Intravenous Ketamine Infusions for Chronic Oral and Maxillofacial Pain Disorders. A Systematized Review

Thesis

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Abstract

Chronic oral and maxillofacial pain conditions represent a diverse group of disorders. Broadly, they can be broken down into temporomandibular disorders (TMDs) and/or orofacial pain disorders. These classifications further detail a series of conditions ranging from joint pains, muscles pains, headaches, to various neuralgias of the head, neck, and face. The presence of depression often complicates these conditions. In addition, chronic noxious stimuli can lead to central sensitization, amplifying and protracting pain. Ketamine, a commonly used general anesthetic agent, has been studied in pre-clinical animal and human clinical trials and has shown great promise for treating chronic pain and depression. It has also been proposed that intravenous ketamine administration plays a role in reversing central sensitization. Albeit simplified, the hypothesized mechanism of action behind ketamine's ability to perform these actions primarily lies within the drug's ability to inhibit N-methyl-D-aspartate receptors (NMDAR) in the central nervous system. However, it is thought that other factors are at play behind ketamine's clinically valuable attributes.

Unfortunately, most research in this field has been studied without regard to the head, neck, and face. The following is a systematized review of ketamine therapy to treat such disorders. Regrettably, the results demonstrated the dental profession's lack of pursuit in

ketamine therapy when treating chronic oral and maxillofacial pain patients. Nevertheless, there was a meaningful amount of data covering the utility of ketamine therapy. Although most clinical trials present with large degrees of design heterogenicity, the overwhelming conclusion of these publications suggests great promise for the use of intravenous ketamine infusions to treat a multitude of chronic pain conditions. Given these results, the dental profession, with its recent addition of two new specialties (i.e., dental anesthesiology and orofacial pain), alongside those in dentistry who have been diagnosing and treating these patients for years (e.g., oral surgeons, general dentist, etc.), is primed with a unique set of clinical knowledge and knowhow to follow suit. Dentistry has the opportunity to pursue and translate the current literature and research into evidence-based practices for chronic oral and maxillofacial pain conditions.

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Chapter 1. Introduction and Background

Imagine a scenario where the smallest and simplest human behaviors (e.g., talking, laughing, eating, kissing, and all those similar) bring on intolerable pain. This associated hurt from underlying dysfunction develops into severe chronic pain with passaging time. Most times, concurrent psychosocial derangements such as anxiety, depression, or lack of life quality are evident. This represents the case for many people who suffer from temporomandibular disorders (TMDs) and other orofacial pain disorders.

TMDs and orofacial pain disorders are highly prevalent and debilitating conditions involving the head, neck, and face.[1] These chronic conditions are often challenging to treat. They involve complex anatomical regions within oral and maxillofacial structures and represent many disease states under the umbrella term of TMDs and orofacial pain disorders. These disorders are often further complicated by an underlying presence of psychiatric or mood disorders.[2] For proper diagnosis and treatment, it is essential for the treating clinician to be well versed and highly aware of these various pain conditions and the pathology that underpins these disease processes. The clinician should recognize any underlying comorbidities to facilitate a multi-modal approach to care. Because of their complexity, an interdisciplinary approach to treatment is thought best. Bridging healthcare providers in both dentistry (i.e., general dentist, oral

maxillofacial surgeons, dentist anesthesiologist, orofacial pain specialist, etc.) and medicine (i.e., physical therapy, psychiatry, integrative health, etc.) is critical to producing favorable clinical outcomes. A biopsychosocial approach to treatment acknowledges the intricacies of these disorders and addresses the entire person and their body alongside any issues that arise secondary to, or become intertwined with, these complex disease states.[1,3]

Many of the painful TMDs (e.g., myalgias, arthralgias) and orofacial pain disorders (e.g., neuralgias) is similar to pain disorders found elsewhere in the body. Thus, the same diagnostic and treatment principles can be applied. Therefore, it is of the utmost importance that integration and translation of the current scientific evidence among medical and dental researchers and clinicians becomes a cornerstone for understanding and treating these pain conditions.[1] Additionally, chronic pain and depression are both leading causes of years lost to disability worldwide, and they are typically refractory to traditional treatments.[4] There is a significant overlap between chronic pain and depression in terms of coexisting prevalence and purposed care models, with various therapies used to treat one being effective for the other.[2] One treatment that interconnects both conditions is Ketamine therapy.

Depression in the Setting of Temporomandibular Disorders & Orofacial Pain Disorders

As described by Okeson,[5,6] orofacial pain can be classified broadly by division into two categories. These are physical and psychosocial. Physical conditions include

temporomandibular disorders, which are disorders of the temporomandibular joint (TMJ) and disorders of the musculoskeletal system (e.g., masticatory muscles and cervical spinal muscles), neuropathic pains (e.g., trigeminal neuralgia), peripheral or centrally mediated pains, and neurovascular disorders (e.g., migraine). Psychological conditions include mood (e.g., depression) and anxiety disorders. It is crucial to highlight the clinical link between pain and depression. This association has long been known, with the prevalence estimates for depression being exaggerated among patients with chronic pain and with the reciprocal holding accurate.[2] Recent results from a world mental health survey showed that the rates of depressive illness and anxiety disorders were elevated among persons with a single pain problem and persons reporting multiple pain conditions.[7] Patients with depression often present with a complex set of overlapping symptoms, including emotional and physical.

Physical symptoms usually include medically unexplained pain[8,9] and patients with physical pain are more likely to develop depression.[8,10,11] Thus, depression can be seen as a powerful predictor of pain, especially persistent pain,[12-14] and has been shown to decrease pain thresholds and increase analgesic requirements.[15] Pain together with depression has a more significant impact than either one disorder alone. The concurrence of depression and chronic pain is associated with increased severity and duration of depressive and physical symptoms, poor treatment response, and is a substantial risk factor for relapse and decreased patient satisfaction with treatment[16-22] This interface between depression and pain symptoms are termed the depression-pain syndrome[23] or the depression-pain dyad,[24] implying that both often coexist, respond similar to treatment,

can exacerbate one another and share common biological pathways and neurotransmitters.[25,26]

Temporomandibular Disorders (TMDs)

Temporomandibular disorders describe many clinical problems involving the masticatory musculature, the temporomandibular joint, and associated nerves and tissues.[27] Masticatory system disorders generally fall into two groups: those associated with functional or structural changes in the TMJ and those associated with pain. The following describes several types of TMDs, as summarized in Table 1[1,3,28]. It is important to note that TMDs are complex and have multi-system components and multiple comorbid medical conditions. A single patient may present with various diagnoses (e.g., myalgia and disc displacement). It is not unusual for various diagnoses of myofascial pain, arthralgia, disc displacement with reduction, and headache attributed to a TMD to be present in the same individual. This overlap can significantly hinder an attempt to deduce primary etiology and conclude the best treatment options.[1,29-31]

Table 1. Summary of Oral and Maxillofacial Pain Disorders.

