Review Article

Use of compounded topical medications for treatment of orofacial pain: a narrative review

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Background and Objective: Orofacial pain is a frequent form of pain perceived in the face and/or oral cavity. It may be caused by diseases or disorders of regional structures, dysfunction of the nervous system, or through referral from distant sources. The objective of the narrative review is to describe the classifications of orofacial pain, potential targets for pharmacotherapeutic treatment and discusses the novel topical administration of already approved medications for management. Actual cases will be presented illustrating administration and efficacy.

Methods: Electronic databases (PubMed, Embase, Ovid Medline, Google scholar, Scopus, Cochrane library) were searched using keywords "Topical medications" and "Orofacial Pain" from 1st January 1974 to 30th November 2021. A total of 280 articles were identified and relevant 105 articles were included in the review.

Key Content and Findings: The multifactorial etiology of orofacial pain requires an accurate diagnosis in order to appropriately treat. Treatment of orofacial pain typically includes pharmacotherapy, which can only be effective if the source of pain is clearly identified. In most cases of orofacial pain, primary treatment includes pharmacotherapy. The pharmacotherapeutic agents required to treat the majority of orofacial pain disorders are associated with significant side effects, interactions, and complications. Administration of medications topically avoids many, if not all side effects. Topical administration of approved medications for neuropathic and musculoskeletal pain offers a unique delivery system that can improve the quality of life while avoiding systemic side effects.

Conclusions: Topical medications offer safe and effective strategy for management of neuropathic and musculoskeletal orofacial pain while avoiding significant side effects. Topical administration is especially useful for the medically complex, compromised, or elderly patients with comorbid medical conditions or those using other medications which may contraindicate the systemic administration of otherwise appropriate pharmacotherapeutics.

Keywords: Topical medications; orofacial pain; neuropathic pain; musculoskeletal pain; pharmacotherapy

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Introduction

Diagnosis is the key. In the 1980s, Dr. Weldon Bell offered a paradigm for classification for orofacial pain disorders (1). He identified sources of pain as arising from musculoskeletal, neuropathic, neurovascular, and symptom somatoform disorders, previously referred to as a psychogenic pain. Only through the process of differential diagnosis, identification of etiologies of chronic complex orofacial pain disorders and temporomandibular dysfunction can treatment hope for predictability of success. Failure to accurately identify specific etiologies may result in indiscriminate therapeutic trials with no specific direction, leading to failed treatment and possibly inappropriate or invasive procedures. Once accomplished, mechanisms can be defined leading to specific pharmacotherapeutic targets, including the use of topical medications.

The objective of the narrative review is to describe the classifications of orofacial pain, potential targets for pharmacotherapeutic treatment and discusses the novel topical administration of already approved medications for management. Actual cases will be presented illustrating administration and efficacy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-22-10/rc).

Methods

Electronic databases searched including PubMed, Embase, Ovid Medline, Google Scholar, Scopus and the Cochrane Library using keywords "Topical medications" and "Orofacial Pain" from January 1, 1,974 through November 30, 2021. Two authors, (GH, GK) conducted the search independently and in case of ambiguity, a third author, CNH, was involved and mutual consensus was obtained by discussion. Case reports, research studies, systematic reviews and meta-analysis were included. Abstract, conference proceedings, letters to editors and articles in language other than English were excluded. A total of 280 articles were identified and relevant, 105 articles were included in the review. The methods and search terms are detailed in *Table 1*.

Discussion

Classification of orofacial pain, pain mechanisms, presentations, and potential therapies:

Classification of an orofacial pain disorder must begin with a complete history and physical evaluation. Osler advised over 100 years ago that listening to the patient carefully will lead to the diagnosis. Clinical observation and the physical examination augment a detailed history (2,3). The judicious use of adjunctive diagnostic testing to confirm or refute a diagnosis is often necessary to achieve the ultimate goal of identification of the source of the patient's pain complaint.

Classification of orofacial pain etiologies begins with the history. The clinician must define the problem by its chronology, location, duration, frequency, intensity, precipitating and ameliorating factors, current and past medications and review and outcome of prior treatments.

The most common source of orofacial pain is of odontogenic origin; therefore, the dental clinician must perform a complete dental evaluation, ruling out odontogenic pain as the primary source. The next most common source of pain is of musculoskeletal origin, followed by neurovascular or headache disorders resulting in pain and the orofacial region (4). As neurovascular orofacial pain and symptom somatoform disorders are not amenable to topical therapies, they will not be considered in this discussion. This discussion will be limited only to neuropathies and musculoskeletal complaints.

