute porphyrias, AV conduction abnormalities, bone marrow depression. Care if presence of HLA-B*1502 allele	Cardiac disease, skin reactions, glaucoma, seizures, acute liver disease, warfarin, OCP

Table 1 (Continued)

Medication	Indications	Mechanism of action	Standard dose regimen	Slow tapering dosing regime	Adverse effects	Absolute contraindications	Relative contraindications
<i>Oxcarbazepine</i> (anticonvulsant)	Trigeminal neuralgia	Blocks Na <sup>+</sup> channels and, therefore, a membrane stabiliser suppressing neuronal firing, decreasing the propagation of synaptic impulses	150 mg OD 1 month, increase to BD for 1 month, can then be increased to 300 mg am, 150 mg pm, building up to a maximum of 300 mg BD, over 2–3 week intervals	This can be increased to 1-week intervals of dose increase, however, a slower and lower dose taper is recommended	Abdominal pain, nausea, dizziness, drowsiness, emotional lability, impaired concentration, SJS/TEN	Acute porphyrias, heart failure, cardiac conduction abnormalities, hyponatraemia. Care if presence of HLA-B*1502 allele	Liver and renal impairment, breastfeeding, pregnancy, OCP
<i>Baclofen</i> (muscle relaxant/ antispasmodic)	Trigeminal neuralgia	GABA <sub>B</sub> receptor agonist. Pre-synaptically decreases neurotransmitter uptake, post-synaptically increases K <sup>+</sup> conductance, hyperpolarising neurones	5 mg TDS, increase up to 60 mg daily in divided doses, max 100 mg/day		Confusion, xerostomia, hypotension, nausea, dizziness, drowsiness, headaches	Active peptic ulceration. Known hypersensitivity	Cardiovascular disease, diabetes, epilepsy, history of peptic ulcers, Parkinson's disease, respiratory impairment, elderly
<i>Lamotrigine</i> (anticonvulsant)	Trigeminal neuralgia	Na <sup>+</sup> and Ca <sup>2+</sup> channel blocker. Stabilises pre-synaptic neuronal membranes. Decreases glutamate neurotransmission, enhancing GABAergic transmission	25 mg OD for 14 days to 50 mg daily in 1–2 divided doses for 14 days, can increase to 100 mg daily in 1–2 divided doses, maintenance dose 200 mg in 1–2 divided doses, max. 400 mg daily		Drowsiness, fatigue, nausea, headaches, xerostomia, agitation, sleep disorders, SJS/TEN	Known hypersensitivity	Parkinson's disease, myoclonic seizures, hepatic/renal impairment

Table 1 (Continued)

Medication	Indications	Mechanism of action	Standard dose regimen	Slow tapering dosing regime	Adverse effects	Absolute contraindications	Relative contraindications
<i>Clonazepam</i> (benzodiazepine)	Burning mouth syndrome	Enhances activity of GABA by opening Cl <sup>-</sup> ion channels, resulting in anxiolytic anticonvulsant and muscle relaxing properties. Decreases neuronal use of serotonin.	500 µg tablet, dissolve in patients mouth forming saliva-clonazepam slurry, held in the affected areas of the mouth for 3 min then spit out, TDS for 14–28 days		Drowsiness, increased oral burning, xerostomia	Myasthenia gravis, acute pulmonary insufficiency, neuromuscular respiratory weakness, alcohol/drug dependency, known hypersensitivity	Personality disorders, elderly
<i>Capsaicin</i>	Burning mouth syndrome	Activates TRPV1 receptors, stimulating an influx of cations into cells. Depletes substance P from nociceptors. Temporary loss of membrane potential, lack of transportation of neurotrophic factors, reversible retraction of nerve fibre terminals	0.075% cream TDS/ QDS, 8% patches, oral rinse 0.02% capsaicin 15 mL TDS 30 s		Abnormal sensation to skin, AV block, eye irritation, nausea, tachycardia, palpitations, gastric irritation	Known hypersensitivity	Uncontrolled hypertension, recent cardiovascular events
<i>Alpha-lipoic acid</i>	Burning mouth syndrome	Antioxidant. Increases intracellular levels of glutathione, eliminates free radicals.	600 mg/day as 200 mg TDS		Low blood sugar, vision changes (rare), urticaria (rare)	Medication interaction is a possibility, e.g. cisplatin, cyclophosphamide, gentamicin and amikacin	Care with diabetes, excessive alcohol use, thyroid disease, known hypersensitivity
<i>Lidocaine hydrochloride</i>	Acute rescue remedy in trigeminal neuralgia	Amino-amide local anaesthetic, reduces Na <sup>+</sup> ion influx across the cell membrane – critical threshold isn't reached and no action potential firing	5% lidocaine ointment applied sparingly on affected area. 10% lidocaine spray applied as necessary to affected area.	Post-herpetic neuralgia – topical lidocaine 50 mg/g patch applied x1/ day up to 12 h then 12-h plaster-free period. Stop if no effect after 4 weeks	Hypotension, oedema, irritation symptoms e.g. erythema at application site, nausea, vomiting, numbness and tingling, drowsiness, tremor, arrhythmia, methaemoglobinaemia	Known hypersensitivity. Avoid if inflamed or infected tissues. Avoid middle ear area due to ototoxicity	Care if using intraorally before eating due to risk of anaesthetising the pharynx which can cause choking



**Table 1** (Continued)

Medication	Indications	Mechanism of action	Standard dose regimen	Slow tapering dosing regime	Adverse effects	Absolute contraindications	Relative contraindications
<i>Benzylamine hydrochloride</i>	Burning mouth syndrome, inflammatory conditions	Weak inhibitor of prostaglandin and tumour necrosis factor- $\alpha$ synthesis. Inhibition of oxidative burst of neutrophils. Membrane stabilisation – lysosome stabilisation and neutrophil granule release	Benzylamine 0.15% mouthwash, 15 mL 1.5–3 hourly, maximum of 7 days. Dilute with water if stinging occurs.		Angioedema, and rarely photosensitivity reactions, respiratory disorders, skin reactions	Known hypersensitivity	Due to possible systemic absorption, interactions may include, among others, risk of gastrointestinal bleeding if prescribed with beclomethasone, increased risk of seizures if prescribed with ciprofloxacin

GABA, gamma aminobutyric acid; NMDA, N-methyl-D-aspartate; Na<sup>+</sup>, sodium; K<sup>+</sup>, potassium; Ca<sup>2+</sup>, calcium; TRPV1, transient receptor potential cation channel subfamily V member;  $\alpha$ , alpha;  $\delta$ , delta; GABA<sub>B</sub>, gamma aminobutyric acid-B; SSR1, selective serotonin reuptake inhibitor; SNRI, selective noradrenaline reuptake inhibitor.

**Table 2** Medication overuse headache<sup>32</sup>

Medication	Frequency to be considered a cause of medication overuse headache
Ergotamine, triptans, opioids, combination analgesics	10 days or more per month for more than 3 months
Simple analgesics, e.g. paracetamol and NSAIDs (including aspirin)	15 or more days per month for more than 3 months

Simple analgesics such as the ones described above have been shown to be effective in the management of TMD, alongside other NSAIDs such as naproxen and topical or oral diclofenac.<sup>34,35</sup> However, some NSAIDs such as celecoxib haven't shown clinically significant improvement in pain control of patients with TMD when compared to naproxen or a placebo.<sup>36</sup>

NSAIDs are known to be beneficial for the acute inflammatory conditions associated with the temporomandibular joint, including acute trauma or disc displacement without reduction. However, there is currently insufficient evidence for conclusive recommendations on the type, dosage and duration of particular NSAIDs for TMD and further research is recommended.<sup>37,38</sup>

### Absolute contraindications

For NSAIDs these include, among others, an active gastrointestinal (GI) ulcer or bleed, severe heart failure, severe hepatic or renal impairment and allergy. All opioids should be avoided in patients with acute respiratory depression and chronic respiratory issues such as obstructive sleep apnoea or if a patient has a head injury or raised intracranial pressure, as opioids interfere with pupillary responses which are used to assess neurological status. Codeine phosphate should be avoided in acute ulcerative colitis. Avoid if known hypersensitivity to paracetamol, NSAIDs, codeine phosphate or their ingredients.

### Relative contraindications

Consider prescribing a proton pump inhibitor, such as Omeprazole 20 mg once daily, with an NSAID, or an alternative to an NSAID, if the patient is at risk of GI adverse effects. Take care with patients who have renal, cardiac or circulatory conditions when prescribing NSAIDs and avoid long-term prescription of weak opioids due to dependence and tolerance. Increased age should also be taken into account when titrating weak opioids as older patients are more susceptible to the adverse effects and may have biological and/or chronological differences in metabolism and excretion of medications. Codeine

phosphate should also be prescribed with care in patients who have adrenocortical insufficiency, asthma and other respiratory issues such as chronic obstructive pulmonary disease, hypotension, hypothyroidism and myasthenia gravis along with bowel disorders. Caution should be taken when prescribing paracetamol for patients with a low body weight ( $\leq 50$  kg) or at risk of hepatotoxicity, for example, chronic alcohol consumption.

### Amitriptyline

Tricyclic antidepressants, amitriptyline and nortriptyline, are a group of medications which are named due to their chemical structure – a group of three rings. They have a myriad of actions including blocking the reuptake of noradrenaline at nerve terminals.<sup>39,40</sup> While these medications were originally designed to treat conditions such as anxiety and depression, research has highlighted their analgesic properties at lower doses can be effective in the management of persistent pain conditions.<sup>41</sup>

Amitriptyline is often used for persistent TMD, neuropathic pain, migraine prophylaxis and for chronic tension-type headache prophylaxis but is no longer a first choice in the management of depression.<sup>42</sup> It is also used for nociplastic pain. Amitriptyline is often taken in the evening due to its sedative effects and may improve sleep quality. Due to the cardiovascular and epileptogenic effects being dangerous in overdose, only a limited amount should be prescribed at any one time. Drowsiness, due to amitriptyline's antihistaminergic effect, may affect tasks such as driving and, therefore, this should be taken into consideration. Amitriptyline will take a minimum of 4 weeks to take effect, and therefore it is advisable to warn the patient of this lag time so that they aren't expecting an overnight improvement in their symptoms.<sup>43</sup> Patients need to be educated that amitriptyline requires a constant dosing schedule and doesn't work on an ad hoc ingestion like simple analgesia does for acute inflammatory pain.