Temporomandibular Pain Disorders		**Orofacial Pain Disorders**	
Temporomandibular Joint Disorder	Masticatory Muscle Disorders	Headaches	Neuropathic
1. Joint Pain Arthralgia Arthritis **2. Joint Disorders** Disc Disorders Hypo-mobility Disorders - Adhesions - Ankylosis Hypermobility Disorders - Dislocations **3. Joint Diseases** Degenerative Joint Disease - Osteoarthrosis - Osteoarthritis Systemic Arthritides Condylysis/Idiopathic Condylar Resorption Osteochondritis Dissecans Osteonecrosis Neoplasm **4. Fractures** **5. Congenital and Developmental Disorders** Aplasia Hypoplasia	**1. Muscle Pain** Myalgia - Local Myalgia - Myofascial Pain - Myofascial Pain with referral Tendonitis Myositis Spasm **2. Contracture** **3. Hypertrophy** **4. Neoplasm** **5. Movement Disorders** Orofacial Dyskinesia Oromandibular **6. Masticatory Muscle Pain Attributed to Systemic/Central Pain Disorders** Fibromyalgia	Headaches attributed to TMD Headaches attributed to Orofacial Pain Disorders Facial Migraine Tension-Type Headache Trigeminal Autonomic Cephalalgias (TACs)	Trigeminal Neuralgia Glossopharyngeal Neuralgia Centralized Trigeminal Neuropathic Pain Atypical Odontalgia Burning Mouth Syndrome Post-Herpetic Neuralgia Post-Traumatic Trigeminal Pain Persistent (Chronic) Idiopathic Facial Pain Giant Cell Arteritis Short Unilateral Neuralgiform Pain with Autonomic Features (SUNA/SUNCT Conjunctival Injection and Tearing Post Stroke Pain

This summary table is based on articles by the National Academy of Sciences[1], Romero-Reyes and Uyanik[3], and Zakrzewska.[28]

Myalgia and Myofascial Pain

Myalgia and myofascial pain originate from muscle and usually present as dull aching sensations.[3] Myalgia refers to pain in a muscle coming from an unknown source or cause

and is identified by a complaint of pain in a localized area.[32] Myofascial pain, on the other hand, is denoted by spreading pain, or pain beyond the initial focal point. Both types of pain can persist for years with no evidence of underlying disease. Typically falling into the category of chronic primary pain.[1]

Arthralgia

Arthralgia refers to pain in the joint and shares characteristics very similar to myalgia. Due to the small size of the TMJ, finding the exact source of the pain or the specific structure responsible for the pain is neither reliable nor clinically useful. Arthralgia may also be accompanied by TMJ disc disorder or degenerative joint disease.[1]

Headache Secondary to TMD Pain

Headache and TMD pain overlap, making it hard to distinguish if the headache is secondary to a painful TMD or a headache disorder in and of itself. Both share underlying pathophysiological mechanisms, clinical characteristics, and neurovascular anatomy. The following criteria must exist for the headache to be diagnosed as a TMD: The headache may be of any type (e.g., migraine, tension, trigeminal autonomic cephalalgias),[3] and a painful TMD diagnosis must be present. Finally, the physical exam must be able to replicate the headache pain.[1,33]

Disc Disorders

Derangement of the disc refers to the dislocation of the articular disc from its usual functional relationship within the mandibular condyle. Most people who experience disc displacement within the TMJ have little or no functional disorder and usually no pain. However, there exists a small population of individuals for whom disc displacement is associated with significant pain, limitations in joint function, and resultant disability. The causes of disc displacements are mainly unknown. It has been suggested that either trauma or growth discrepancies between the condyle and the developing occlusion may play a role. Milder forms of the disorder present with a disc that typically returns to its normal position during movement. A popping or clicking noise sometimes accompanies disc reduction (i.e., the return of the disc to the expected location). The disc can remain displaced in more severe forms of the disorder throughout the opening cycle. This can result in mechanical obstruction to opening from the displaced disc. Chronically, the posterior attachment of the disc stretches to allow for normal mobility, albeit in the presence of a symptomatic and functionally limited joint.[1,34-36]

Degenerative Joint Disease

Osteoarthritis, osteoarthrosis, and degenerative joint disease are all terms for the breakdown of cortical bone of the TMJ condyle. Osteoarthritis is a condition in which pain is present, whereas osteoarthrosis is used when pain is absent. As with other joints in the body, degenerative joint disease of the TMJ results from chronic abnormal

mechanical loading to the anatomy. Degenerative joint disease may also occur due to long-term advanced internal derangements in the TMJ. These derangements have been known to lead to pain and furthered joint dysfunction. Depending on the severity of the disease, surgical intervention (i.e., arthrocentesis, arthroscopy, open joint arthroplasty, or total joint replacement) may be required to relieve symptoms and restore function.[1,37-40]

TMJ Subluxation and Luxation

The mandibular condyle has an expected course and range of motion during normal function. However, the condyle can exceed these limits, which causes problems to arise. This added movement can cause the condyle to either become momentarily stuck in position (subluxation) or in a manner that requires manual reduction of the joint to relocate the condyle back into the fossa (luxation or dislocation). A suspected cause of this condition involves angulation of the eminence that bounds the anterior extent of the joint space.[1,41-44]

Orofacial Pain Disorders

The major classes of orofacial pain are musculoskeletal, neuropathic, and visceral. Several types of TMDs overlap these areas. The painful conditions within TMDs are simultaneously grouped within a broader set of orofacial pain conditions within the International Classification of Orofacial Pain.[1,45] The following sub-sections briefly describe several types of orofacial pain disorders outlined in Table 1.[1,3,28]

Neuropathic Pain

Derived from neuroplastic changes involving the peripheral and central nervous system and immune responses, they are thought to be the underlying mechanisms involved in developing and maintaining chronic neuropathic pain.[46] Orofacial neuropathic pain conditions are divided into episodic pain disorders (e.g., trigeminal neuralgia (TN), and glossopharyngeal neuralgia) and continuous pain disorders, usually as a result of interruption or destruction of the afferent connections of nerve cells (deafferentation) after injury in either the peripheral or central nervous system (e.g., neuromas, atypical odontalgia (AO) and other idiopathic trigeminal neuropathic pains).[47-49]

Trigeminal Neuralgia

Described as a severe, knifelike, and electric-like pain, trigeminal neuralgia is a chronic paroxysmal neuropathic pain condition. TN is typically localized to the second (V2), and third (V3) branches of the trigeminal nerve (cranial nerve V) or occurs in both simultaneously. A trigger zone is typically present within the trigeminal distribution, which results in severe attacks upon stimulation. These attacks can last up to minutes, and an individual may experience several attacks daily.[47,50,51] The cause of TN is associated with vascular compression[52], which is hypothesized to result in focal demyelination. [53] It is also suggested that the superior cerebellar artery may compress on the trigeminal root as a cause for attacks of TN.[54] Nonvascular compression means of triggering TN attacks

have also been described by compression via a cerebellopontine angle neoplasm (i.e., acoustic neuroma, meningiomas, cholesteatomas, and neurofibromas).[55,56]