Mechanisms must briefly be discussed

Nociceptive pain

Nociceptive pain begins with a noxious stimulus which activates a primary afferent nociceptor. Nociceptors are high threshold neurons which produce action potentials in the presence of a stimulus capable of causing tissue damage or perceived as a potentially tissue damaging stimulus. Nociceptive pain is discriminative in that it is easily localized, of short duration, and terminates when the noxious stimulus is removed. The mechanism of initiating an action potential as a result of the noxious stimulus applied to a nociceptor begins with the transduction of noxious mechanical, chemical, or thermal stimuli capable of activating high threshold afferent neurons. This normal physiologic response acts as a protective mechanism resulting in withdrawal and avoidance of further noxious stimuli. Nociceptive pain is typically acute and of short duration, and not in need of chronic management (5).

Nociceptive pain is consistent with a high intensity mechanical, chemical or thermal stimulus. Nociception ends, as does the painful response, upon withdrawal from the noxious stimulus. An example might be a gentle but painful prick of a pin without tissue damage, resulting in

Table 1 Methods and search terms used for this review

Items	Specification
Date of search	1st December, 2021
Databases and other sources searched	PubMed, Embase, Ovid Medline, Google scholar, Scopus, Cochrane library
Search terms used including MeSH and free text search terms and filters	("topical"[All Fields] OR "topically"[All Fields] OR "topicals"[All Fields]) AND ("medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields]) AND ("facial pain"[MeSH Terms] OR ("facial"[All Fields] AND "pain"[All Fields]) OR "facial pain"[All Fields] OR ("orofacial"[All Fields] AND "pain"[All Fields]) OR "orofacial pain"[All Fields])
Timeframe	January 1,1974 through November 30, 2021
Inclusion and exclusion criteria	Case reports, research studies, systematic reviews and meta-analysis were included; abstract, conference proceedings, letters to the editor and articles in language other than English were excluded
Selection process	Two authors (GH, GK) conducted the search independently; in case of ambiguity, a third author (CNH) was involved and mutual consensus was obtained by discussion

a reflex arc and withdrawal from the noxious stimulus, at which point nociception ends.

Inflammatory pain

The mechanism of inflammatory pain is more complex. Assuming that tissue damage has occurred, the result is infiltration of mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts (6,7). Inflammatory mediators in the area of tissue damage include histamine, serotonin, ATP, substance P and CGRP, frequently referred to as "inflammatory soup", which sensitize high threshold nociceptors in the area of inflammation, lowering their firing threshold. Nociceptors become responsive to non-noxious stimuli, especially light touch, and non-noxious thermal stimulation (5). This phenomenon is referred to as peripheral sensitization. As a result, sensitized nociceptors can produce action potentials in the presence of non-noxious stimuli. Inflammatory pain persists until tissue damage resolves and inflammatory mediators dissipate. Inflammatory pain is consistent with allodynia, a painful response to a nonpainful stimulus, and hyperalgesia, a greater response than expected to a painful stimulus.

An example of inflammatory pain may be compared to the tissue damage following a burn. The tissue damaging results in immediate nociceptive pain, followed by inflammatory pain. The propagates of the inflammatory mediators in the injured area perpetuates allodynia and hyperalgesia. A previously non-painful stimulus, such as washing the hand with cool water now results in pain.

Peripheral sensitization can lead to central sensitization by activation of A-delta and C-fiber nociceptors resulting in the release of neurotransmitters including glutamate, substance P, calcitonin gene -related peptide (CGRP) and adenosine triphosphate (ATP) within the spinal dorsal horn or brainstem that the sub nucleus, caudalis of the trigeminal nerve. This component of central sensitization activates previously inactive second order N-methyl-D-aspartate (NMDA) receptors, increasing post synaptic sensitivity. As central sensitization increases, transmission of noxious signals via second-order neurons is amplified.

Neuropathic pain

Neuropathic pain is defined as 'pain caused by a lesion or disease of the somatosensory nervous system (8). Variations of neuropathic pain commonly seen by the orofacial pain clinician include painful posttraumatic trigeminal neuropathy and sympathetically maintained pain (9). Trauma along the course of a primary afferent nociceptive such as seen in post dental implant injuries or following oral surgical trauma can result in alteration of cell membrane physiology. Sodium channels and adrenergic receptors migrate to the site of injury resulting in ectopic activity as well as action potentials in response

to circulating noradrenaline affecting adrenergic receptors that populate the site of trauma. In the case of an increase in the representation of sodium channels at the site of trauma, ectopic activity results in persistent pain, typically of a burning quality with occasional paroxysmal episodes. With an increased representation of cholinergic receptors, stress, physical activity, or even cold weather may result in a sympathetically maintained hyperactivity of the traumatized nerves characterized by an increased perception of burning pain and sudomotor activity associated with facial flushing and burning discomfort (10).