Other common adverse effects of amitriptyline to warn the patient of include xerostomia, blurred vision, increased ocular pressure (hence, certain

types of glaucoma are a relative contraindication to use) and urinary retention due to bladder neck restriction – these are all related to the anticholinergic action of activation of the muscarinic receptors.<sup>44</sup>

## Pharmacology

Amitriptyline is a TCA which has a broad pharmacodynamic nature and works by being a non-selective blocker of monoamine reuptake from the synapse in the CNS. Amitriptyline attaches to multiple CNS receptors increasing availability of substances such as serotonin and noradrenaline in the synapse, allowing them to transmit on the post-synaptic neuron. Amitriptyline has antihistaminergic activity which results in its sedative effects. Amitriptyline also blocks sodium, potassium and calcium ion channels, all of which are involved in neuronal firing and the generation of action potentials, stabilising the membrane potential of neurons. Lastly, it enhances gamma aminobutyric acid (GABA) peripherally and is a weak N-methyl-D-aspartate receptor (NMDA) antagonist which is an excitatory neurotransmitter. Amitriptyline is metabolised in the liver to its active metabolite nortriptyline.<sup>39,40,44,45</sup>

## Absolute contraindications

Heart block, immediate recovery period after a myocardial infarction, arrhythmias and during the manic phase of bipolar disorder. Avoid if known hypersensitivity to amitriptyline or its ingredients.<sup>44</sup>

## Relative contraindications

Care with prescribing for patients with conditions such as diabetes (affects glycaemic control by an increased insulin release due to the blocking of the alpha-adrenoreceptors), epilepsy (decreases the seizure threshold), bipolar disorder, liver disease, hyperthyroidism (increases the risk of arrhythmias and increases the activity of thyroid hormone), glaucoma (due to increased intraocular pressure via its anticholinergic action) or in patients at risk of suicide (due to risk of fatality in overdose). Caution should be exercised for doses above 75 mg in the elderly or those with cardiovascular disease. Those over the age of 60 also need to be monitored carefully as they are more susceptible to the adverse effects of this medication including the cardiac side effect of QT interval prolongation as a result of blocking of alpha-adrenoreceptors (resulting in an increased risk of arrhythmias) and postural

hypotension which could potentially result in an increased risk of falls with the associated morbidity and mortality.<sup>39,44</sup>

Care should also be taken if prescribing with other sedating agents or when prescribed with other serotonergic medications such as tramadol or selective noradrenaline reuptake inhibitors (SNRI). This can result in serotonin syndrome, signs and symptoms of which include cognitive and behavioural changes, such as disorientation, autonomic dysfunction including tachycardia and neuromuscular effects, such as trismus and muscle rigidity.<sup>40</sup> Prompt recognition of serotonin syndrome is crucial and management is driven by the severity of presentation, which includes discontinuation of the serotonergic medication and appropriate supportive therapy based on the presenting symptoms.<sup>46</sup>

## Dosing regimen

Initially 10–25 mg once daily in the evening. If tolerated can be increased in steps of 10–25 mg every 3–7 days in divided doses, but in practice, dose increases are often performed every 4–8 weeks to help with accommodation to side effects and also truly assess response to each increment. Usual dose is 25–50 mg daily, with a target dose ranging from 30 to 70 mg at night. Expert-based anecdotal practice often indicates a much slower and lower taper, such as 10 mg nocte, increasing by 10 mg every 1–2 weeks. This can aid in decreasing adverse effect profiles and/or allowing patients to adjust to them. In the event of significant morning drowsiness, taking the dose earlier in the evening may alleviate this side effect. Care should also be taken if stopping the medication due to the risk of withdrawal symptoms which can be severe – amitriptyline should be withdrawn slowly over at least 4–8 weeks or longer if necessary.<sup>44</sup>

## Nortriptyline

Nortriptyline is used for the treatment of persistent TMD, depression and neuropathic pain; however, it is unlicensed for use in neuropathic pain and, therefore, it is important to ensure the patient is aware of this.<sup>42,47</sup>

This medication has many similar adverse effects to amitriptyline such as dry mouth and increased appetite, however, nortriptyline has less of a sedative effect in comparison and therefore may be better tolerated. Patients should still be warned of the potential consequences of adverse effects such as

drowsiness and therefore the possibility this may impact on performance of skilled tasks such as driving.<sup>47</sup> Anecdotally, a common claim surrounding nortriptyline is regarding its 'superior' side-effect profile when compared with amitriptyline. Some of the key issues regarding nortriptyline concern its cost, as it is much more expensive to prescribe than amitriptyline and, furthermore, that nortriptyline is in fact not listed in the national guidelines for neuropathic pain management. As a result, GPs often encounter difficulties in continuing a nortriptyline prescription outside of the secondary care setting.

### Pharmacology

As mentioned above, nortriptyline is the active metabolite of amitriptyline and has a similar mode of action. It is a TCA and inhibits the reuptake of noradrenaline along with blocking sodium, potassium and calcium ion channels. It blocks NMDA, muscarinic cholinergic, H1-histaminergic and alpha-adrenergic receptors.<sup>47,48</sup>

### Absolute contraindications

Similar contraindications to amitriptyline – arrhythmias, heart block, immediately after a myocardial infarction and during the manic phase of bipolar disorder. Avoid if known hypersensitivity to nortriptyline or its ingredients.<sup>47</sup>

### Relative contraindications

Due to similar reasons as explained with amitriptyline, care needs to be taken when prescribing in patients with, but not exclusive to, cardiac disease, diabetes, glaucoma, hyperthyroidism (risk of arrhythmias) and liver disease. Similarly, care needs to be taken when prescribing this for elderly patients.<sup>47</sup>

Tricyclic antidepressants have a narrow therapeutic index and therefore the likelihood of overdose is high. Excessive alcohol consumption with nortriptyline or amitriptyline should be avoided due to its potentiating effects, possibly resulting in overdose or increased suicide attempts, especially in patients who have a history of suicidal ideation or emotional disturbance.

### Dosing regimen

Ten mg once daily at night-time, with higher doses to be given alongside specialist supervision. While

this dose can be gradually increased up to a maximum 75 mg daily, it is the author's experience that it is rarely necessary to go above 50 mg. Above 50 mg, adverse effects such as drowsiness, dizziness and blurred vision can outweigh any perceived benefits.<sup>47</sup> Expert-based anecdotal practice often uses a much slower and lower taper, such as titrating by 10 mg every 1–2 weeks.

### Gabapentin

As per NICE guidelines on the management of neuropathic pain, gabapentin is one of the four main medications recommended for this.<sup>15</sup> It is also used as an adjunct for the management of focal seizures, menopausal symptoms and multiple sclerosis.<sup>49</sup>

In the UK and many other countries both gabapentin and pregabalin have been listed as controlled drugs – in the UK under the Misuse of Drugs Act 1971 as Class C substances and are Schedule 3 drugs under the Misuse of Drugs Regulations (2001).<sup>50</sup> This is because of concerns about recreational use of both drugs, which has been noted in multiple countries including Canada, the UK and the USA.<sup>51–53</sup> As part of the patient assessment, health-care professionals need to be aware if the patient has a history of drug dependence or may be at risk of drug dependence and this will need to be monitored at the review appointments.<sup>54</sup>

Adverse effects to warn patients of include confusion, weight gain, xerostomia, constipation or diarrhoea, visual impairment and hypertension, among others.<sup>49</sup> Adverse effects frequently resolve within the first 2 weeks of commencing treatment.<sup>55</sup>

### Pharmacology

Gabapentin is a chemical analogue of GABA but does not act as a GABA-receptor agonist. It binds to a specific site in the CNS, gabapentin-binding protein and interacts with  $\alpha 2\delta$  calcium channels. It is not protein bound and freely crosses the blood–brain barrier. It increases GABA synthesis and release, but its exact mechanism of action is complex and not fully understood. Food and certain medications such as morphine increase the bioavailability of gabapentin by slowing intestinal peristalsis, increasing the transit time of gabapentin in the small intestine.<sup>48,56</sup>

### Absolute contraindications

Avoid if known hypersensitivity to gabapentin or its ingredients.

### Relative contraindications

Gabapentin is associated with an increased risk of severe respiratory depression. Care needs to be taken when prescribing for elderly patients or people with already compromised respiratory function including obstructive sleep apnoea, neurological disease and concomitant use of CNS depressants or renal impairment. Prescribing gabapentin and pregabalin with opiates must be avoided, as this can increase respiratory depression risk due to it being a CNS depressant. This also applies for alcohol, with a potentially fatal outcome. Due to these additive effects when more than one CNS depressant is taken, there have been reports of respiratory failure and coma in patients, with these medications being mentioned on death certificates as adjunctive substances contributing to death.<sup>51</sup> Consult product literature for dose if estimated glomerular filtration rate (eGFR) is less than 30 mL/min.<sup>49,57</sup>

Caution also needs to be applied when prescribing for patients with diabetes and a history of psychotic illness, substance dependence or seizures. The dose may need to be altered for people with a low body weight. Unless potential benefit outweighs risk, avoid in pregnancy due to animal studies showing toxicity, with an increased risk of teratogenicity associated with the use of antiepileptic drugs, especially if used during the first trimester.<sup>58</sup>

### Dosing regimen

Initially 300 mg once daily on day 1, 300 mg twice daily on day 2, 300 mg three times daily on day 3, then increase in steps of 300 mg every 2–3 days in three divided doses up to a maximum of 3600 mg/day. In practice, it is sometimes worthwhile to start even lower, for example, 100 mg and titrate even slower over weeks rather than days again to help with accommodation to side effects and ensure lowest effective dose for pain management is achieved.<sup>49</sup>

### Pregabalin

Pregabalin is used for neuropathic pain, generalised anxiety disorder, fibromyalgia and as an adjunct for focal seizures.<sup>15</sup> Similar to gabapentin, it has been reclassified as a Class C controlled drug. Adverse effects are also similar to gabapentin.<sup>59</sup>

### Pharmacology

Pregabalin, like gabapentin, is a chemical analogue of GABA but does not act as a GABA-receptor

agonist. Both drugs bind to the regulatory subunit of pre-synaptic N- and P/Q-type voltage-gated  $\alpha 2\delta$  calcium channels, reducing calcium influx and, therefore, release of neurotransmitters such as glutamate, substance P and noradrenaline. Pregabalin has a binding affinity six times greater than that of gabapentin.<sup>60</sup>

### Absolute contraindications

Avoid if known hypersensitivity to pregabalin or its ingredients.