Glossopharyngeal Neuralgia

A rare condition associated with pain in the region supplied by the glossopharyngeal nerve (cranial nerve IX), termed glossopharyngeal neuralgia, has been associated with pain in areas of the nasopharynx, posterior portion of the tongue, the posterior oropharynx, and laryngopharynx (throat, tonsils, and larynx) and the ear. The pain from this disorder has been described at shooting paroxysms that occur multiple times a day with stimulation of the oropharyngeal region.[57,58] Known triggers of the mechanical stimulation zone range from activities including chewing, swallowing, coughing, talking, and head movement. It has also been noted that glossopharyngeal neuralgia may coincide with cardiac dysrhythmias (i.e., bradycardia, asystole, and syncope).[59]

Peripheral Trigeminal Neuropathic Pain

Peripheral trigeminal neuropathic pain is brought about secondarily to a traumatic nerve injury. This results in chronic aching, continuous burning-like pain at the injury site. Additionally, it is common to see the presence of allodynia and hyperalgesia at the area of nerve injury or adjacent to it.[60] When such damage occurs, the transected nerve may sometimes heal itself via axonal sprouting, resulting in a traumatic neuroma.[61,62]

Centralized Trigeminal Neuropathic Pain

Central neural changes may be produced from prolonged stimulation of peripheral nociceptors.[46,63] The pain is described as continuous, aching and burning, and is associated with the presence of hyperalgesia and allodynia.[60]

Atypical Odontalgia (AO)

Classified as a centralized trigeminal neuropathy, atypical odontalgia (AO) is often localized in a single tooth or a generalized tooth area. AO is frequently misdiagnosed and often results in many unnecessary dental treatments in attempts to relieve the pain.[64] The pain associated with AO is described as persistent idiopathic pain, either throbbing or burning in nature.[47,65]

Central Sensitization and Neuronal Plasticity

Acute pain can be defined as the physiological sensation of "hurt" that results from activating nociceptive pathways by sufficiently intense stimuli that represent the possibility of tissue damage (noxious stimuli).[66] Nociception, the detection of noxious stimuli,[67] is a protective process that helps prevent injury (e.g., generation of withdrawal). This protective process is enhanced further through the process of sensitization. Sensitization is initiated after encountering several repeated noxious stimuli. The result is a decrease in the threshold for activation, and the response to any additional inputs becomes amplified.[68-70] This state of heightened sensitivity can return to baseline over

time, provided ongoing stimuli or tissue injury is absent. This nociceptor-induced sensitization of the somatosensory system is adaptive, with the system becoming hyperalert in situations where the additional risk of tissue damage is high. This central sensitization process details use-dependent synaptic plasticity triggered by nociceptor input in the central nervous system (CNS).[71] Central sensitization is thought to be a component of neuropathic[72] and inflammatory pain,[73-75] migraine,[76] and may also play a vital role in the pain of patients with fibromyalgia.[77-81] It produces abnormal responsiveness to both noxious and innocuous stimuli and the spread of tenderness beyond the lesion sites.

Clinically, there are many conditions where pain no longer becomes protective. Rather, pain arises spontaneously and can be brought about by innocuous stimuli (allodynia), is often amplified and protracted in response to noxious stimuli (hyperalgesia), and may spread beyond the site of injury (secondary hyperalgesia). Central sensitization provides a systematic explanation for these threshold changes in pain perception in acute and chronic settings. It underscores the importance of changes in the CNS that generate these abnormal pain sensitivities. Additionally, central sensitization produces pain hypersensitivity in noninflamed tissues by changing the sensory response from regular inputs and increasing pain sensitivity long after the initiating cause is no longer present and without any underlying peripheral pathology. Because this sensitization is secondary to changes in the property of neurons in the CNS, the pain no longer correlates to the presence, intensity, or duration of peripheral stimuli (as is observed with acute nociceptive pain). Here, pain is produced due to the changes

seen in the CNS, which are responsible for altering the way one responds to sensory inputs (opposed to being delivered from peripheral noxious stimuli). Central sensitization can also result in the feeling of pain occurring in the complete absence of either peripheral pathology or noxious stimuli.

In these situations, the target for treatment must be the CNS, not the periphery.[63] This sensitization correlates to the heightened functionality of neurons and nociceptive pathways via increased membrane excitability, synaptic transmissibility, or a decrease in signaling inhibition. Collectively, these changes result in a subthreshold synaptic input's ability to either generate, increase, or argument action potential output (i.e., facilitation, potentiation, or amplification of information).[82] It is also known that these responsive fields of somatosensory neurons are not fixed. They are highly malleable. This plasticity is the critical component of the effects of central sensitization.[63]

Central sensitization is an activity- or use-dependent form of functional synaptic plasticity that leads to hypersensitivity to pain after noxious stimuli input. The plasticity develops in dorsal horn neurons by information from C-nociceptors, as shown by various models.[71,83-87] For central sensitization to establish, the noxious stimuli must be of specific characteristics (i.e., having sufficient intensity, repeated stimuli, or sustained stimuli). Peripheral tissue injury is not a prerequisite; however, if tissues injury is present, this degree of noxious stimuli is typically sufficient to induce central sensitization (central sensitization is often seen as the result of post-traumatic or surgical injury). Additionally, it has been shown that the nociceptor afferents of the muscles or joints produce a longer-lasting central sensitization than those that innervate the skin.[83]

One of the first and significant insights into the induction and maintenance of activity-dependent central sensitization is the role played by N-methyl-D-aspartate (NMDA) receptors and the neurotransmitter glutamate (glutamate is known to bind several receptors on postsynaptic neurons in the dorsal horn of the spinal cord, including ionotropic amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartate (NMDA), Kainate receptors (KA), and several metabotropic (mGluR) glutamate receptor subtypes).[88-91] Central sensitization can be broken down into two progressive phases, each with distinctive characteristics. First is the phosphorylation-dependent (within the dorsal horn, AMPA and NMDA phosphorylation events increase the activity and density of these receptors, leading to postsynaptic hyperexcitability) [92-101] transcription-independent phase, brought about by changes in glutamate receptor and ion channel properties.[69,102] "Windup" also contributes to furthering the degree of central sensitization (a series of events played out by several enzymes and receptors that ultimately enable NMDA receptor activation by removing the receptor's allosteric inhibitor, magnesium).[102-107] This is followed by a longer-lasting, transcription-dependent phase that drives the production of new proteins. The latter is responsible for the central sensitization of many pathological conditions.[69]

Activation of NMDA receptors is a fundamental step in initiating and maintaining activity-dependent central sensitization. Its blockade by NMDA antagonist prevents and, more importantly, can reverse the hyperexcitability of nociceptive neurons.[102,108] It is also of importance to note that alongside the action of NMDA receptors, there is much interplay among several other factors that constructs the biological reality surrounding

the makeup of central sensitization (i.e., AMPA, mGLuR, brain-derived neurotrophic factor (BDNF), calcitonin gene-related peptide (CGRP) substance P (SP), nitric oxide (NO), and bradykinin).[109-141] Clearly, pain, as described by Latremoliere et al., is much more than the summation of noxious peripheral inputs or pathologies. Instead, it is a multilayered portrait of central neuronal plasticity, and it is this plasticity that represents a significant target for therapeutic intervention.[63]

Nomenclature of Chronic Pain

The etiologic classifications for pain can be neuropathic, nociceptive, or mixed. Neuropathic pain is pain caused by a lesion or disease affecting the somatosensory system; it can be central, peripheral, or mixed (e.g., diabetic neuropathy, postherpetic neuralgia).[142] Nociceptive pain comes secondary from an injury or disease affecting somatic structures (skin, muscle, bone, and joints) and can be further classified as bodily (e.g., arthritis) or visceral (e.g., inflammatory bowel disease).[143] Additionally, nociplastic pain arises from altered nociception despite no noticeable evidence of actual tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.[144] These conditions (e.g., fibromyalgia) are marked by the lack of biomarkers or objective diagnostic tests. Proposed mechanisms include amplification of sensory processing, reduced central inhibitory pathways, and abnormal responses to physical and emotional stressors.[145] Mixed pain contains any combination of neuropathic, nociceptive, and nociplastic pain (e.g., cancer pain).