The best example of neuropathic pain is postherpetic neuralgia (PHN). The herpes virus travels from the dorsal root trigeminal ganglion towards the periphery resulting in damage to the peripheral receptors as well as along the course of the primary afferent nociceptive neurons. Sensitization of the peripheral receptors, and changes along the axonal membrane increase sensitivity to circulating noradrenaline in the case of sympathetically maintained pain (SMP), as well as unstable sodium channels, result in persistent discomfort. As with other forms of neuropathic pain, PHN has a burning quality with occasional spontaneous or provoked paroxysms of pain. Significant allodynia and hyperalgesia are also characteristic of neuropathic pain (11).

Nociplastic pain

Nociplastic pain is a fourth classification of pain. While the clinical presentation is nearly identical to traumatic neuropathy, it does not result from, or is caused by ongoing inflammation or damage to tissues, or neuropathic pain following neuronal damage (12). In the case of nociplastic pain, there may be no history of trauma or disease of the sensory system to account for the complaints.

Typical therapy for neuropathic pain

Treatment of neuropathic pain through pharmacotherapeutic mechanisms involves a variety of classifications of medication. This includes topical local anesthetics affecting primary afferent receptors, tricyclic antidepressants, antiseizure medications, gabanoids for the purpose of stabilizing neuronal cell membranes, and on rare occasion opioids for pain (13) (*Table 2*).

First line systemic medications used for the treatment of neuropathic pain includes topical anesthetics, tricyclic antidepressants, calcium channel blockers affecting the alpha 2-delta logins such as gabapentin and pregabalin, selective serotonin reuptake inhibitors (SSRIs). Opioids and medications including tramadol considered second line. These medications are accompanied by a variety of side effects, potential complications, and interactions with other medications (13).

The target mechanisms of tricyclic antidepressants are as membrane stabilizers preventing ectopic activity, sodium channel stabilizers and cholinergic receptor antagonists. The efficacy of tricyclic antidepressants in the presence of traumatic nerve injury is the reduction of ectopic activity of unstable neuronal membranes, reduction of the activity of circulating noradrenaline on cholinergic receptors which may also result in action potentials, and finally to increase the efficiency of the descending pain inhibitory system (15). Side effects include sedation, hyposalivation and appetite stimulation. Patients must be warned of side effects including the perceptions of hunger, sleepiness, and thirst. The sedative effect of these medications may result in an inability to continue in certain occupations, e.g., fire and police personnel, those who drive for their occupation, etc. Tricyclics are also contraindicated for patients with narrow angle glaucoma and arrhythmias, and urinary retention. These side effects can be potentiated when given with other drugs with a similar profile. Serotonin syndrome must also be considered. Hepatic and hematopoietic disorders can preclude the use of these medications (13,15).

Antiseizure medications including carbamazepine, oxcarbazepine and lamotrigine specifically target sodium channels for neuronal stabilization. These medications may result in bone marrow suppression, potentially irreversible anemias, and elevated liver function. They require strict monitoring with repeated serological testing. Lamotrigine and other antiseizure medications at the risk of Stevens Johnson Syndrome (13).

Gabanoids such as pregabalin or gabapentin regulate alpha-2 delta subunit sodium channels of traumatized neurons limiting exocytosis and the release of neurotransmitter at the primary to second-order synapse. Both medications carry side effects of sedation and in some cases especially in the elderly, disequilibrium. They can be contraindicated in the presence of kidney function disorders (13,15).

Opioids have little effect on neuropathic pain and are rarely used except in the most extreme cases. Opioids have a plethora of side effects including constipation, sedation, respiratory depression, and addiction (13,15).

Topical medication alternatives for neuropathic pain

Table 3 lists topical compounds for neuropathic pain

Table 2 Currently available treatment options for neuropathic pain with mechanism, side effects, other benefits, precautions, and doses (13,14)