### Relative contraindications

Care should be taken when prescribing pregabalin for patients who have conditions which may precipitate encephalopathy or with severe congestive heart failure. As with gabapentin, be wary of patients who have a history of substance dependence and monitor for signs of pregabalin dependence at review appointments. Signs of potential misuse of these medications include prescription forgery, 'lost' or early requests for prescriptions, loss of interest in their normal activities as they become more focused on the medication itself, worsening mental health status and misuse of related illicit drugs, among others.<sup>61</sup> Avoid abrupt withdrawal by tapering off slowly over at least 4 weeks, unless on minimal dose. As with gabapentin, unless potential benefit outweighs risk, avoid in pregnancy due to animal studies showing toxicity, with an increased risk of teratogenicity associated with the use of antiepileptic drugs, especially if used during the first trimester.<sup>58,59</sup>

### Dosing regimen

Daily dose of 150 mg in two to three divided doses to start and then increased after 3–7 days up to 300 mg daily in two to three divided doses. This can be increased further after another 3–7 days up to 600 mg daily in two to three divided doses. However, a lower dose can be used if necessary or asymmetric doses may be considered, both of which can help decrease the adverse effect profile as will a slower taper over the course of several weeks as many patients won't tolerate a rapid regime. Initial adverse effects decrease significantly within 2 weeks in most cases.<sup>59</sup>

### Duloxetine

The national guidelines for neuropathic pain management stipulate that duloxetine, alongside all four

neuropathic pain medications, can be considered a first-line intervention, depending on the individual case presented; it can be indicated in the management of depression, persistent neuropathic pain, nociplastic pain and is also used in generalised anxiety disorder.<sup>15</sup> Duloxetine significantly improved the symptoms of what one study termed 'non-specific chronic orofacial pain' in which they included BMS and atypical odontalgia with pain relief appearing from 2 weeks of treatment of 20–40 mg of duloxetine daily.<sup>14,47</sup>

The analgesic effect of duloxetine is also helpful for treatment of fibromyalgia and is thought to result from the increased activity of serotonin and noradrenaline receptors within the CNS by modulating and enhancing descending pain inhibitory pathways.<sup>62</sup>

Adverse effects to warn the patient of include nausea and vomiting, cardiovascular effects including a prolonged QT interval and hypertension, sexual dysfunction, increased urinary frequency and hepatic damage.<sup>63</sup>

## Pharmacology

Duloxetine is an SNRI which acts on both the serotonergic and the noradrenergic systems. Duloxetine inhibits the pre-synaptic neuronal reuptake of both serotonin and noradrenaline and of dopamine to a lesser extent. Unlike amitriptyline, it has few post-synaptic antagonistic effects at muscarinic,  $\alpha$ -adrennergic or H1-receptors. It has little effect on cognitive or motor performance.<sup>64</sup>

## Absolute contraindications

Epilepsy, glaucoma (increased risk of mydriasis), hepatic damage (increased risk of liver damage if pre-existing liver damage is present) or renal conditions (as up to 70% of duloxetine is excreted by the kidneys as metabolites), psychiatric illness and uncontrolled hypertension.<sup>65</sup> Avoid if known hypersensitivity to duloxetine or its ingredients.<sup>63</sup>

## Relative contraindications

Elderly patients or patients who are hypovolaemic may develop hyponatremia with duloxetine and therefore care needs to be taken. Care also needs to be taken in patients with bleeding disorders, cardiac conditions (duloxetine can increase heart rate) and hypertension.<sup>63,65</sup>

## Dosing regimen

Start with 20 or 30 mg once daily and titrate up towards a total daily dose of 60–90 mg slowly over 4–8 weeks between increments. Duloxetine may be prescribed as 30 mg twice daily or 60 mg once daily, however, expert-based anecdotal practice often indicates titration up to 60 mg twice daily.<sup>63</sup>

## Carbamazepine

Carbamazepine is an anticonvulsant medication primarily used in the management of epilepsy and is the first-line medication in the management of trigeminal neuralgia. The number needed to treat (NNT) to achieve 50% pain reduction is <2.<sup>66</sup> However, the side effect profile can be problematic, with the majority of adverse effects arising within the first 6 weeks. These can include weight gain, nausea and vomiting, dizziness, drowsiness, xerostomia, fatigue and blood abnormalities such as thrombocytopenia, hyponatremia and leukopenia, of which the patient needs to be warned. If the patient suffers from drowsiness as a side effect, they may need to notify the regulatory body in their country for driving, for example, this would be the Driver and Vehicle Licensing Agency (DVLA) in the UK. The patient should also be advised to monitor for Steven-Johnson's syndrome and liver disorders.<sup>67</sup> Monitoring after prescription of carbamazepine includes a full blood count, liver function tests and urea and electrolytes (U + Es) two to four weekly for the first 2–4 months before decreasing this to two to three times per year.<sup>68</sup>

Other options for treating trigeminal neuralgia would include the addition of baclofen to carbamazepine due to its synergistic effects or to decrease and/or cease the carbamazepine and add lamotrigine instead. Acute rescue medications for exacerbations of trigeminal neuralgia include local anaesthetic – namely, lidocaine via a variety of methods including topically or injected via a nerve block or trigger point injection. Other medications include phenytoin or intravenous (IV) fosphenytoin and subcutaneous or nasal sumatriptan. These medications have the potential to abort an acute attack and therefore enable the long-term symptom control medications such as carbamazepine to be more effective.<sup>69</sup> However, if none of these medications are beneficial to the patient then it may be worth reconsidering your original diagnosis.

## Pharmacology

The mode of action is not completely understood. Carbamazepine is a sodium and calcium channel blocker and reduces the flux of these ions across neuronal membranes – inhibiting ionic channels results in ‘membrane stabilisation’. It binds preferentially to voltage-gated sodium channels which prevents firing of an action potential, slowing neuronal recovery after activation. Its metabolite 10,11-epoxycarbamazepine limits repetitive firing across neurons which is thought to relate to its antiepileptic properties.<sup>70</sup>

### Absolute contraindications

Acute porphyrias, AV conduction abnormalities unless paced and any history of bone marrow depression are absolute contraindications for the use of carbamazepine.<sup>67</sup> Case–control studies have found that there is an association between the presence of the HLA-B\*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.<sup>71</sup> This allele is often found in people of Thai ancestry or 8% of Han Chinese ancestry, compared to 1–2% of Caucasians.<sup>72,73</sup> Therefore, it is important to avoid in this group or check for the relevant allele. Carbamazepine is not recommended for use during pregnancy or breastfeeding due to teratogenicity. Avoid if known hypersensitivity to carbamazepine or its ingredients.<sup>67</sup>

### Relative contraindications

Relative contraindications for carbamazepine include cardiac disease, haematological reactions to other medications, skin reactions, glaucoma and may exacerbate absence and myoclonic seizures. Stop immediately if there is evidence of acute liver disease or dysfunction. Vitamin D supplementation may need to be considered in patients who have low sun exposure or are immobilised for long periods of time. Carbamazepine can increase the metabolism of warfarin and the hormones in the oral contraceptive pill (OCP), reducing its effectiveness.<sup>67</sup> Erythromycin can decrease the metabolism of carbamazepine and therefore increase the level within the body. Grapefruit juice inhibits CYP3A4 enzymes in the liver and GI tract, which can increase the bioavailability of carbamazepine.

### Dosing regimen

Orally, using immediate-release medicine, initially 100 mg one to two times a day, increasing gradually

according to response up to a maximum of 1600 mg daily in divided doses. A therapeutic dose is often around 200 mg three to four times a day, but therapeutic effects can occur at much lower doses than this. If using a prolonged release medication such as Tegretol Retard<sup>TM</sup>, then initially 100–200 mg in two divided doses, usually up to 600–800 mg daily in two divided doses, up to a maximum of 1600 mg daily in two divided doses.<sup>67</sup>

## Oxcarbazepine

This medication is also primarily used for the treatment of epilepsy and bipolar disorder or as a second-line treatment in the management of trigeminal neuralgia.<sup>74,75</sup> Monitoring of plasma-sodium concentration when using oxcarbazepine is recommended in patients at risk of hyponatremia.

Adverse effects to warn the patient of include but are not limited to abdominal pain, nausea, dizziness, drowsiness, emotional lability and impaired concentration – which may therefore have an impact on the patient’s ability to operate machinery and drive safely.<sup>74</sup> If this is the case then the patient may need to notify the regulatory body in their country for driving, for example, the Driver and Vehicle Licensing Agency (DVLA) in the UK.<sup>76</sup> Although, alongside carbamazepine, this drug is not a first-line DVLA notifiable medication, studies have shown deterioration of driving performance associated with these medications and as such would be recommended to inform the DVLA.<sup>77</sup>

As with carbamazepine, patients should be schooled on Stevens-Johnson syndrome so they can recognise this, should it develop. If the patient develops a rash previously with carbamazepine use, then they shouldn’t be prescribed oxcarbazepine as an alternative as Stevens-Johnson syndrome is just as likely with either medication.

## Pharmacology

As above with carbamazepine, this medication blocks sodium channels and therefore is a membrane stabiliser by suppressing neuronal firing and decreasing the propagation of synaptic impulses. Unlike carbamazepine, oxcarbazepine does not have an epoxide metabolite, this being mainly responsible for carbamazepine’s toxic adverse effects. Instead, oxcarbazepine is metabolised to 10,11-dihydrocarbamazepine, its clinically relevant metabolite, which has antiepileptic properties. As opposed to carbamazepine, oxcarbazepine is metabolised outside of the cytochrome system and

consequently has a much better profile with regards to potential interactions, which lends to oxcarbazepine providing a better alternative in patients who present with a polypharmacy issue.<sup>78–80</sup>

### Absolute contraindications

Avoid in patients with acute porphyrias, heart failure, cardiac conduction disorders and hyponatremia.<sup>74</sup>

### Relative contraindications

Caution is advised in patients with severe liver impairment and decreased doses are recommended for patients with renal impairment. Avoid when breastfeeding, limited evidence currently to establish the risk of teratogenicity with use during pregnancy.<sup>75</sup> As with carbamazepine, patients of Thai or Han Chinese origin should be screened for the HLA-B\*1502 allele.<sup>71</sup> Furthermore, care should be taken with women taking the OCP as there is the risk of oxcarbazepine reducing its efficacy.<sup>80</sup>

### Dosing regimen

This is an off-label prescription. A slow upwards titration regime may start at 150 mg once daily for 1 month and then increase as needed to twice daily for 1 month. It is possible, however, to accelerate the titration rate where circumstances necessitate, for example, 150 mg once daily in week 1, 150 mg twice daily in week 2, etc. Doses can then be increased to 300 mg in the morning and 150 mg in the evening, building up to a maximum of 300 mg twice daily usually over 2- to 3-week intervals. However, as before, this can be increased to 1-week intervals of dose increase, depending on patient response and side-effect profile.<sup>81</sup>

## Clonazepam

Clonazepam is a benzodiazepine which is mainly used in the management of epilepsy.<sup>82</sup> However, it can be used in BMS, as either a topical mouthwash or taken orally.<sup>83</sup>

Within the UK, clonazepam is a DVLA notifiable medication due to it being a Category C controlled drug under the Misuse of Drugs Act 1971 and Schedule 4 Part 1 under the Misuse of Drugs Regulations 2001.<sup>50</sup> Even though clonazepam is described as a topical treatment via a mouthwash in BMS, there is still the risk of systemic absorption and

therefore systemic adverse effects. Within the UK, the threshold limit in blood is 50 µg/L and, therefore, patients need to be made aware that they need to notify and discuss this with the DVLA (UK) or other relevant regulatory bodies if outside of the UK if they feel their driving is impaired.<sup>84,85</sup>

Adverse effects include drowsiness, increased oral burning, xerostomia, include acute porphyrias, suicidal ideation, airway obstruction, depression and cerebellar ataxia.<sup>82,86</sup>

### Pharmacology

Clonazepam enhances the activity of GABA, an inhibitory neurotransmitter, resulting in its anxiolytic, anticonvulsant and muscle relaxant properties. Benzodiazepines enhance the action of GABA by increasing the opening of chloride ion channels, which increases the inhibitory effects of GABA. It also decreases neuronal use of serotonin.<sup>87</sup>