A multidimensional pain model describes three components of chronic pain (i.e., sensory-discriminative, affective-motivational, and cognitive-evaluative domains).[146] The sensory-discriminative aspect is predominantly influenced by the inputs of nociceptive signals from the periphery (information such as the location and intensity of pain). It is processed at the spinal cord (lowest level of processing). The affective-motivational aspect refers to pain's negative emotions and is processed at the reticular and limbic systems levels. The cognitive-evaluative part provides contextual information based on past experiences and probable outcomes and is processed through higher CNS structures (highest level of processing). Lower-level aspects of pain are subservient to the higher-level aspects of pain.[143]

Current Treatment for TMDs and Orofacial Pain Disorders

Orofacial pain management can present many challenges and should be addressed multidisciplinary. Initial treatments should stress conservative and reversible methods. Primary treatment options include patient self-care, medical care (non-surgical), and surgical care. The treatment goals for TMDs and orofacial pain should be to reduce pain, restore normal range of motion, and restore normal masticatory and jaw function as much as possible[3]

Patient Self-Care

Home care should either be the first approach to treatment or at least part of a more complex treatment plan. Home care includes resting the masticatory muscles, limiting jaw movements, parafunctional habit modification, stressing a soft diet, and heat or ice therapy.[147]

Medical Care - Physical Therapy

Physical Therapy is beneficial in restoring normal function to the TMJ, muscles of mastication, and cervical muscles. It has also been shown to help reduce inflammation and promote repair and strength.[148-150]

Medical Care - Pharmacotherapy

Many medications have proven to manage TMDs and orofacial pain disorders' symptomatology effectively.[6] Some commonly used medications include analgesics, nonsteroidal anti-inflammatory drugs, local anesthetics, topical ointments and creams, oral and injectable corticosteroids, sodium hyaluronate injections, muscle relaxants, botulinum toxin injections, and antidepressants.[47,151-153]

Medical Care - Occlusal Appliance Therapy

Oral appliances of varying designs have been successfully used in managing TMDs. Most of the justified use for such devices is found in the treatment of myalgia and arthralgia of the masticatory system.[154-157]

Surgical Care

Surgery is only indicated when other non-surgical therapies have been unsuccessful. Surgery should not be performed in asymptomatic, mildly symptomatic patients or as a preventative measure.[158] Types of surgery that treat TMDs and orofacial pain disorders include arthrocentesis and arthroscopy,[158] microvascular decompression of nerves, radiofrequency thermocoagulation, and gamma knife radiosurgery, or rhizotomy.[57,159]

Ketamine

Introduction to Ketamine

Ketamine, a chemical derivative of phencyclidine, and sold under the brand name Ketalar in the United States, is described by US Food and Drug Administration[160] as a non-barbiturate rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. Ketamine (di 2-(O-chlorophenyl)-2-

(methylamino) cyclohexanone hydrochloride) exerts its effects on the body primarily due to antagonism of the N-methyl-D-aspartate (NMDA) receptors in the central nervous system (CNS). The imparted impacts on the body by ketamine include hypnotic, analgesic, and amnestic properties.[161]

Pharmacodynamics and Pharmacokinetics

Ketamine is a racemic mixture of R(-) and S(+) stereoisomers. The S(+) isomer is roughly 3 to 4 times more potent compared to the R(-) isomer secondary to the S(+) isomer's greater affinity for the phencyclidine binding site on the NMDAR.[162] Additionally, the S(+) isomer has a shorter duration of action and has greater neuroprotective and analgesic properties than the R(-) isomer.[162,163]

Ketamine can be given by many different routes (i.e., intravenous, intramuscular, intranasal, inhalation, oral, topical, and rectal).[161] It is both lipid and water-soluble, which accounts for extensive rapid distribution throughout the body and the ability to cross the blood-brain barrier. Metabolism is via hepatic microsomal enzymes (cytochrome P450 system). The half-life in plasma is approximately 2.3 +/- 0.5 hours. The drug is rapidly metabolized to norketamine, hydroxynorketamine, and dehydronorketamine, with norketamine having one-fifth to one-third of the activity at the NMDAR compared to its original form. The metabolite 2R,6R hydroxyketamine, an active inhibitor at the AMPA glutamate, and the alpha-7 subtype of the nicotinic cholinergic receptor is thought to contribute to ketamine's anti-depressant effects.[164-166]

Low-dose ketamine accounts for analgesia and sedation, whereas high-dose ketamine produces general anesthesia. The administration of ketamine generally results in an increased heart rate, systolic and diastolic blood pressures, increased salivary and tracheobronchial secretions, and bronchodilation. These effects are precipitated through ketamine's ability to stimulate the CNS. There is minimal effect on airway reflexes and respiratory rate in clinically administered doses.[162,167] Ketamine does exhibit a dose-dependent depression on the cardiac muscle, which is realized only in catecholamine-depleted states.[168]

Ketamine's dissociative properties result from reduced activation of the thalamocortical system and increased activity in the limbic system and hippocampus.[162] This effect may be reduced or eliminated with benzodiazepines or alpha-2 agonists coadministration. The action is to minimize the psychomimetic impact by decreasing the cholinergic effects, reducing excessive stimulation of downstream corticolimbic neurons.[169,170]

Mechanism of Action

Ketamine's many behaviors (i.e., analgesic, antidepressant, and psychomimetic) are mediated through several biochemical pathways. However, the primary mechanism of action is via a non-competitive antagonism of the phencyclidine binding site of NMDA receptors within the CNS. This antagonism decreases the frequency of channel opening and the duration of time spent in the active (open) state.[171] Within the CNS, these ligand-gated NMDA receptors (NMDAR) are activated by the body's primary excitatory

neurotransmitter, glutamate. Stimulation of NMDARs plays a significant role in cognition, chronic pain, opioid tolerance, and mood regulation and is considered a fundamental receptor involved in central sensitization.[167,172-175]

Ketamine's effects include activation of the opioid receptors (these analgesic effects persist even upon administration of naloxone, indicating endogenous opioid receptors are not the primary source of antinociception).[176,177] Additionally, there is a myriad of non-NMDA pathways that play essential roles in pain and mood regulation (e.g., antagonism of nicotinic and muscarinic cholinergic receptors, antagonism of sodium and potassium channels, activation of high-affinity D_2 dopamine receptors and L-type voltage-gated calcium channels, enabling of gamma-aminobutyric acid A (GABA-A) signaling, and enrichment of descending modulatory pathways.[162,178-180]