Class	Drugs	Mechanism of action	Side effects	Other benefits	Precautions	Doses range
First line						
Calcium channel α2-đ ligands	Gabapentin, gabapentin extended release, pregabalin	α2-đ subunit voltage gated calcium channel and may inhibit the release of glutamate, NE, etc.	Drowsiness, dizziness peripheral edema	No significant drug interactions	Renal insufficiency	Gabapentin: 1,200–3,600 in divided doses tid; Gabapentin extended release: 1,200–3,600 in divided doses bd; Pregabalin: 300–600 mg in divided doses bd
SNRIs	Duloxetine, venlafaxine	Serotonin and norepinephrine reuptake inhibitors	Dizziness, nausea, dry mouth, insomnia	Beneficial in depression	Caution in patients with alcohol abuse, hepatic dysfunction, tramadol	Duloxetine: 60–120 mg od; Venlafaxine extended release: 150–225 mg od
Tricyclic antidepressants	Nortriptyline, desipramine	Serotonin and norepinephrine reuptake inhibitors, sodium channels blockers, anticholinergics	Sedation, drowsiness, anticholinergic effects	Beneficial in sleep disturbance and depression	Caution in patients with seizure disorders, Glaucoma, cardiac disease	25–150 mg od or divided doses bd
Second line						
Topical lidocaine	5% lidocaine patch	Sodium channel blockade	Local irritation, rash, erythema	None	None	1 to 3 patches per day
Capsaicin	Capsaicin 8% patches	Substance P	Local irritation, rash, erythema	None	None	1 to 4 patches for 30–60 min once in 3 months
Opioid agonists	Tramadol	μ-receptor agonist, serotonin, and norepinephrine reuptake inhibitors	Drowsiness, constipation, nausea, vomiting	–	Serotonin syndrome if used in combination with TCA	50 mg once daily or tid/400 mg daily as long-acting drug
Third line						
Opioids	Morphine, oxycodone, methadone	μ-receptor agonists	Nausea vomiting, dizziness, constipation	Rapid onset of analgesia	Substance abuse, driving impairment, suicide risk	Morphine: 10–15 mg every 4 h

SNRIs, serotonin and norepinephrine reuptake inhibitors; NE, norepinephrine; TCA, tricyclic antidepressant.

and dosages available without the need for custom compounding.

Depending on the target for treatment, and effective topical preparation for treating neuropathic pain may include any of the following (*Table 4*; note: percentages may vary; therefore, the term custom compounding). However, the most effective active ingredients from the following list have proven to be pregabalin 10%. The base compound includes pregabalin 10% in a lipoderm vehicle. The other components may vary. Intraorally, topical medications are held in place by what is referred to as a neurosensory stent or drug delivery device.

An example of a neurosensory stent used to apply topical medication in the area of the long buccal nerve injury in the area of a first molar extraction is seen in *Figure 1* an anterior neurosensory stent placed for post endodontic neuropathic pain in the maxillary anterior region. Facilitation of retention of these stents is via a chemically inactive dextrose based dental adhesive.

Clinical case of neuropathic pain

This case illustrates the potential use and efficacy of topical

Table 3 The initial and maximal doses of the topical agents (16)

Agent	Initial dose	Maximum dose	Comments
Lidocaine ointment (5%)	Topical application of 5 g/day (250 mg of lidocaine base); equivalent to a 6 in. of ointment	17 to 20 g of ointment (850 to 1,000 mg of length lidocaine base) per day	Apply to intact skin only
Lidocaine patch (5%)	Apply up to three patches topically at one time, for up to 12 hours within a 24-hour period	–	Apply to intact skin only; patches may be cut into smaller sizes
Capsaicin (0.025–0.075%)	Apply as a thin film to the affected area three to four times per day; gently rub in until fully absorbed	–	Apply to intact skin only; application for up to 8 weeks may be necessary; wash hands thoroughly immediately after use; apply to intact skin no more frequently than every 3 months
Capsaicin patch (8%)	Apply up to four patches every 3 months for 60 min as needed	–	

Table 4 Typical ingredients of a custom compounded neuropathic pain medication

Agent	Action	Percentage
Ketamine	NMDA antagonist	4%
Carbamazepine	Sodium channel stabilizer	4%
Lidocaine	Topical local anesthetic and sodium channel stabilizer	1%
Ketoprofen	Anti-inflammatory	4%
Gabapentin	Alpha-2 delta membrane stabilizer, GABA-glutamate antagonist	4%
Pregabalin	Alpha-2 delta membrane stabilizer	10%
Lipoderm	Inert vehicle; lipoderm is the transdermal gel base	Lipoderm QS volume 100 mL
Oral adhesive paste	Inert material to maintain the stent in place	Carboxymethylceluose, gelatin, pectin, xanthan gum, oleabase plasticizer, range 2–4%
Ethoxy diglycol	Inert vehicle modifier for depth and speed of penetration	Range 2–5%
Flavoring of choice	If desired	Typically tangerine flavoring

NMDA, N-methyl-D-aspartate; GABA, gamma-aminobutyric acid; QS, Quantum Statis.