### Absolute contraindications

Myasthenia gravis, acute pulmonary insufficiency, neuromuscular respiratory weakness, alcohol or drug dependency and respiratory depression are absolute contraindications for its use. Avoid in patients with known hypersensitivity to clonazepam or its ingredients.<sup>82</sup>

### Relative contraindications

Personality disorders, the elderly (reduce the dose) and prolonged use or abrupt withdrawal as dependency issues may be in play as a result of clonazepam being a benzodiazepine from possible systemic absorption.<sup>82,88</sup>

### Dosing regimen

Five-hundred micrograms clonazepam tablet, letting the tablet dissolve in the patient's mouth to form a saliva-clonazepam slurry which can be held in the affected areas of the mouth for 3 min without swallowing and then spitting out three times a day. There is a degree of variation on how long it will take to be effective, but generally it should be used for 14–28 days.<sup>88–90</sup>

### Capsaicin

Capsaicin is used for pain management, often as a topical dermal 8% patch but this is elsewhere on the



body. The topical cream can be used intra- and extraorally as long as it is kept away from the nose and the eyes; however, there is still a small risk of systemic absorption.<sup>91</sup> This is relatively safe and of modest efficacy, supported by numerous studies with benefits including good patient compliance and low risk for systemic adverse effects or medication interactions.<sup>92</sup>

Adverse effects when using a transdermal patch include abnormal sensation of the area of skin applied to. Rarer adverse effects include but not limited to atrioventricular block, eye irritation, nausea, tachycardia and palpitations. Limitations of use of capsaicin include gastric irritation (if used systemically) and temporary pain increase.<sup>93,94</sup>

### Pharmacology

The main mechanism of action of capsaicin is via activation of the TRPV1 receptors, stimulating an influx of cations into cells. Capsaicin is a naturally occurring compound which causes a 'hot' sensation in the oral cavity when ingested.<sup>95</sup> Another mechanism of action is thought to be depletion of substance P from nociceptors.<sup>92</sup> However, further studies indicate that other mechanisms of action in topical patches include a temporary loss of membrane potential, lack of transportation of neurotrophic factors and reversible retraction of nerve fibre terminals, all of which result in what one paper terms 'dysfunctionalisation of nociceptive fibres'.<sup>92</sup>

### Absolute contraindications

There is no known absolute contraindication for use of capsaicin. Avoid in individuals if known hypersensitivity to capsaicin.

### Relative contraindications

Few contraindications exist being a topical treatment, however, there is still a small risk of systemic absorption. Avoid contact with broken or inflamed skin, the face, close proximity to mucous membranes and don't use under a tight bandage. Don't use it after a hot shower or bath as this can increase the burning sensation. Avoid inhaling the vapours.<sup>91</sup>

If using a transdermal application, avoid in patients with uncontrolled hypertension or recent cardiovascular events. Wash your hands immediately after use. Blood pressure needs to be monitored during the use of a transdermal patch.<sup>91</sup>

### Dosing regimen

For localised neuropathic pain, a 0.075% cream can be used sparingly three to four times a day, however, it is unlicensed for this indication. A 0.025% cream is also available, used sparingly four times a day, however, generally this is used for symptomatic relief of osteoarthritis.<sup>91</sup> In Scotland, the 8% capsaicin patches are licensed for use in patients with post-herpetic neuralgia who have not tolerated or achieved adequate pain control using first- or second-line treatments. This has been decided by the Scottish Medicines Consortium (2011).<sup>91</sup>

Preliminary studies indicate potential benefits of using a capsaicin oral rinse for BMS, one such study using a 15 mL 0.02% capsaicin rinse three times a day for 30 s at a time.<sup>93</sup>

There is some evidence to support the use of topical capsaicin in the form of five to six drops of Tabasco sauce mixed with one teaspoon of water as a mouthwash four times a day to help alleviate the burning sensation from BMS; this may require gradual dose increase from one to two drops initially.<sup>96,97</sup>

### Baclofen

Baclofen is a further option in the management of trigeminal neuralgia, along with being used in palliative care and in conditions such as multiple sclerosis.<sup>17,98</sup> It may also be used for persistent neuropathic orofacial pains and TMD. Adverse effects include confusion, xerostomia, hypotension, nausea, dizziness, drowsiness and headaches.<sup>98</sup>

### Pharmacology

Baclofen is a CNS depressant, as shown by its sedative adverse effects. It is a derivative of the neurotransmitter GABA and is a GABA<sub>B</sub> receptor agonist. The exact mode of action is currently unknown; however, does involve pre- and post-GABA<sub>B</sub> receptors. Pre-synaptically it decreases neurotransmitter uptake and post-synaptically it increases potassium conductance and, therefore, hyperpolarises neurones.<sup>99</sup>

### Absolute contraindications

Baclofen is to be avoided in patients with active peptic ulceration and/or known hypersensitivity to baclofen or its ingredients.<sup>98</sup>

### Relative contraindications

Care needs to be taken when prescribing in patients who suffer from cardiovascular disease, diabetes, epilepsy, history of peptic ulcers, Parkinson's disease, respiratory impairment and the elderly.<sup>98</sup>

### Dosing regimen

Initially 5 mg three times a day which can be gradually increased up to 60 mg daily in divided doses, with a maximum dose of 100 mg a day.<sup>17</sup> Baclofen could also be used in conjunction with carbamazepine and this has been found to be an effective combination in managing trigeminal neuralgia.<sup>81</sup> When used in conjunction with carbamazepine, baclofen should be added as per its normal dosing schedule (5–15 mg three times a day) increasing in 5–10 mg increments every other day, to a maximum of 50–80 mg, with carbamazepine reduced to 500 mg/day to maintain a putative synergistic effect.<sup>100–103</sup>

### Lamotrigine

Lamotrigine is an anticonvulsant and is an option in the management of trigeminal neuralgia after using the second-line option of oxcarbazepine. Lamotrigine plays a key role in the management of trigeminal autonomic cephalalgias, for which it has a more profound role than it does for trigeminal neuralgia management and is also commonly used in the management of epilepsy and bipolar disorder.<sup>102,104</sup>

Adverse effects include nausea, headaches, diarrhoea, xerostomia, agitation and sleep disorders. Care needs to be taken if adverse effects such as drowsiness and fatigue are noted due to the possible impact on driving. Care also needs to be taken to avoid Steven-Johnson syndrome, and therefore the patient needs to be schooled on the relevant symptoms to watch for – most rashes occur in the first 8 weeks of use.<sup>104</sup>

### Pharmacology

Lamotrigine is a sodium and calcium voltage-dependent channel blocker which stabilises pre-synaptic neuronal membranes. It also decreases glutamate neurotransmission (an excitatory neurotransmitter in the CNS), enhancing GABAergic transmission.<sup>105</sup>

### Absolute contraindications

Avoid if known hypersensitivity to lamotrigine or its ingredients.

### Relative contraindications

Care with Parkinson's disease and patients who suffer from myoclonic seizures as both of these may be exacerbated. Dose adjustments required in patients with hepatic or renal impairment.<sup>104</sup>

### Dosing regimen

Start with a gradual increase in lamotrigine, initially at 25 mg once daily for 14 days, then 50 mg daily in one to two divided doses for 14 days. This can then be increased to 100 mg daily in one to two divided doses before a maintenance dose of 200 mg daily in one to two divided doses, with a maximum of 400 mg daily.<sup>104</sup>

### Alpha-lipoic acid

Alpha-lipoic acid (ALA) (thioctic acid) is an antioxidant coenzyme which has been used in the management of BMS alongside other conditions such as diabetic neuropathy.<sup>83,106</sup> The most up-to-date Cochrane review on BMS indicates that the evidence supporting use of ALA in BMS is very weak with a high risk of bias.<sup>89</sup> This refutes previous evidence which showed ALA as a promising treatment modality in the management of BMS.<sup>83,106</sup>

### Pharmacology

Alpha-lipoic acid is an antioxidant and increases the intracellular levels of glutathione. It also eliminates free radicals and one theory is that BMS, having neuropathy features, is caused by toxic free radical production, which is then counteracted by the ALA eliminating these free radicals.<sup>107</sup> Preliminary data indicate that ALA could be more effective in conjunction with gamma-linolenic, which is also used in the management of diabetic peripheral neuropathy.<sup>108</sup>

### Absolute contraindications

Avoid if known hypersensitivity to ALA.

### Relative contraindications

Alpha-lipoic acid is known to possibly interact with cisplatin, cyclophosphamide, gentamicin and amikacin and therefore should be avoided in patients taking these medications.<sup>106</sup>

### Dosing regimen

Studies support the use of 200 mg/day alpha-lipoic three times daily.<sup>106,107</sup>

### Lidocaine hydrochloride

Lidocaine hydrochloride is an anaesthetic which can be used as a local infiltration, topical ointment or spray, or as a medicated patch. However, the oral topical spray isn't licensed for pain relief of oral lesions.

Indications for use include as an acute rescue remedy in trigeminal neuralgia, and post-herpetic neuralgia.<sup>66,109</sup>

Side effects include hypotension, oedema, irritation symptoms such as erythema at the application site and/or skin irritation, nausea, vomiting, numbness and tingling, drowsiness, tremor, arrhythmia and rarely methaemoglobinaemia.<sup>109</sup> Hypersensitivity reactions to lidocaine are rare and studies have highlighted that most allergic reactions are to the antioxidant (metabisulphite) and/or preservative (methylparaben) present in some lidocaine preparations.<sup>110</sup>

As with other topical medications, as systemic absorption can follow use of topical lidocaine formulations, the possibility of interactions should always be considered, for example, lidocaine interactions with beta-blockers which can increase the risk of cardiovascular side effects when the medications are taken together.<sup>109</sup>

### Pharmacology

Lidocaine is an amino-amide local anaesthetic which reversibly blocks nerve conduction by reducing the influx of sodium ions which decreases the rate of rise of the depolarising phase of the action potential. There is little to no change in the potassium efflux and, therefore, minimal change to the resting potential. As the cell membrane is less permeable to sodium ions, there is a subsequent reduction in degree of polarisation and therefore an action potential isn't fired as the threshold isn't reached, resulting in no nerve conduction.<sup>111</sup>

### Absolute contraindications

Avoid in individuals if known hypersensitivity to lidocaine hydrochloride. If using as a local injection, avoid injection into inflamed or infected tissues, as an altered local pH can reduce its effectiveness.