Ketamine for Depression

There are several proposed mechanisms on ketamine's action as an antidepressant (i.e., disinhibition hypothesis, inhibition of extra-synaptic NMDARs, blockage of spontaneous NMDAR activation, ketamine hydroxynorketamine (HNK) metabolites, and inhibition of NMDAR-dependent burst firing activity or lateral habenula (LHb) neurons).[181] Most of these hypotheses highlight an essential role in inhibiting the NMDAR. However, this is growing evidence that suggests additional mechanisms are likely involved in mediating the properties of ketamine as an antidepressant. Nonetheless, the NMDAR inhibition-independent hypothesis of the antidepressant actions of ketamine provides a solid guiding framework on which to build for future research. Many studies show ketamine as a rapid

and potent agent. When given intravenously at subanesthetic does result in a marked decrease in depressive symptoms, with the onset of relief within hours and lasting relief of up to seven days.[182-185] Although after a single infusion, results are short-lived, it has been shown that repeated doses of intravenous ketamine help to sustain the short-term antidepressant effects.[184,186-188]

Ketamine for Pain and its Effect on Central Sensitization

The primary therapeutic benefits of ketamine are believed to involve its antagonist effects at NMDARs. NMDARs play a significant role in neuroplasticity, central sensitization, opioid tolerance, and hyperalgesia.[189-191] Ketamine's antinociceptive effects have mainly been studied clinically in cases related to neuropathic pain models. In addition, ketamine has proven to have analgesic effects in animal studies simulating inflammatory conditions.[192,193] An incomplete yet straightforward way of describing ketamine's role in relieving chronic pain is that ketamine allows for a reset within the CNS. It takes advantage of the concept of neuroplasticity by reversing the adverse effects of central sensitization through its antagonistic effects at NMDARs centrally.[102] Understanding the complexity surrounding the concept of pain and the associated phenomenon of central sensitization, the complete answer to ketamine's role has yet to be elucidated.[194] The reversal of central sensitization via central NMDAR blockade is likely the principal mode of ketamine's analgesic effects,[195] however it is also plausible that other systems (e.g., hyperpolarization activated cyclic nucleotide gated potassium channel 1 (HCN1), cholinergic, aminergic, and opioid pathways) also play a part.[196] Ketamine's analgesic

effects might not solely be related to modulation of the sensory-discriminative system, but as mentioned above (ketamine for depression), might also be secondary to modulation of the affective-motivational component of pain. These physiological changes that mediate the benefits related to ketamine prevail in the CNS and are associated with enhanced neural activity in the prefrontal cortex and reduced activity in the amygdala and hippocampus.[197,198] The efficacy of ketamine for chronic neuropathic pain and conditions with features related to neuropathic pain has been studied (double-blind random controlled trials).[199-220] Several of these trials have reported that ketamine infusions, under ideal clinical conditions, were associated with more significant pain reductions than control conditions.

Ketamine in the Setting of an Opioid Epidemic

The recent surge in opioid use and overdose deaths has led to a rise in non–opioid-based treatment options. In preclinical studies, ketamine has been shown to reduce opioid tolerance and hyperalgesia. [202,215]

Guidelines for the use of Intravenous Ketamine Infusion for Chronic Pain

As the title of the paper implies, a consensus of guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologist was published in 2018 by Cohen et al.[161] The authors of the paper

concluded there was evidence to support the use of ketamine for chronic pain. Still, the level of evidence[221] varies by condition treated and dose range of ketamine infused. Most studies of ketamine efficacy were small, uncontrolled, and were either unblinded or ineffectively blinded. The adverse effect was reported as few (e.g., psychomimetic, blurry vision, nausea, vomiting, hepatic toxicity, headache, cystitis, spinal injury with intrathecal injection) with more risk associated with a repeated infusion or higher dose regimens. The authors conclude that more extensive studies are needed to evaluate a wider variety of conditions better to quantify ketamine's efficacy, improve patient selection, refine the therapeutic dose range, and better understand long-term risk. Summaries of the recommendations and levels of evidence for ketamine infusions for chronic pain[161] are provided in Table 2.

Table 2. Summaries of Recommendations for Ketamine Infusions for Chronic Pain.

Recommendation Category	**Recommendation**	**Level of Evidence[221]**
Indications	(1) For spinal cord injury pain, there is weak evidence to support short-term improvement (2) In CRPS, there is moderate evidence to support improvement for up to 12 wk (3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement	(1) Grade C, low certainty (2) Grade B, low to moderate certainty (3) Grade D, low certainty
Dosing range and dose response	(1) Bolus: up to 0.35 mg/kg (2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings (3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h	(1) Grade C, low certainty (2) Grade C, low certainty (3) Grade C, low certainty

Recommendation Category	Recommendation	Level of Evidence[221]
Relative contraindications	(1) Poorly controlled cardiovascular disease, pregnancy, active psychosis (2) Severe hepatic disease (avoid), moderate hepatic disease (caution) (3) Elevated intracranial pressure, elevated intraocular pressure (4) Active substance abuse	(1) Grade B, low certainty (2) Grade C, low certainty (3) Grade C, low certainty (4) Grade C, low certainty
Role of oral NMDA receptor antagonist as follow-on treatment	(1) Oral ketamine or dextromethorphan, and intranasal ketamine can be tried in lieu of serial infusions in responders	(1) Grade B, low certainty for oral preparations, moderate certainty for intranasal ketamine
Pre-infusion tests	(1) No testing is necessary for healthy individuals (2) In individuals with suspected or at high risk of cardiovascular disease, baseline ECG testing should be used to rule out poorly controlled ischemic heart disease. (3) In individuals with baseline liver dysfunction or at risk of liver toxicity (e.g., alcohol abusers, people with chronic hepatitis), and those who are expected to receive high doses of ketamine at frequent intervals, baseline and post-infusion liver function tests should be considered on a case-by-case basis	(1) Grade C, low certainty (2) Grade C, low certainty (3) Grade C, low certainty
Positive response	(1) A positive response should include objective measures of benefit in addition to satisfaction such as ≥30% decrease in pain score or comparable validated measures for different conditions (e.g., Oswestry Disability Index for back pain)	(1) Grade C, low-to-moderate certainty
Personnel and monitoring	(1) Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician) who is ACLS certified and trained in administering moderate sedation (2) Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation (3) Setting: at dosages exceeding 1 mg/kg per hour, a monitored setting containing resuscitative equipment and immediate access to rescue medications and personnel who can treat emergencies should be used, although this dose may vary based on individual characteristics	(1) Grade A, low certainty (2) Grade A, low certainty (3) Grade A, low certainty

This summary table is based on articles by Cohen et al.[161] and the GRADE Working Group.[221]

Candidates for Therapy

For complex regional pain syndrome (CRPS), there is moderate evidence supporting ketamine infusions (22mg/h for four days or 0.35 mg/kg per hour over four hours daily for ten days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty).