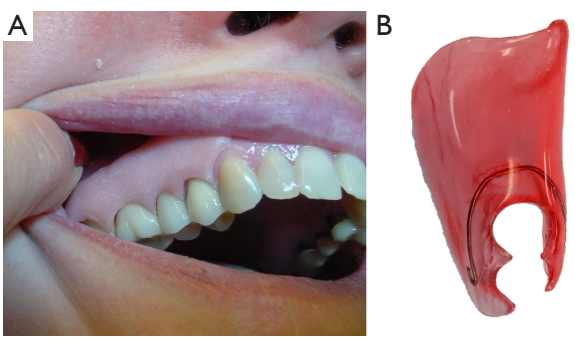

Figure 1 An anterior neurosensory stent placed for post endodontic neuropathic pain in the maxillary anterior region (A) and a neurosensory stent placed in the right posterior mandibular region following long buccal nerve trauma incurred during the first molar extraction (B).

intra-oral medications.

A 34 male-old male presented to the Center for Temporomandibular Disorders and Orofacial Pain, at Rutgers School of Dental Medicine, with the chief complaint of severe burning pain at the intersection of the of the right soft and hard palate. Pain began within 24 hours following the extraction of the non-restorable tooth #1 (maxillary right third molar). The anesthetic used during the procedure was mepivacaine. The patient reported an anesthetic effect lasting for approximately 36 hours. A severe burning sensation began in the anesthetized area 4–5 days following the extraction. Pain intensified during the subsequent several months and spread over a wider area. One year post extraction, the pain was reported as severe.

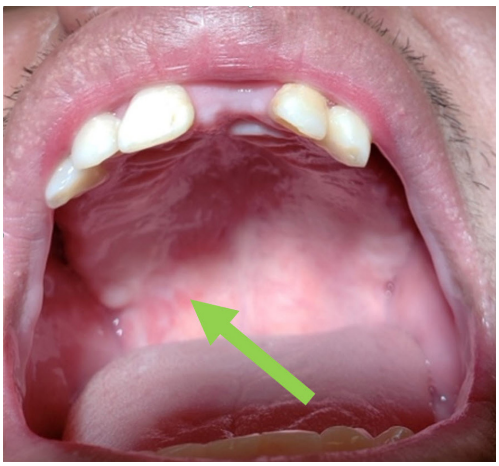

Figure 2 Clinical presentation: erythematous lesion at the intersection of the hard palate and soft palate on the right side.

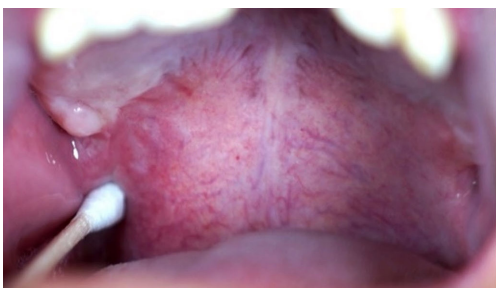

Figure 3 Cold test: application of ethyl chloride intensified the spread of symptoms.

The distribution of the pain was in the area supplied by right greater and lesser palatine nerve and described as continuous burning, sharp and throbbing. The intensity of pain 10 out of 10 on visual analogue scale during exacerbations. Aggravating factors included eating, drinking cold water, bending, and sleeping on the right side of the face. There were no identified alleviating factors. The patient reported painful swelling radiating to the right temple and zygomatic area, as well as along the right arm during exacerbations.

The patient sought relief from numerous health care providers including dentists and otorhinolaryngologists with no success. In the absence of a diagnosis, no specific treatment was provided. Prior treatments included acetaminophen, amoxicillin, and extraction of tooth number #2, with no benefit.

There was no relevant medical history, and the patient was not taking any medication at the time of the initial visit. Sleep history was within normal limits, but the patient reported that severe pain frequently awakened him from sleep.

During the physical exam, an erythematous area was observed in the area of pain. The right side (*Figure 2*) while the borders were erythematous, the center was blanched with the appearance of leukoplasia in the center. The affected area presented with allodynia and hyperalgesia.

As a diagnostic test, a cotton swab with a vapor: spray (ethylchloride) was applied first at the gingiva on the contralateral side and also at the palatal mucosa of painful site in the area of the extracted tooth #1. There was no significant response to the cold application at the contralateral side. The cold aftersensation disappeared immediately following removal of the stimulus. No physical changes were observed (17).

The identical cold sensation applied to the contralateral side was painful and reproduced the burning sensation. The cold after sensation persisted for more than 60 seconds following removal of the cold stimulus. Additionally, following the application of the cold, the erythematous area intensified and spread (*Figure 3*). A local anesthetic infiltration was administered to the painful area utilizing 3% mepivacaine. Prior to the injection, the VAS was 10 out of 10 and 5 minutes after the injection decreased to only 8 out of 10, therefore. The effect of local anesthesia was equivocal. At the same visit a topical compound was applied (Lidocaine, Ketoprofen, Gabapentin, Pregabalin, Ketamine). The VAS prior to application of the topical was 8 out of 10 and decreased to 3 out of 10 within 30 seconds and 0 out of 10 after 5 minutes after. The erythematous area decreased in intensity and size as well.