Don't apply topically to damaged skin and avoid application to the middle ear as this can cause ototoxicity.<sup>109</sup>

### Relative contraindications

Care if using on inflamed or broken skin. Care needs to be taken if used before eating to avoid producing anaesthesia of the pharynx if used intraorally, as this could lead to choking.<sup>112</sup>

### Dosing regimen

Lidocaine ointment, 5% can be prescribed as a 15 g tube and rubbed sparingly on the affected areas. Alternatively, 50ml of lidocaine spray 10% can be prescribed, to be applied as necessary using a cotton bud to the affected area. The lidocaine 10% spray is unlicensed for oral ulceration.<sup>112</sup> A topical lidocaine 50 mg/g patch may be used for post-herpetic neuralgia, applied once daily for up to 12 h, followed by a 12-h plaster-free period. Discontinue if no effect after 4 weeks. Medicated patches need to be applied to clean, dry, intact skin, with minimal hair to allow the patch to stick.<sup>109</sup>

### Benzydamine hydrochloride

Benzydamine hydrochloride is a topical anti-inflammatory drug, often prescribed as a topical mouthwash or spray commonly used in the management of painful inflammatory conditions of the oropharynx or oral cavity. This can be helpful for controlling mucosal discomfort or oral lesions such as major aphthae.<sup>112</sup>

Side effects include angioedema and can rarely include photosensitivity reactions, respiratory disorders or skin reactions.<sup>113</sup>

### Pharmacology

Benzydamine is a weak inhibitor of the synthesis of prostaglandins and the inflammatory cytokine tumour necrosis factor-alpha. Other mechanisms of action include inhibition of the oxidative burst of neutrophils and membrane stabilisation involving lysosome stabilisation and granule release from neutrophils.<sup>114</sup>

### Absolute contraindications

Avoid if known hypersensitivity to benzydamine hydrochloride or its ingredients.

## Relative contraindications

Since there is the possibility of systemic absorption after topical application, systemic effects do need to be borne in mind, along with possible interactions. Possible interactions include but are not limited to; increased risk of gastrointestinal bleeding when prescribed with beclomethasone or dexamethasone and therefore caution is recommended, increased risk of seizures when prescribed with ciprofloxacin, among others.<sup>115</sup>

## Dosing regimen

This may be prescribed as benzydamine mouthwash 0.15%, rinse or gargle 15 ml every 1.5–3 h for not more than 7 days, spitting out after rinsing. This can be diluted with equal volume of water if stinging occurs. An oromucosal spray is often used if there is a specific lesion, prescribed as benzydamine oromucosal spray 0.15%, 4–8 sprays every one 1.5–3 h on to the affected area.<sup>113</sup>

## Discussion

Orofacial pain comprises some of the most debilitating and prevalent pain conditions of the head and neck. The descending pain pathway modulates the ascending noxious information carried by primary afferent A $\delta$ - and C-fibres through a variety of mechanisms.<sup>13</sup> The noxious information arises following stimulation of nociceptors in the free-nerve endings of the nerve fibres in the orofacial region, which then excites the nociceptive neurons – this is termed nociceptive pain. This results in a release of excitatory neurotransmitters that initiate central processing of the information to the cortical and limbic circuits, via the nuclei in the brainstem and thalamus in a four-stage process; transduction, transmission, modulation and perception (Figs 1–3).<sup>13,116</sup> Neuropathic pain, on the other hand, arises as a direct consequence of a lesion or disease affecting the somatosensory system, that is, direct association with injury or disease of nerve tissue.<sup>1,117</sup> Descriptors such as ‘stabbing’, ‘shooting’ or ‘electric shock-like’ are pathognomonic for neuropathic pain and can be triggered by even the lightest touch or gentlest movement as seen in many cases of trigeminal neuralgia.<sup>117</sup>

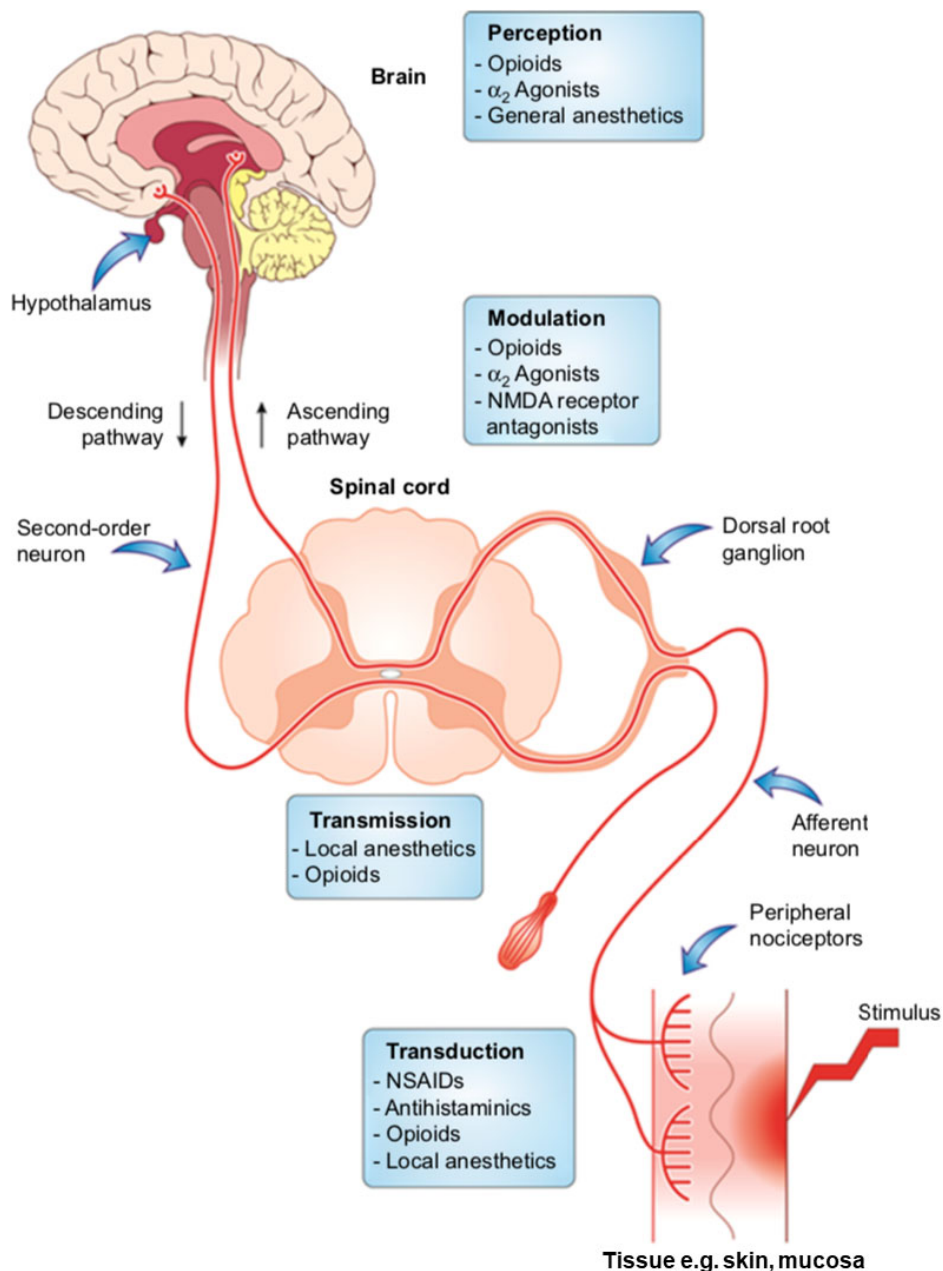
The descending pain pathway can become dysfunctional in patients with orofacial pain conditions, for example, TMDs resulting in enhanced sensitivity to noxious stimuli.<sup>13,118</sup> There is growing evidence to support links between disorders characterised by persistent pain such as fibromyalgia and orofacial

pain conditions such as TMDs.<sup>119</sup> Pain, in particular, is pathognomonic for TMD diagnosis; with both fibromyalgia and TMDs systematically classified as ‘central sensitisation syndromes’ due to their central dysregulation in the descending pain modulation pathway.<sup>120</sup> This is an example of nociplastic pain, as mentioned previously, where there is no clear evidence of tissue damage yet the patient still reports pain.<sup>1</sup>

The patient’s GP is often more suitably placed to prescribe the medication once the orofacial pain clinician has had an in-depth consultation with the patient regarding their diagnosis and the most beneficial management plan, as these medications will often also require monitoring for progress and adverse effects as well as regular blood tests. The clinic report can then be sent to the patient’s GP stating your request for them to consider, with an appropriate patient information leaflet included for the patient to read through at home, including potential adverse effects. Slow and low taper increases over 4–8 weeks between increments as a general principle will help reduce adverse effects and patients accommodating to side effects. They also give a chance for a realistic trial of that dose’s efficacy.

Many of the medications aimed at management of orofacial pain may interfere with a patient’s visual, cognitive and motor skills and therefore impact on the driving ability of a patient.<sup>121</sup> Therefore there is an obligation to ensure that the patient appreciates the impact a medication could have on their ability to concentrate for longer periods of time, potentially impacting whether they would be safe to drive. Within the UK, the DVLA introduced drug drive legislation in 2015 which for the first time included prescription medications alongside guidance that it may be advisable for patients to carry documentary evidence from their GP that they are taking a medication for legal reasons if, for example, subject to a roadside impairment testing by the police.<sup>84</sup> The main DVLA notifiable medication with regard to orofacial pain management is clonazepam.<sup>25,50,121</sup> The side-effect profiles of other medications, however, such as carbamazepine and oxcarbazepine, are not on the DVLA-notifiable list, may cause drowsiness and may only be reported by patients during specialist pain clinic appointments, and can therefore also have a direct impact on a patient’s ability to drive safely.<sup>25,50,121</sup>

Patients will also need to ensure they are compliant with regulations surrounding foreign travel with regard to either checking their medication is legal in



**Figure 3** Descending pain pathway. Adapted from ref.<sup>116</sup> [Colour figure can be viewed at wileyonlinelibrary.com]

the country they are travelling to via the embassy of the intended destination and ensuring they understand if their medication is a controlled drug. For example, in the UK if their medication is a Schedule 2, 3 or 4 on the controlled drugs list, then the patient needs to be able to prove it is prescribed to them or get a licence if carrying 3 months' worth of that medication or travelling for at least 3 months. Local regulatory authorities governing firearm use and storage, for example, in the UK is the Home

Office Drug and Firearms Licensing Unit, need to be contacted by the patient before travelling if the medication was prescribed abroad or contains a Schedule 1 controlled drug.<sup>84</sup>

Substance addiction is characterised by behavioural changes associated with biochemical brain changes following prolonged substance use, whereas dependence refers to a physical or psychological reliance on a substance alongside symptoms of tolerance and withdrawal. The two conditions often occur at

the same time, however, a patient can be dependent on a substance without being addicted to it.<sup>122</sup> A prescribing clinician has three main responsibilities: avoid creating dependence by introducing medications to patients without sufficient reason; ensure that the patient does not gradually increase the drug dose to where dependence becomes more likely and avoid being used as an unwitting source of supply for addicts.<sup>123</sup> Care has to be taken with the prescription of benzodiazepines and opioids due to the increased risk of misuse and iatrogenic drug dependence.<sup>122</sup> Misuse of gabapentinoids has long been reported in the UK.<sup>61</sup> International reports from Finland, Germany and the USA are suggestive that this may be a global problem, with prevalence of gabapentinoid misuse estimated between 1.1 and 1.6% of the general population, rising to over a fifth (22%) within circles of known opioid misuse and dependence.<sup>124,125</sup> It is for this reason that regular review of the prescription by the patient's GP is encouraged.