Contraindications to Therapy

Ketamine should not be used in patients with poorly controlled cardiovascular disease and should be avoided in individuals with certain poorly controlled psychoses (grade B evidence, moderate level of certainty).

For hepatic dysfunction, if the impairment is severe, administration of ketamine should be avoided. For moderate impairment, administration of ketamine should be judicious along with properly monitoring (grade C evidence, low level of certainty). In patients with elevated intracranial and intraocular pressure, ketamine should be avoided or used only in lower doses with extreme caution (grade C evidence, low level of certainty).

Serial ketamine infusions should not be undertaken in patients with active substance use disorders. They should be used along with universal precautions to monitor abuse (grade C evidence, low level of certainty).

Therapeutic Dosing

There is moderate evidence to support higher dosages of ketamine over more extended periods and more frequent administration for chronic pain. It is reasonable to start dosing with a single outpatient infusion at a minimum of 80mg lasting more than 2 hours and reassess before initiating further treatments (grade C recommendation, low level of certainty).

Oral/Nasal Ketamine

Low-level evidence supports oral ketamine and other NMDA-receptor antagonists as follow-up therapy. There is moderate evidence supporting intranasal ketamine (1-5 sprays of ketamine 10mg, 0.2--.4 mg/kg (S)-ketamine, and single-dose ketamine 25mg every 6 hours as needed) as a treatment for breakthrough pain. From a clinical practice perspective, oral ketamine presents with abuse potential. For patients with a history of abuse or at high risk of abuse, the risk of chronically prescribing ketamine should be weighed against the potential benefits. Proper surveillance, similar to what is done for chronic opioid therapy, should be used.

Pre-infusion Testing

There is insufficient evidence supporting pre-infusion testing before administering IV ketamine for chronic neuropathic pain conditions in healthy individuals. In individuals at high risk of cardiovascular events or present with symptoms of cardiovascular disease, baseline ECG testing may be considered. In individuals with baseline liver dysfunction,

at risk for liver toxicity (e.g., alcohol abusers, chronic hepatitis), baseline and post-infusion liver function tests should be considered (grade C evidence, low level of certainty).

Administration of Ketamine

Ketamine doses at levels that may result in severe adverse sequelae (bolus dose of greater than or equal to 0.35 mg/kg and infusion of greater than or equal to 1 mg/kg per hour) should be administered by clinicians experienced in ketamine administration in a unit that contained trained nurses available for monitoring and individuals trained in airway management and Advanced Cardiac Life Support (e.g., anesthesiologist, nurse anesthetist, emergency department physician) who are immediately available to address any potential emergencies. For elderly individuals and those with significant comorbidities, lower thresholds should trigger the requirements for more intensive monitoring and safety measures. Higher cutoffs using subanesthetic dosage may also be utilized in inpatient and outpatient settings in appropriately resourced settings. During the infusion, basic monitoring requirements (ECG, blood pressure) and respiratory monitoring (end-tidal carbon dioxide and oxygen saturation) are needed. Availability of personnel and equipment for resuscitation is mandatory (grade A recommendation, low level of certainty).

Preemptive Medications

There is limited evidence to support preemptive use of benzodiazepine and alpha-2 agonists and no evidence to support antidepressant, antihistamine, or anticholinergic premedication before initiating subanesthetic ketamine for chronic pain (grade C recommendation, low level of certainty).

Positive Treatment Response

It is recommended that a positive outcome be considered as 30% pain relief or greater in conjunction with patient satisfaction and more objective indicators of meaningful benefits, such as a 20% or greater reduction in opioid use. Duration of benefit, considering patient satisfaction, greater than three weeks following a single outpatient infusion and greater than six weeks following an inpatient or series of infusions are appropriate designations. A consecutive "series" of infusions should not be administered by rote but tailored to patient response. Considering the risk of long-term treatment, limiting treatments to no more than 6 to 12 infusions per year is reasonable, with exceptions for exceptional circumstances (grade C recommendation, low to moderate level of certainty).

Chapter 2. Methods

This systematized narrative review of intravenous ketamine infusion therapy to treat chronic pain conditions was limited to regions of the oral and maxillofacial anatomy with the conditions as outlined in the introduction. The challenge to this review was finding articles studying ketamine therapy to treat TMDs and orofacial pain disorders. However, a significant amount of literature reviews intravenous ketamine therapies to treat depression and chronic pain not of oral and maxillofacial origins. To fill in knowledge gaps due to the lack of published research specific to the original search question, this review also includes an overview of any recently published systematic reviews of intravenous ketamine for treating chronic pain.

Search Strategy

Titles and abstracts were systematically searched and screened from Cochrane Library, Embase, Google Scholar, Web of Science, and PubMed from inception through January 2022. The search was limited to those in the English language. The author reviewed the full texts of the relevant articles. See Table 3 for the search terms used for each of the databases searched.

Table 3. Search Terms for the Databases Searched.

Database Searched	Search Terms
PubMed	(((("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[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])) OR (("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND "oral-maxillofacial"[All Fields] AND ("pain"[MeSH Terms] OR "pain"[All Fields])) OR (("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("toothache"[MeSH Terms] OR "toothache"[All Fields] OR ("dental"[All Fields] AND "pain"[All Fields]) OR "dental pain"[All Fields])) OR ("temporomandibular"[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields])) OR "TMD"[All Fields] OR ("trigeminal neuralgia"[MeSH Terms] OR ("trigeminal"[All Fields] AND "neuralgia"[All Fields]) OR "trigeminal neuralgia"[All Fields]) OR (("temporomandibular joint"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields]) OR "temporomandibular joint"[All Fields]) AND ("arthralgia"[MeSH Terms] OR "arthralgia"[All Fields] OR "arthralgias"[All Fields])) OR (("temporomandibular joint"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields]) OR "temporomandibular joint"[All Fields] OR "tmj"[All Fields]) AND ("arthralgia"[MeSH Terms] OR "arthralgia"[All Fields] OR "arthralgias"[All Fields])) OR (("face"[MeSH Terms] OR "face"[All Fields] OR "facial"[All Fields] OR "facials"[All Fields]) AND ("myalgia"[MeSH Terms] OR "myalgia"[All Fields] OR "myalgias"[All Fields])) OR (("atypic"[All Fields] OR "atypical"[All Fields] OR "atypicalities"[All Fields] OR "atypicality"[All Fields] OR "atypically"[All Fields] OR "atypicals"[All Fields] OR "atypism"[All Fields] OR "atypisms"[All Fields]) AND ("toothache"[MeSH Terms] OR "toothache"[All Fields] OR "odontalgia"[All Fields] OR "odontalgias"[All Fields] OR "toothaches"[All Fields]))) AND ("esketamine"[Supplementary Concept] OR "esketamine"[All Fields] OR "ketamine"[All Fields] OR "ketamine"[MeSH Terms] OR "ketamin"[All Fields] OR "ketamine s"[All Fields] OR "ketamines"[All Fields] OR ("norketamine"[Supplementary Concept] OR "norketamine"[All Fields]) OR ("esketamine"[Supplementary Concept] OR "esketamine"[All Fields] OR "s ketamine"[All Fields]) OR ("N-methyl-D-aspartate"[All Fields] AND ("antagonist"[All Fields] OR "antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "antagonists"[All Fields])) OR (("n methylaspartate"[MeSH Terms] OR "n methylaspartate"[All Fields] OR "nmda"[All Fields]) AND ("antagonist"[All Fields] OR "antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "antagonists"[All Fields])))