A prescription for a custom compounded topical neuropathic pain medication was provided. The topical compound was applied every 3–4 hours. The patient presented to the clinic for a follow-up visit 2 weeks later. Symptoms were significantly reduced not only on intensity to VAS of 2–3 out of 10, but also the frequency change from continuous to only occasionally episodic. Within six months, the patient was pain free. While this is an unusual case, the response to topical compounded medications is typical. Furthermore, the patient is a construction worker, constantly working on ladders and rooftops. In any of the more conventional pharmacotherapeutic agents indicated for his problem would have put them at risk for injury due to side effects.

Table 5 Commonly used muscle relaxants [adapted from Wecker *et al.* (22)]

Agent	Initial dose	Comment	Indications are adverse effects
Cyclobenzaprine	10 mg hs	5-Methylidene-5H-dibenzo [a,d] cycloheptene A centrally acting skeletal muscle relaxant structurally related to tricyclic antidepressants	Relieves local skeletal muscle spasm does not interfere with muscle function (23); side effects include sedation, thirst, and stimulation of appetite
Diazepam	Dose: initial 2 mg/day, gradually increase to maximum 60 mg/day (5 mg tid)	Cl-channels; enhances GABA-A receptors; inhibition at presynaptic and postsynaptic sites in the spinal cord; acts in the brain as hypnotic, sedative	Sedation, weakness, hypotension, memory impairment, ataxia, confusion, depression; chronic effects: dependency, withdrawal, and tolerance possible; chronic effects: dependency, withdrawal, and tolerance possible
Baclofen	Dose: orally 5 mg three times daily, gradually increase to 20 mg	K+ channels; acts presynaptically at GABA-B receptors in the spinal cord to reduce transmitter, antispasmodic; lets K+ out	Adverse effects: muscle weakness, sedation, hypotonia, ataxia, confusion, fatigue, nausea, liver toxicity
Tizanidine	Dose: initial 4 mg three times daily increase to 36 mg/day	Acts presynaptically at $\alpha 2$ adrenergic receptors; inhibits spinal motor neurons	Adverse effects: drowsiness, dizziness, dry mouth, orthostatic hypotension; chronic effects: rebound hypertension with rapid withdrawal
Botulinum toxin	Up to 100 units depending on size of muscle	Prevents ACh release at the myoneural junction	May cause muscle unexpected muscle weakness, allergic response

GABA-B, gamma-aminobutyric acid-B.

Musculoskeletal pain

Musculoskeletal pain is characterized by a typically dull and aching sensation which is exacerbated by movement of the affected region. Musculoskeletal pain, myogenous or arthrogenous, is peripheral and often a consequence of overuse, abuse, or injury of musculoskeletal structures (18). The most common form of chronic musculoskeletal pain is myofascial pain.

Myofascial pain is characterized by hypersensitive bands of muscle tissue with focal areas of local tenderness and referral of pain to distant locations outside the territory of the involved muscle. They currently accepted cause for myofascial pain due to miniature motor and plate potentials at the myoneural junction. Acetylcholine leaking from the presynaptic motor neurons at the motor neurons synaptic cleft results in focal contraction of small fibers within the affected muscle (19). Constant muscle activity leads to anaerobic activity and buildup of lactic acid. The acidic environment leads to the destruction of acetylcholinesterase, increased levels of acetylcholine and muscle contraction (20,21). Anaerobic activity and muscle ischemia produces algetic compounds that activate muscle nociceptors. The clinical presentation of the patient with chronic myofascial pain is typically of chronic dull aching pain. Pain may be sharp during certain movements, with fatigue of the muscles and limited range of movement. Chronic myofascial pain can refer to distant sites outside the border of the affected muscle, making a diagnosis even more difficult. The consequence of chronic musculoskeletal pain is the activation of the previously mentioned peripheral and central pain mechanisms. Another form of a myogenous pain is myositis. Myositis is an inflammatory disorder involving the mechanisms of myofascial pain with a concomitant presence of inflammatory mediators similar to that of nociceptive pain.

Typical therapy for musculoskeletal pain

Treatment of musculoskeletal pain includes homecare, physical therapy and perhaps the use of muscle relaxants such as cyclobenzaprine, methocarbamol, baclofen and tizanidine. Commonly prescribed muscle relaxants are listed in *Table 5*.

All of the medications listed above have an effect on muscle activity either locally at the muscle itself or through spinal cord mechanisms and have the potential for sedation is a primary side effect. As therapeutic levels are approached, side effects are unavoidable.