Opioids, although effective in providing short-term analgesia for some very specific forms of acute pain, are not usually effective for acute exacerbations of pain in orofacial conditions such as trigeminal neuralgia.<sup>126,127</sup> In addition, opioid analgesics are relatively ineffective for odontogenic pain alongside having an associated unpleasant side-effect profile.<sup>128</sup> Little evidence exists concerning the benefit of long-term opioid use for non-malignant pain, with problems of drug use, addiction, opioid-induced hyperalgesia and medication overuse headache as just some of the deleterious effects associated with opioid use, alongside effects on the neuroendocrine system such as infertility, decreased sexual function, anxiety, depression and even osteoporosis from long-term opioid therapy.<sup>126,129,130</sup>

Once a patient obtains optimal pain control for at least 6–8 months, consideration can be given to tapering the medication off with input from the patient's GP, especially medications which are associated with long-term dependency issues, for example, gabapentin and pregabalin.<sup>131</sup> This 6- to 8-month time period allows the patient's persistent pain status to have evolved through three phases of drug therapy: the acute phase, in the initial weeks of treatment until the patient has achieved a significant clinical response; the continuation phase, which (if tolerated) aims to consolidate the initial acute response (i.e. lack of symptoms or agreed level of symptom improvement) at the dose which brought about the response and, finally, the maintenance phase, which aims to prevent the recurrence of any

orofacial pain again at the dose which brought about the initial response, if tolerated. If maintenance phase treatment is not planned for patients after the continuation phase, they may be considered for tapering down and discontinuation of treatment.<sup>131–133</sup>

Routine monitoring and reviewing of patients by their GP is encouraged due to possible adverse effects, especially in those taking antidepressants, and may significantly reduce risks of adverse events.<sup>134</sup> Understandably, some patients may be resistant to tapering off from a medication that is giving them pain relief and for this reason, abrupt withdrawal is avoided and tapering a dose over a 6- to 8-week period is the 'standard' course of action, with even more gradual tapering by, for example,  $\frac{1}{4}$  of the treatment dose recommended every 4–6 weeks following.<sup>131</sup> Patients need to be warned regarding 'discontinuation syndrome', with symptoms such as dizziness, nausea, lethargy and headache reported in the literature.<sup>131</sup> If the patient suffers from any relapse of their orofacial pain, they can taper back to the dose they were last comfortable at and a discussion should be had regarding long-term goals and non-pharmacological management.<sup>57</sup> Possible tapering off further could then be revisited again in another 6 to 8 months' time.

Treatment outcomes should be agreed prior to commencement of medical management of orofacial pain to counsel patients that a 100% response following initial treatment is rarely achieved, and a likely improvement of 30–50% is suggested and/or the ability to resume normal daily activities.<sup>57</sup> At subsequent review appointments it can then be useful to specifically ask the patient a percentage improvement if applicable to assist with monitoring patients over a length of time.

Topical medications are showing promise in the management of orofacial pain, especially in neuropathic pain caused by peripheral nerve sensitisation and in those centralised neuropathies that have allodynic triggers.<sup>135</sup> Topical medications can reduce the extraoral stimulation that maintains central sensitisation, for example, trigeminal neuralgia and act alongside systemic medications for more moderate-to-severe pain, or when systemic medications require titration to effective levels.<sup>135</sup> Topical medications offer the advantage of site-specific delivery, improved compliance and reduced systemic side effects which may be crucial for use in elderly patients and the medically compromised.<sup>136</sup> Current research is looking at the use of amitriptyline, carbamazepine and gabapentin as topical preparations with promising preliminary results shown in initial *in vitro* studies.<sup>137</sup>

A multimodal approach to the management of orofacial pain gives credence to the use of the biopsychosocial model of pharmacological management, psychological support and physical therapies.<sup>17</sup> The biopsychosocial model acknowledges a tripartite, reciprocal relationship between the biological, psychological and sociological effects or consequences of any given disease or disorder.<sup>138</sup> The aim of this approach is to facilitate an increase in the therapeutic yield of the pharmacological management.<sup>138</sup> Orofacial pain produces significant biopsychosocial impacts and affects patients' everyday lives; the psychological aspects of the biopsychosocial model can only be identified when patients discuss their experiences in detail and as such can address the multifactorial nature of orofacial pain.<sup>17,139,140</sup> Due to the chronic nature of many facial pain conditions, it would be reasonable to expect some aspect of pain management alongside a biopsychosocial approach. In addition to the therapeutic approaches mentioned in this review, non-pharmacological approaches such as patient education, physical exercises, relaxation techniques, physiotherapy and clinical psychology also aid promotion of patient self-management that is geared towards improving the quality of a patient's life, despite the persistent nature of an underlying orofacial pain condition.<sup>141</sup>

## Conclusion

It is crucial that orofacial pain conditions are managed by the right person, in the right place, at the right time. By the time a patient visits secondary care they have often seen a whole host of different health-care providers who may not be able to provide definitive answers to their complaint. Pain has a high impact on a patient's quality of life, as it is not just how it hurts, but how it can then interfere with normal, everyday activities. The biopsychosocial approach is here to stay, and can be utilised in the future, to ensure intervention outcomes do not suffer from lack of diverse approaches and that patient-dentist relationships continue to thrive. Pharmacological management is just one aspect in the expansive management of orofacial pain conditions and, as we see advances in target-specific medications, will continue to be for years to come.

## Acknowledgements

We gratefully acknowledge Dove Press and the Journal of Pain Research for permitted use and adaptation of their diagrams.

## Conflicts of Interest

We have no conflicts of interest to declare.

## References

1. IASP. 2020. IASP Terminology. Available from URL: <https://www.iasp-pain.org/terminology?navItemNumber=576#Neuropathicpain> [accessed May 2020].
2. Clauw DJ. Fibromyalgia: a clinical review. *JAMA* 2014;311:1547–55.
3. Tasmanian Health Service. 2014. Understanding Persistent Pain. Available from URL: [https://outpatients.tas.gov.au/\\_\\_data/assets/pdf\\_file/0003/172578/CSS\\_-\\_Physiotherapy\\_-\\_Understanding\\_Persistent\\_Pain\\_Booklet.pdf](https://outpatients.tas.gov.au/__data/assets/pdf_file/0003/172578/CSS_-_Physiotherapy_-_Understanding_Persistent_Pain_Booklet.pdf) [accessed May 2020].
4. Coakley R, Schechter N. Chronic pain is like.. The clinical use of analogy and metaphor in the treatment of chronic pain in children. *Pediatr Pain Lett* 2013;15:1–8.
5. Zakrzewska JM. Differential diagnosis of facial pain and guidelines for management. *Br J Anaes* 2013;111:95–104.
6. Kosek E, Cohen M, Baron R, Gebhart GF, Mico J-A, Rice ASC *et al.* Do we need a third mechanistic descriptor for chronic pain states? *Pain* 2016;157:1382–6.
7. Trouvin AP, Perrot S. New concepts of pain. *Best Pract Res Clin Rheumatol* 2019;33:101415.
8. Burgmer M, Pleiderer B, Maihöfner C, Gaubitz M, Wessolleck E, Heuft G *et al.* Cerebral mechanisms of experimental hyperalgesia in fibromyalgia. *Eur J Pain* 2012;16:636–47.
9. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. *PLoS One* 2014;9:106–33.
10. British National Formulary. 2020. Neuropathic Pain. Overview and Management. Available from URL: <https://bnf.nice.org.uk/treatment-summary/neuropathic-pain.html> [accessed 5 February 2020].
11. Renton T. Introduction to pain. *Prim Dent J* 2018;7:17–21.
12. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. *Neuron* 2006;52:77–92.
13. Iwata K, Takeda M, Baeoh S, Shinoda M. Neurophysiology of orofacial pain In: Farah CS *et al.*, Contemporary Oral Medicine. New York: Springer Reference 1–23. Available from URL: [https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-28100-1\\_8-1](https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-28100-1_8-1) [accessed 5 February 2020].
14. Durham J, Touger-Decker R, Nixdorf DR, Rigassio-Radler D, Moynihan P. Oro-facial pain and nutrition: a forgotten relationship? *J Oral Rehab* 2015;42:75–80.

15. National Institute for Health and Care Excellence [NICE]. 2013. Neuropathic Pain – Pharmacological Management (NICE Clinical Guideline 173). Updated 2019. Available from URL: <https://www.nice.org.uk/guidance/cg173> [accessed 11 June 2020].
16. National Institute for Health and Care Excellence [NICE], 2013. Neuropathic Pain - Pharmacological Management. Guideline Consultation Comments Table. Available from URL: <https://www.nice.org.uk/guidance/cg173/documents/neuropathic-pain-pharmacological-management-guideline-consultation-comments2> [accessed 5 February 2020].
17. Ghurye S, McMillan R. Orofacial pain – an update on diagnosis and management. *Br Dent J* 2017;223:639–47.
18. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database Syst Rev* 2010;<https://doi.org/10.1002/14651858.CD004715>.pub2.
19. Medicines & Healthcare products Regulatory Agency [MHRA]. Regulatory Authority. Available from URL: [https://clinregs.niaid.nih.gov/country/united-kingdom#\\_top](https://clinregs.niaid.nih.gov/country/united-kingdom#_top) [accessed 22 March 2020].
20. British National Formulary. 2020. Dental Practitioners' Formulary. Available from URL: <https://bnf.nice.org.uk/dental-practitioners-formulary/> [accessed 22 March 2020].
21. Wandsworth Clinical Commissioning Group. 2019. Pharmacological Management of Neuropathic Pain in Primary Care. Available from URL: <http://www.wandsworthccg.nhs.uk/aboutus/Prescribing%20Guidelines%20v20/Neuropathic%20Pain%20in%20Primary%20Care%20-%20Pharmacological%20Management.pdf> [accessed 22 March 2020].
22. Bannon AW, Decker MW, Holladay MW, Curzon P, Donnelly-Roberts D, Puttfarcken PS *et al.* Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. *Science* 1998;279(5347):77–81.
23. Shader RI. Safety versus tolerability. *Clin Therapeut* 2018;40:672–3. <https://doi.org/10.1016/j.clinthera.2018.04.003>.
24. National Institute for Health and Care Excellence [NICE], 2015. Analgesia - Mild-to-Moderate Pain (Scenario: Choice of Analgesic). Revised September 2015. Available from URL: <https://cks.nice.org.uk/analgesia-mild-to-moderate-pain#!scenario> [accessed 5 February 2020].
25. Home Office 2019. Controlled Drugs: Personal Licence. Available from URL: <https://www.gov.uk/guidance/controlled-drugs-personal-licences> (accessed 22 March 2020).
26. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochr Datab Syst Rev* 2013;<https://doi.org/10.1002/14651858.CD010210>.pub2.
27. NHS Ipswich and East Suffolk - Clinical Commissioning Group. Guidance for Review of Patients taking Pregabalin or Gabapentin for Neuropathic Pain in Primary Care. Available from URL: <http://www.ipswichandeastsuffolkccg.nhs.uk/Portals/1/Content/Members%20Area/Clinical%20Area/Medicine%20management/Medical%20conditions/Pain/Pregabalin%20and%20Gabapentin%20discontinuation%20guidance%20v1%202018%20final.pdf> [accessed 22 March 2020].
28. NHS Surrey and Sussex, 2011. Guidelines for the Management of Chronic Non- Malignant Pain (CNMP) in Primary Care. Available from URL: <https://www.surreyandsussex.nhs.uk/wp-content/uploads/2013/04/NHS-Surrey-Chronic-Pain-Management-non-malignant2.pdf> [accessed 22 March 2020].
29. Specialist Pharmacy Service. 2019. How do you switch between tricyclic, SSRI and related antidepressants? Available from URL: [https://www.sps.nhs.uk/wp-content/uploads/2019/10/UKMI\\_QA\\_How-do-you-switch-between-TCA-SSRI-related-antidepressants\\_update\\_Oct-2019.pdf](https://www.sps.nhs.uk/wp-content/uploads/2019/10/UKMI_QA_How-do-you-switch-between-TCA-SSRI-related-antidepressants_update_Oct-2019.pdf) [accessed 22 March 2020].
30. Worcestershire Area Prescribing Committee. 2010. Guidelines for Analgesic Treatment of Chronic Pain. Available from URL: <http://www.worcestershire.nhs.uk/EasySiteWeb/GatewayLink.aspx?allid=5860> [accessed 22 March 2020].
31. National Institute for Health and Care Excellence [NICE], 2017. Headache - Medication Overuse (Scenario: Management of Medication Overuse Headache). Revised September 2015. Available from URL: <https://cks.nice.org.uk/headache-medication-overuse#!scenario> [accessed 5 February 2020].
32. NICE. 2017. Headache – Medication Overuse. Available from URL: <https://cks.nice.org.uk/headache-medication-overuse#!diagnosisSub> [accessed April 2020].
33. Derry CJ, Derry S, Moore R. Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Datab Syst Rev* 2014;<https://doi.org/10.1002/14651858.CD009281>.pub3.
34. Ouanounou A, Goldberg M, Haas DA. Pharmacotherapy in temporomandibular disorders: a review. *J Can Dent Assoc* 2017;83:h7.
35. Di Rienzo Businco L, Di Rienzo Businco A, D'Emilia M, Lauriello M, Coen Tirelli G. Topical versus systemic diclofenac in the treatment of temporo-