Database Searched	Search Terms
Embase	(((((((chronic AND orofacial AND pain or chronic) AND 'oral maxillofacial' AND pain OR chronic) AND dental AND pain OR temporomandibular) AND disease or tmd OR trigeminal) AND neuralgia OR temporomandibular) AND joint AND arthralgia or tmj) AND arthralgia OR facial) AND myalgias OR atypical) AND odontalgia AND ((ketamine OR 'n methylketamine' OR norketamine OR 's ketamine' OR 'n methyl d aspartate') AND antagonist OR nmda) AND antagonist
Cochrane Library, Web of Science, and Google Scholar	(Chronic orofacial pain OR chronic oral-maxillofacial pain OR chronic dental pain OR temporomandibular disease OR TMD OR trigeminal neuralgia OR temporomandibular joint arthralgia OR TMJ arthralgia OR facial myalgias OR atypical odontalgia) AND (ketamine OR n-methylketmaine OR norketamine OR s-ketamine OR N-methyl-D-aspartate antagonist OR NMDA antagonist)

Expanded Criteria for Considering Publications

Due to the lack of research published related to the purposed PICO search strategy, these expanded inclusion criteria allowed for a significant derivation from the original question.

Participants – Patients with chronic oral and maxillofacial pain conditions

In addition to human clinical trials, pre-clinical animal models were reviewed and discussed.

Intervention vs. Comparators – Intravenous ketamine infusion therapy vs. placebo

Although the goal was to study intravenous ketamine infusions for chronic oral and maxillofacial pain, other methods of ketamine administration were considered (e.g., intra-articular injection of the TMJ and intramuscular (IM) injection). Additionally, studies without controls were also taken into account.

Outcomes – Relief of pain as measured by pain scores at least 48 hours or more after completion of treatment

The aim was to access long-term relief of pain symptoms following ketamine therapy. This criterion was expanded to include pain assessment at any time point during and after treatment.

Data Extraction

Of the clinical studies, the following data points were extracted for discussion: 1) route of ketamine administration, 2) dose of ketamine used, 3) follow-up period, and 4) outcomes of interest/post-procedural pain scores. Of the pre-clinical studies, the following data points were extracted: 1) pain model/medical condition studied, 2) animal studied, 3) pain category studied, and 4) pertinent outcomes/findings.

Chapter 3. Results

A total of 157 articles were identified as meeting the keyword search between the databases, as elucidated in Table 4. After screening and removing duplicates, *zero* articles met the original inclusion criteria, and eight were included after allowing for the previously discussed expansions to the search strategy. Within these eight articles, a total of 128 participants were analyzed. Sample sizes ranged from 1 to 32. Approximate participant ages ranged from 20 to 88. Data was collected during the ketamine injection or infusion, with follow-up only happening up to 90 days post-treatment (however, most studies only reported results to a maximum of 3 days). Table 5 provides a summary of the findings. Of the 157 articles searched, 15 pre-clinical animal studies mentioned oral and maxillofacial pain conditions related to either ketamine or the relevance of the NMDARs. Table 6 summarizes these findings.

Table 4. Number of Citations Identified in Each of the Databases Searched.

Database	**Dates Covered**	**Date Searched**	**Number of Citations**
PubMed	Inception to Jan 2022	1/5/2022	86
Embase	Inception to Jan 2022	1/5/2022	1
Cochrane Library	Inception to Jan 2022	1/5/2022	15
Web of Science	Inception to Jan 2022	1/5/2022	49
Google Scholar	Inception to Jan 2022	1/5/2022	6

Table 5. Clinical Studies Evaluating Ketamine for Antinociception.

Studies	**Pain Model/Medical Condition**	**Pain Category**	**Ketamine Dose**	**Findings**
Ayesh et. al., 2008[222]	TMJ arthralgia	Nociceptive	0.55 mg intra-articular injection (TMJ) – single ketamine dose	**Study Design:** Double-blind, placebo-controlled, cross-over **Population:** 18 participants (20-39 yo) **Control:** Saline **Outcomes:** VAS and QST **Pain Assessment Time Point:** continuously for 15 min after injection and at 1, 3, and 24h post injection. **Conclusion:** Intra-articular injection of ketamine showed NO significant effect on spontaneous VAS pain measures, pain on jaw opening, or any other somatosensory measures
Baad-Hansen et. al, 2007[223]	Atypical odontalgia	Neuropathic	0.05 mg/kg (10 min infusion) followed by 0.07 mg/kg (20 min infusion) of (S)-ketamine – single ketamine infusion	**Study Design:** Randomized, double-blind, placebo-controlled, cross-over **Population:** 10 participants ketamine group (48.1 +/- 11.7 yo) 10 participants control group (40.6 +/- 11.9 yo) **Control:** Saline **Outcomes:** VAS and QST **Pain Assessment Time Point:** continuously for 15 min after initiation of therapy, after removal of painful stimuli and 30 min post transfusion. **Conclusion:** IV ketamine infusion produced no analgesic effect as measured during the infusion and up to 30 min after the infusion ended

Studies	Pain Model/Medical Condition	Pain Category	Ketamine Dose	Findings
Castrillon et. al., 2008[224]	TMD - chronic myofascial pain	Nociceptive	2mg IM ketamine into most painful portion of masseter muscle. – single ketamine dose	**Study Design:** Randomized, double-blind, placebo-controlled, cross-over **Population:** 14 participants (10 woman 28.7 +/- 2.0 yo, 4 men 26.3 +/- 2.5 yo) **Control:** Saline **Outcomes:** VAS and NRS **Pain Assessment Time Point:** q5 min post-injection up to the first 15 min and at 1, 3, and 24h post-injection. **Conclusion:** IM ketamine injection of masseter muscle showed no effect of treatment after measured up to 24 h
Castrillon et. al., 2012[225]	TMD - myofascial pain (temporalis and masseter mms)	Nociceptive	0.2mL of 2 mmol/L ketamine co-administered with 0.5 mol/L glutamate to temporalis and masseter muscles – single ketamine dose	**Study Design:** Randomized, double-blind, placebo-controlled, cross-over **Population:** 32 participants (16 woman 25.8 +/- 1.3 yo, 16 men 22.6 +/- 0.9 yo) **Control:** Saline **Outcomes:** VAS and NRS **Pain Assessment Time Point:** q5 min for first 20 min after injection **Conclusion:** Ketamine significantly decreased glutamate-evoke peak pain
Chang et. al., 2003[226]	Trigeminal neuralgia	Neuropathic	10 mg ketamine + 1 mg morphine in 2mL of bupivacaine. – multiple trigeminal region nerve blocks	**Study Design:** case-series **Population:** 3 participants (unknown ages) **Control:** Normal saline **Outcomes:** NRS **Pain Assessment Time Point:** 3 months post-injections **Conclusion:** After repeated trigeminal nerve blocks pain was gradually reduced to a score of 2-3/10 from a previous 8-9/10 and well-controlled in a 3-month follow-up