Clinical case of musculoskeletal pain

The 57-year-old African American male presented with the chief complaint of severe unilateral musculoskeletal pain of

Table 6 Typical ingredients of muscle relaxants topical medication

Ingredient	Volume or percentage	Action
Guaifenesin	10%	Convert to methyl, and after skin penetration
Menthol	0.1%	Counter irritant and penetration enhancer
Ketoprofen	10%	Anti-inflammatory when necessary for myositis
Isopropyl alcohol 70%	May be replaced with ethoxy diglycol 10 mL	Controls depth and speed of penetration; solubilizer
PLO base	Base QS (final volume): 100 mL	Inert vehicle
Phenoxybenzamine	2%	Four into adrenergic effect with sympathetically maintained pain and for the activation of muscle nociceptors

PLO, pluronic lecithin organogel; QS, Quantum Statis.

the right cheek. The onset of this problem was related to biting into a hard object which he encountered unexpectedly while eating what he thought was a soft textured food. He experienced sudden onset of severe pain associated with the right masseter muscle which became progressively worse.

A review of systems and past medical history found that the patient suffers from high blood pressure and sickle-cell anemia. Medications included amlodipine and hydroxycarbamide. He has not had a recent sickle-cell event in approximately 3 years.

The patient was a well-nourished individual of approximately 5'11" and weighing 190 pounds. The clinical evaluation found in a limited mandibular range of movement associated with severe pain in the area of the superficial masseter muscle. A palpatory evaluation of the remaining masticatory musculature found generalized moderate tenderness; however, the superficial right masseter reproduced familiar pain. The patient was fully dentate with no signs of abnormal tooth wear consistent with bruxism. The Malampatti score was 2. Linea alba and tongue scalloping were absent.

A panoramic radiograph was taken to rule out sickle-cell infarcts. Imaging was negative.

Considering the sudden onset of pain associated with encountering a hard object during mastication, and the localization of an acute myofascial trigger point which, when provoked reproduced the patient's familiar pain, the differential diagnosis was acute myofascial pain. Under normal circumstances, a trigger point injection would be suggested followed by home care and physical therapy. However, given this patient's history, risk of infection secondary to medications and risk of inciting a sickle-cell event with an injection, phenoxybenzamine in a topical preparation was used as an alternative. A compounding pharmacy provided an emergency supply of phenoxybenzamine for the next day which was applied topically which resulted in a reduction of pain from 10/10 on a visual analog scale to 2/10 within a time period of 15 minutes. This treatment was continued for times daily for approximately three weeks and combine with home care including hot and cold applications and self-massage. At that time, the patient's complaints are completely resolved.

This case illustrates a prime example of the alternative use of topical medications in an attempt to avoid a more invasive procedure for medically compromised patient.

Topical treatment of musculoskeletal pain

A topical alternative treatment for myogenous pain includes a compound of guaifenesin and anti-inflammatory medications such as ketoprofen. Topical application of guaifenesin permeates the tissue transdermally and is broken down to methocarbamol as it passes through the skin. Methocarbamol is and effective muscle relaxant. The direct effect of methocarbamol on muscle tissue results in relaxation of musculature and a calming effect on muscle nociceptors that may have been sensitized by local inflammation. The addition of ketoprofen enhances the anti-inflammatory response. In addition, the active pharmaceutical ingredients (API) agent phenoxybenzamine has a strong anticholinergic antagonist effect, also decreasing local pain by regulating sympathetic maintained nociceptor active in the area of myogenous pain (24).

A typical compound used for the treatment of myofascial/myogenous temporomandibular disorders includes the following ingredients (*Table 6*).

The inert vehicle, pluronic-lecithin organogel (PLO) can carry different APIs through skin. This particular transdermal gel base is stable in extreme temperatures without breaking the chemical surfactant bridge. Penetration enhancers are already combined into this formula base. Their benefit is to increase skin permeation of APIs through

the skin. It is important to choose penetration enhancers that will not cause irritation or toxicity to the patients' skin. Their addition in this formula creates a synergy effect with the PLO gel, facilitating the transport of the APIs through the layers of skin. These penetration enhancers are chemically stable and should not contain odor, color, or taste if possible, and do not irritate the skin of patients. Other commonly used penetration enhancers in compounded pharmaceuticals include ethanol, propylene glycol, oleic acid, sodium oleate, urea, isopropyl myristate, isopropyl palmitate, polyethylene glycol, menthol, and ethoxydiglycol.

Topical medication alternatives

Neuropathic and musculoskeletal pain are amenable to the topical application of pharmacotherapeutic agents.