- mandibular joint dysfunction symptoms. *Acta Otorhinolaryngol Ital* 2004;24:279–83.
36. Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. *Pain* 2004;111:13–21.
  37. Kulkarni S, Thambar S, Arora H. Evaluating the effectiveness of nonsteroidal anti-inflammatory drug (s) for relief of pain associated with temporomandibular joint disorders: a systematic review. *Clin Exp Dent Res* 2020;6:134–46.
  38. Hersh EV, Balasubramaniam R, Pinto A. Pharmacologic management of temporomandibular disorders. *Oral Maxillofac Surg Clin North Am.* 2008;20:197–210.
  39. Lawson K. A brief review of the pharmacology of amitriptyline and clinical outcomes in treating fibromyalgia. *Biomedicines.* 2017;5:24.
  40. Pacher P, Kecskemeti V. Trends in the development of new antidepressants. Is there a light at the end of the tunnel? *Curr Med Chem* 2004;11:925–43.
  41. Dalton CB, Drossman DA. The Use of Antidepressants in the Treatment of Irritable Bowel Syndrome and Other Functional GI Disorders. Chapel Hill, NC: UNC School of Medicine.
  42. Haviv Y, Rettman A, Aframian D, Sharav Y, Benoliel R. Myofascial pain: an open study on the pharmacotherapeutic response to stepped treatment with tricyclic antidepressants and gabapentin. *J Oral Facial Pain Headache* 2015;29:144–51.
  43. NHS Medicines. 2020. Amitriptyline. Available from URL: <https://www.nhs.uk/medicines/amitriptyline-for-depression/> [accessed 22 March 2020].
  44. British National Formulary. Amitriptyline. Available from URL: <https://bnf.nice.org.uk/drug/amitriptyline-hydrochloride.html> [accessed 22 March 2020].
  45. Eijkelkamp N, Linley JE, Baker MD, Minett MS, Clegg R, Werdehausen R *et al.* Neurological perspectives on voltage-gated sodium channels. *Brain* 2012;135:2585–612.
  46. Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician* 2008;54:988–92.
  47. British National Formulary. Nortriptyline. Available from URL: <https://bnf.nice.org.uk/drug/nortriptyline.html> [accessed 22 March 2020].
  48. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 2005;96:399–409.
  49. British National Formulary. Gabapentin. Available from URL: <https://bnf.nice.org.uk/drug/gabapentin.html> [accessed 22 March 2020].
  50. Home Office. 2019. List of Most Commonly Encountered Drugs Currently Controlled Under the Misuse of Drugs Legislation. Available from URL: <https://www.gov.uk/government/publications/controlled-drugs-list-2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation> [accessed 22 March 2020].
  51. Public Health England. 2014. Advice for Prescribers on the Risk of the Misuse of Pregabalin and Gabapentin. Redditch: NHS England. Available from URL: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/385791/PHE-NHS\\_England\\_pregabalin\\_and\\_gabapentin\\_advice\\_Dec\\_2014.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/385791/PHE-NHS_England_pregabalin_and_gabapentin_advice_Dec_2014.pdf) [accessed April 2020].
  52. Wells C, Adcock A. Abuse and Misuse of Gabapentin: Clinical Evidence, Safety, and Guidelines. CADTH Rapid Response Report: Summary of Abstracts, 2017. Available from URL: <https://www.cadth.ca/sites/default/files/pdf/htis/2017/RB1146%20Gabapentin%20Misuse%20Final.pdf> [accessed April 2020].
  53. FDA. FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression. Available from URL: 2019 <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression> [accessed April 2020].
  54. Narain T, Adcock L. Gabapentin for Adults with Neuropathic Pain: A Review of the Clinical Effectiveness. Canadian Agency for Drugs and Technologies in Health. Available from URL: <https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0970%20Gabapentin%20for%20neuropathic%20pain%20Final.pdf> [Accessed 22 March 2020].
  55. Christo PJ, Cauley BD. Postherpetic Neuralgia. *Current Therapy in Pain.* H. S. Smith. Philadelphia: Saunders Elsevier, 2009 p. 263.
  56. Palliative Drugs. Gabapentin. Available from URL: <https://www.palliativedrugs.com/download/GABAPENTINnewsletter111203.pdf> [accessed 22 March 2020].
  57. NHS Mid-Essex CCG. Neuropathic Pain. Available from URL. 2017. <https://midessexccg.nhs.uk/medicines-optimisation/clinical-pathways-and-medication-guidelines/chapter-4-central-nervous-system-2/172-pain-management-of-neuropathic-pain-sep-2009-1/file>. [accessed 22 March 2020]
  58. British National Formulary. 2020. Epilepsy. Available from URL: <https://bnf.nice.org.uk/treatment-summary/epilepsy.html> [accessed 22 March 2020].
  59. British National Formulary. Pregabalin. Available from URL: <https://bnf.nice.org.uk/drug/pregabalin.html> [accessed 22 March 2020].
  60. Palliative Drugs. Pregabalin. Available from URL: <https://www.palliativedrugs.com/download/pregabalin140105aw.pdf> [accessed 22 March 2020].
  61. Parsons G. Guide to the Management of Gabapentinoid Misuse. Available from URL: <https://www.>

- prescriber.co.uk/article/guide-to-the-management-of-gabapentinoid-misuse/ [accessed May 2020].
62. Skljarevski V, Zhang S, Iyengar S, D'Souza D, Alaka K, Chappell A *et al.* Efficacy of duloxetine in patients with chronic pain conditions. *Current Drug Therapy* 2011;6:296–303.
  63. British National Formulary. Duloxetine. Available from URL: <https://bnf.nice.org.uk/drug/duloxetine.html> [accessed 22 March 2020].
  64. Palliative Drugs. Duloxetine. Available from URL: <https://www.palliativedrugs.com/download/DuloxetineUSAjunejulynewsletter.pdf> [accessed 22 March 2020].
  65. Smith HS, Bracken D, Smith JM. Duloxetine: a review of its safety and efficacy in the management of fibromyalgia syndrome. *J Cent Nerv Syst Dis* 2010;2:57–72.
  66. Wiffen P, Derry S, Moore A, McQuay HJ. Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev.* 2011;19.
  67. British National Formulary. Carbamazepine. Available from URL: <https://bnf.nice.org.uk/drug/carbamazepine.html> [accessed 22 March 2020].
  68. Reisner L, Pettengill CA. The use of anticonvulsants in orofacial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;91:2–7.
  69. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. *Br J Anaesth* 2019;123:E385–96.
  70. Flynn S, Ali Babi M. Anticonvulsants in Dowd, F., Johnson, B., Mariotti, A. *Pharmacology and Therapeutics for Dentistry (Seventh Edition)*. St. Louis, MO: Mosby, 2017:176–92.
  71. Ferrell PB, McLeod HL. Carbamazepine, *HLA-B\*1502* and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* 2008;9(10):1543–6.
  72. Pimthanotai N, Charoenwongse P, Mutirangura A, Hurley CK. Distribution of HLA-B alleles in nasopharyngeal carcinoma patients and normal controls in Thailand. *Tissue Antigens* 2002;59:223–5.
  73. Chung WH, Hung SI, Hong HS, Hsieh M-S, Yang LC, Ho H-C *et al.* Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004;428:486.
  74. British National Formulary. Oxcarbazepine. Available from URL <https://bnf.nice.org.uk/drug/oxcarbazepine.html> [accessed 22 March 2020].
  75. Jorns TP, Zakrzewska JM. Evidence-based approach to the medical management of trigeminal neuralgia. *Br J Neurosurg* 2007;21:253–61.
  76. DVLA. 2020. Available from URL: <https://www.gov.uk/government/organisations/driver-and-vehicle-licensing-agency> [accessed April 2020].
  77. Kausner Y, Kenntner-Mabiala R, Hoffmann S, Klatt J, Tracik F, Krüger HP. Effects of oxcarbazepine and carbamazepine on driving ability: a double-blind, randomized crossover trial with healthy volunteers. *Psychopharmacology* 2010;210:53–63.
  78. Kennedy KA, Ryan M. Neurotoxic effects of pharmaceutical agents III. In: Dobbs MR, editor. *Clinical Neurotoxicology, Syndromes, Substances, Environments*. Philadelphia, PA: Elsevier, 2009:358–71.
  79. Johnnesen SI. Chapter 9 - Therapeutic drug monitoring of antiepileptic drugs. In: Bogusz MJ. *Handbook of Analytical Separations Volume 5*. Oxford, UK: Elsevier, 2004, 221–53.
  80. May TW, Korn-Merker E, Rambeck R. Clinical pharmacokinetics of oxcarbazepine. *Clin Pharmacokinet* 2003;42(12):1023–42.
  81. Al-Quliti K. Update on neuropathic pain treatment for trigeminal neuralgia. *Neurosciences*. 2015;20:107–14.
  82. British National Formulary. Clonazepam. Available from URL: <https://bnf.nice.org.uk/drug/clonazepam.html> [accessed 22 March 2020].
  83. Zakrzewska JM, Forssell IH, Glennly AM. Interventions for the treatment of burning mouth syndrome. *Cochr Database Syst Rev* 2005; Issue 1. Art. No.: CD002779.
  84. Department for Transport. 2015. Drug Drive Legislation: Am I Fit to Drive? Available from URL: <https://www.gov.uk/government/news/drug-drive-legislation-am-i-fit-to-drive> [accessed 22 March 2020].
  85. DVLA. 2014. Guidance for Healthcare Professionals on Drug Driving. Department for Transport. Available from URL [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/325275/healthcare-profs-drug-driving.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/325275/healthcare-profs-drug-driving.pdf) [accessed May 2020].
  86. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. *Oral Dis* 2018;24:325–34.
  87. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J.* 2013;13:214–23.
  88. Gremeau-Richard C, Woda A, Navez ML, Attal N, Bouhassira D, Gagnieu MC *et al.* Topical clonazepam in stomatodynia: a randomised placebo-controlled study. *Pain* 2004;108:51–7.
  89. McMillan R, Forssell H, Buchanan JA, Glennly A-M, Weldon JC, Zakrzewska JM. Interventions for treating burning mouth syndrome. *Cochr Database Syst Rev* 2016;11:CD002779.
  90. Woda A, Navez ML, Picard P, Gremeau C, Pichard-Leandri E. A possible therapeutic solution for stomatodynia (burning mouth syndrome). *J Orofac Pain* 1998;12:272–8.

91. British National Formulary. Capsaicin. Available from URL: <https://bnf.nice.org.uk/drug/capsaicin.html> [accessed 22 March 2020].
92. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011;107:490–502.
93. Silvestre FJ, Silvestre-Rangil J, Tamarit-Santafe C, Bautista D. Application of a capsaicin rinse in the treatment of burning mouth syndrome. *Med Oral Patol Oral Cir Bucal* 2012;1:E1–4.
94. Petruzzi M, Lauritano D, De Benedittis M, Baldoni M, Serpico R. Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study. *J Oral Pathol Med* 2004;33:111–4.
95. Smutzer G, Devassy RK. Integrating TRPV1 receptor function with capsaicin psychophysics. *Adv Pharmacol Sci* 2016;<https://doi.org/10.1155/2016/1512457>.
96. Kahn MA. Chapter 16. Burning mouth syndrome, neuralgia, and myofascial pain. In *Your Pocket-size Dental Drug Reference: A Handbook of Commonly Used Dental Medications Useful in the Management of Oral Diseases and Conditions*. Shelton, CT: People's Medical Publishing House (PMPH), 83–4.
97. Mínguez-Serra MP, Salort-Llorca C, Silvestre-Donat FJ. Pharmacological treatment of burning mouth syndrome: a review and update. *Med Oral Patol Oral Cir Bucal* 2007;12:E299–304.
98. British National Formulary. Baclofen. Available from URL: <https://bnf.nice.org.uk/drug/baclofen.html> [accessed 22 March 2020].
99. McCleane G. Muscle relaxants. In Smith HS, editor. *Current Therapy in Pain*. Philadelphia, PA: Elsevier, 2009:470–5.
100. Raskin NH. *Trigeminal Neuralgia*. New York: Churchill Livingstone, 1998.
101. Parekh S, Shah K, Kotdawalla H. Baclofen in carbamazepine resistant trigeminal neuralgia – a double-blind clinical trial. *Cephalgia* 1989;9(10):392–3.
102. Singh MK, Egan RA. Trigeminal Neuralgia Treatment and Management. Available from URL: <https://emedicine.medscape.com/article/1145144-treatment#d13> [accessed May 2020].
103. Napenas JJ, Zakrzewska JM. Diagnosis and management of trigeminal neuropathic pains. *Pain Manag* 2011;1:353–65.
104. British National Formulary. Lamotrigine. Available from URL: <https://bnf.nice.org.uk/drug/lamotrigine.html> [accessed 22 March 2020].
105. Bentley P, Sharma P. *Neurological disorders - epilepsy, Parkinson's disease and multiple sclerosis*. In *Clinical Pharmacology*, Eleventh Edition. London, UK: Churchill Livingstone, 2012.
106. Palacios-Sanchez B, Moreno-Lopez LA, Cerero-Lapiedra R, Llamas-Martinez S, Esparza-Gomez G. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. *Med Oral Patol Oral Cir Bucal* 2015;20:e435–40.
107. Femiano F, Scully C. Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med*. 2002;31:267–9.
108. Hounsom L, Horrobin DF, Tritschler H, Corder R, Tomlinson DR. A lipoic acid-gamma linolenic acid conjugate is effective against multiple indices of experimental diabetic neuropathy. *Diabetologia* 1998;41:839–43.
109. British National Formulary. Lidocaine Hydrochloride. Available from URL: <https://bnf.nice.org.uk/drug/lidocaine-hydrochloride.html> [accessed 10 June 2020].
110. Haas DA. Localized complications from local anesthesia. *J Calif Dent* 1998;26:677–82.
111. Evers H, Haegerstam G, Hakansson L. *Pharmacodynamic Aspects Introduction to Dental Local Anaesthesia* 1990, second edition. Switzerland: Mediglobe 22.
112. Scottish Dental Clinical Effectiveness Programme. 2016 Drug Prescribing For Dentistry Third Edition, Section 9 - Mucosal Ulceration and Inflammation. Available from URL: <http://www.sdcep.org.uk/wp-content/uploads/2016/03/SDCEP-Drug-Prescribing-for-Dentistry-3rd-edition.pdf> [accessed 10 June 2020].
113. British National Formulary. Benzydamine Hydrochloride. Available from URL: <https://bnf.nice.org.uk/drug/benzydamine-hydrochloride.html> [accessed 10 June 2020].
114. Quane PA, Graham GG, Ziegler JB. Pharmacology of Benzydamine. *Inflammopharmacology* 1998;6:95–107.
115. British National Formulary. Benzydamine. Available from URL: <https://bnf.nice.org.uk/interaction/benzydamine.html> [accessed 10 June 2020].
116. Dureja GP, Iyer RN, Das G, Ahdal J, Narange P. Evidence and consensus recommendations for the pharmacological management of pain in India. *J Pain Res* 2010;10:709–36.
117. Government of Western Australia. 2020. Department of Health. painHEALTH Pain Types. Available from URL: <https://painhealth.csse.uwa.edu.au/pain-module/pain-types/> [accessed May 2020].
118. King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL 3rd. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. *Pain* 2009;143:172–8.
119. Furquim BD, Flamengui LMSP, Conti PCR. TMD and chronic pain: a current view. *Dental Press J Orthodont* 2015;20:127–33.

120. Monaco A, Cattaneo R, Marci MC, Pietropaoli D, Ortu E. Central sensitization-based classification for temporomandibular disorders: a pathogenetic hypothesis. *Pain Res Manag* 2017;2017:1–13. <https://doi.org/10.1155/2017/5957076>.
121. Faculty of Pain Medicine - Royal College of Anaesthetists. 2019. Driving and Pain. Guidance for Faculty of Pain Medicine Members. Available from URL: <https://fpm.ac.uk/sites/fpm/files/documents/2019-07/FPM-Driving-and-Pain-members-information.pdf> [accessed 22 March 2020].
122. The British Pain Society. 2007. Pain and Substance Misuse: Improving the Patient Experience. Available from URL: [https://www.britishpainsociety.org/static/uploads/resources/misuse\\_0307\\_v13\\_FINAL.pdf](https://www.britishpainsociety.org/static/uploads/resources/misuse_0307_v13_FINAL.pdf) [accessed 22 March 2020].
123. British National Formulary. 2020. Controlled Drugs and Drug Dependence. Available from URL: <https://bnf.nice.org.uk/guidance/controlled-drugs-and-drug-dependence.html> [accessed 22 March 2020].
124. Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. *Addiction* 2016;111:1160–74.
125. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs* 2017;77:403–26.
126. Faculty of Pain Medicine - Royal College of Anaesthetists. Opioids Aware. Available from URL: <https://fpm.ac.uk/opioids-aware> [accessed 22 March 2020].
127. Anderson P. 2019. New Guideline for Trigeminal Neuralgia Released. Medscape. Available from URL: [https://www.medscape.com/viewarticle/915265#vp\\_2](https://www.medscape.com/viewarticle/915265#vp_2) [accessed 22 March 2020].
128. British National Formulary. 2020. Analgesics. Available from URL: <https://bnf.nice.org.uk/treatment-summary/analgesics.html> [accessed 22 March 2020].
129. Portenoy RK. Opioid therapy for chronic non-malignant pain: a review of the critical issues. *J Pain Symptom Manage* 1996;11:203–17.
130. Seyfried O, Hester J. Opioids and endocrine dysfunction. *Br J Pain* 2012;6:17–24.
131. British Medical Journal. Withdrawing patients from antidepressants. *Drug Ther Bull* 1999;37:49–52.
132. Mauri MC, Volonteri LS, Colasanti A, Panza G. Acute, continuation and maintenance phases of antidepressant treatment. *Minerva Psichiatr* 2005;46:89–98.
133. Gautam S, Jain A, Gautam M, Vahia VN, Grover S. Clinical practice guidelines for the management of depression. *Indian J Psychiatr* 2017;59:34–50.
134. Johnson CF, Williams B, MacGillivray SA, Dougall NJ, Maxwell M. ‘Doing the right thing’: factors influencing GP prescribing of antidepressants and prescribed doses. *BMC Family Pract* 2017;18:1–13.
135. Padilla M, Clark GT, Merrill RL. Topical medications for orofacial neuropathic pain: a review. *J Am Dental Assoc* 2000;131:184–95.
136. Nasri-Heir C, Khan J, Heir GM. Topical medications as treatment of neuropathic orofacial pain. *Dent Clin N Am* 2013;57:541–3.
137. Al-Musawi M, Durham J, Whitworth JM, Stone SJ, Nixdorf DR, Valentine RA. Effect of topical neuro-modulatory medications on oral and skin keratinocytes. *J Oral Pathol Med* 2017;46:134–41.
138. Ohrbach R, Durham J. Biopsychosocial aspects of orofacial pain. In: Farah CS, Balasubramaniam R, McCullough MJ, editors: *Contemporary Oral Medicine*. Heidelberg: Springer Meteor, 2018:1–21.
139. Durham J, Nixdorf DR. Healthcare pathway and biopsychosocial impact of persistent dentoalveolar pain disorder: a qualitative study. *Int Endod J* 2014;47:1151–9.
140. Durham J, Shen J, Breckons M, Steele J, Araújo-Soares V, Exley C *et al.* Healthcare cost and impact of persistent orofacial pain. *J Dental Res* 2016;95:1147–54.
141. McMillan R. Therapeutics of pain management. In: Wray D, editor: *Essential Dental Therapeutics*. New Jersey: Wiley Blackwell, 2017:56.