Topical treatment of neuropathic pain

Commonly used medications for palliative treatment of neuropathic pain include analgesics, antidepressants, antihypertensives such as beta-adrenergic antagonists and calcium channel blockers, antiepileptic medications anxiolytics, muscle relaxants corticosteroids and local anesthetics. Problematic with these medications are often intolerable side effects and contraindications for medically complex patients. Typical complaints of side effects include sedation and problems with concentration. Anticholinergic effects of most of the antidepressants, even in low dosage, can present a significant problem for many patients. The use of effective therapeutic levels of medications may even be impossible for the medically compromised patient taking other medication. An alternate route of delivery for providing pharmacotherapeutic treatment, directed at the site of pain is through topical applications of custom compounded medications. Custom compounded medications containing similar pharmacological agents are effective at targeting local sources of pain while, at the same time showing minimal or no side effects or systemic uptake (25,26).

Transdermal delivery of topical medications

Identification of a therapeutic targets and management of chronic pain with a custom compounded transdermal medication represents a unique and effective route of delivery, while avoiding or minimizing systemic side effects and drug interactions. Most already approved medications are available in powder form, and can be reduced to a molecular size and transported through the dermis or mucosa to local sites of musculoskeletal or neuropathic pain. Compounded APIs can be transported transdermally or transmucosal when incorporated into various liposomal bases containing penetration enhancers. Transmucosal delivery is enhanced by the use of neurosensory stents for maintaining the compound in intimate contact with the underlying mucosa. These medications have a local effect on a specific therapeutic target and do not require a systemic blood level concentration for efficacy.

Accumulating evidence suggests the presence of variable receptors in the peripheral nervous system (27,28), supporting the treatment of chronic pain with various topical medications (29). Recent studies have demonstrated a local peripheral analgesic effect of antidepressants. The combination of ketamine and amitriptyline has been shown to significantly chronic neuropathic (30).

Mechanisms of transdermal delivery

The skin is a protective barrier from infectious organisms. Custom compounded pharmaceuticals are able to penetrate the layers of the skin and mucosa resulting in local effects and can gain access to the general circulation. Transdermal compounds are designed to transport medications through the skin or mucosa; the medication is delivered transdermally as an alternative to oral or parenteral administration (31). This route of administration is particularly indicated for patients where systemic administration is contraindicated or when effective levels of medications could cause unacceptable complications, interactions, or side effects. This method of administration is especially suited to localized neuropathic conditions when a variety of systemic neuropathic medications have been tried with equivocal benefit. Targets of musculoskeletal and neuropathic pain successfully treated while avoiding systemic uptake.

In creating a custom compounded topical medication, molecules of the medication are absorbed into a matrix within a PLO or other inert vehicle carrier bases. The medications absorbed into micelles, that essentially form a soap bubble type structure surrounding the molecules medications. The head of the molecule is hydrophilic or water-soluble, while the interior is hydrophobic or lipid soluble. This arrangement prevents the penetration of water into the core of the sphere Under proper conditions, micelles form lipid bilayers called liposomes. These lipid bilayers are fundamental to the structure of all biologic membranes. The liposome can penetrate the lipid-soluble epidermis layer (32). A schematic representation of the micelle is shown in *Figure 4*.

PLO is a transdermal gel base that acts as inert carrier

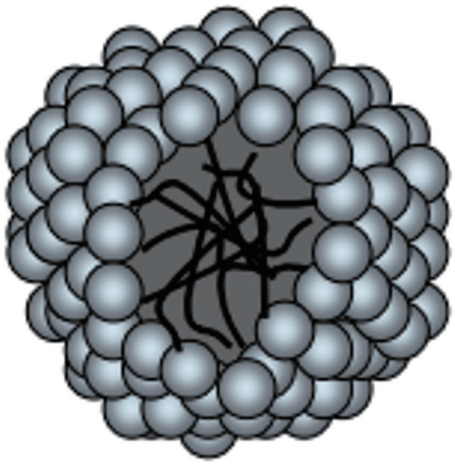

Figure 4 Schematic representation of a spherical micelle. The hydrophilic groups are represented by spheres and the hydrocarbon tails a lipophilic (33).

for the liposome incorporating the medication and moving it through the skin or mucosa producing local effects. Regardless of lipophilicity, size, or polarity, active pharmaceutical ingredients can be incorporated into the PLO. The resultant liposome packets or micelles contain the medication and pass it through the skin, mucosa or targeted underlying soft tissue. After passing through the skin or mucosa, the micelle breaks down, releasing the enclosed API, resulting in its local effect.

Conclusions

Topical administration of approved medications for neuropathic and musculoskeletal pain offers a unique delivery system that can improve the quality of life while avoiding systemic side effects. Topical administration is especially useful for the medically complex, compromised, or elderly patients with comorbid medical conditions or those using other medications which may contraindicate the systemic administration of otherwise appropriate pharmacotherapeutics.

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