Studies	Pain Model/Medical Condition	Pain Category	Ketamine Dose	Findings
Mathisen et. al., 1995[228]	Acute orofacial pain (removal of impacted 3rds) and chronic orofacial pain (nerve damage in the trigeminal region)	Nociceptive and Neuropathic respectively	*Acute orofacial pain*: 0.45 - 1.80 mg/kg ketamine IM injection – single dose *Chronic orofacial pain:* 0.5 – 2 mg/kg IM +/- 0.4 – 1.8 mg/kg IV bolus +/- 25 – 40mg infusion over 30 min	**Study Design:** Randomized double-blind, no placebo-control, cross-over *and* non-blinded, no placebo-control **Population:** 16 (20 - 29 yo) *and* 7 (42 - 79 yo) participants **Control:** No control, both portions of the study **Outcomes:** VAS **Pain Assessment Time Point:** q5 min up to 80 min post IM injection *and* for up to a max period of 3 days post various ketamine therapy. **Conclusion:** Acute Postoperative pain was rapidly relieved by all versions of IM ketamine injections. Chronic orofacial pain provided pain relief lasting from 24 h to 3 days in 3 of 7 study participants
Rabben and Oye, 2001[229]	Chronic orofacial pain	Neuropathic	0.4 mg/kg IM ketamine (+ 0.05 mg/Kg midazolam) – single ketamine dose. Followed up one week later with 4 mg/kg PO ketamine for 3 days	**Study Design:** Randomized, double-blind, no placebo-control **Population:** 17 participants (32 - 88 yo) **Control:** No control **Outcomes:** VAS **Pain Assessment Time Point:** q5 min for 1h post-injection and later that evening, and every morning and evening after taking PO ketamine **Conclusion:** IM ketamine injection produced transient analgesia (for up to one hour after injection) in 13 of 17 participants, and analgesia lasting several hours (long-term effect) in 7 of 17 participants. The 7 participants who reported long-term effects from the IM ketamine dose also reported continued relief with the oral ketamine

Studies	Pain Model/Medical Condition	Pain Category	Ketamine Dose	Findings
Shiiba et. al., 2021[227]	Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome (SUNCT)	Mixed	0.4 mg/kg IV ketamine infusion for 1 h, QD for 1 week. Followed by the same infusion metrics twice a week for month, and again followed by another month of infusion therapy once per week	**Study Design:** case report **Population:** 1 participant (56 yo male) **Control:** No control **Outcomes:** relief of symptoms **Pain Assessment Time Point:** 3 months end-point in a series of IV ketamine infusion **Conclusion:** Intravenous ketamine therapy effectively treat SUNCT syndrome opening, or any other somatosensory measures

Table 6. Pre-Clinical Studies Evaluating Ketamine or NMDAR Relationships to Oral and Maxillofacial Pain Conditions.

Studies	Pain Model/Medical Condition	Animal Studied	Pain Category	Findings
Bereiter et. al., 2000 [230]	Acute injury to the TMJ region (injection of inflammatory irritant)	Rat	Nociceptive	Morphine and NMDA receptor antagonism reduce c-fos expression in the spinal trigeminal nucleus, suggesting these pathways play a critical role in mediating the sensory and/or reflex aspects of pain after acute injury to the TMJ region
Brian et. al., 1999[231]	Tooth pulp and facial hair mechanoreceptors	Cat	Nociceptive	Electrophysiologic results indicate that a nonselective suppression of orofacial somatosensory information occurs during ketamine anesthesia

Studies	Pain Model/Medical Condition	Animal Studied	Pain Category	Findings
Cao et. al., 2009[232]	Occlusal interference resulting in masticatory muscle hyperalgesia	Rat	Nociceptive	Systemically administered NMDA antagonist MK801, in a dose dependent manner, attenuated the occlusal interference-induced hyperalgesia
Christensen et. al., 1999 [233]	Trigeminal pain (constriction injury to the infraorbital nerve)	Rat	Neuropathic	Systemically administered NMDA receptor antagonist and morphine attenuates pain-related behavior, and may represent a useful approach for the clinical management of trigeminal neuropathic pain disorders
Claudino et. al., 2018[234]	Facial pain (constriction injury to the infraorbital nerve)	Rat	Neuropathic	Intranasal ketamine produces analgesic effects in inflammatory and neuropathic facial pain models and may represent an adjuvant in the treatment of such conditions
De Oliveira et. al., 2020[235]	Acute and chronic orofacial pain (injection of irritant and infraorbital nerve transection respectively)	Mouse	Mixed	Acute and chronic pain models show that nifedipine can suppress orofacial nociceptive behavior through NMDA and other receptor systems
Dong et. al., 2006 [236]	Headache and chronic craniofacial pain disorders (TMDs) related to temporalis muscle	Rat	Nociceptive	Ketamine administration significantly decreases NMDA evoked afferent discharges
Fujimi et. al., 2006[237]	tooth pulp electrical stimulation	Rat	Nociceptive	NMDA and non-NMDA receptor antagonist suppress the superior sagittal sinus-evoked activity of C1 spinal neurons in response to electrical stimulation of tooth pulp
Guo et. al., 2007 [238]	Trigeminal model of inflammatory hyperalgesia	Rat	Neuropathic	glial-cytokine-neuronal interactions underlie the mechanism of persistent pain. In this model, attenuation of hyperalgesia is seen with NMDA receptor phosphorylation
Kayser et. al., 2011[239]	Trigeminal model of inflammatory hyperalgesia	Rat	Neuropathic	Combined administration of NMDA-receptor antagonist and 5-HT(1B/1D)-receptor agonist may be a promising approach for alleviating trigeminal neuropathic pain

Studies	Pain Model/Medical Condition	Animal Studied	Pain Category	Findings
Lee et. al., 2012[240]	Trigeminal pain	Rat	Neuropathic	Functional interactions between NMDA receptors and TRPV1 in trigeminal sensory neurons mediate mechanical hyperalgesia
Li et. al., 2020[241]	TMD, fibromyalgia syndrome, orofacial inflammation	Rat	Mixed	Intrathecal injection of NMDAR antagonist or 5-HT3 receptor antagonist blocked stress-induced wide-spreading hyperalgesia
Piovesan et. al, 2008[242]	Acute inflammatory trigeminal pain (injection of inflammatory irritant)	Rat	Nociceptive	NMDA antagonist are more potent than non-NMDA antagonist in the control of pain in the inflammatory phase
Wong et. al., 2014[243]	Myofascial TMDs	Rat	Nociceptive	The study suggest that NGF-induced sensitization of masseter nociceptors is mediated, in part, by enhanced peripheral NMDA receptor expression. NMDA receptor expression may be useful as a biomarker for myofascial TMDs
Xu et. al., 2019[244]	Occlusal interference resulting in chronic masticatory pain	Rat	Nociceptive	Glutamate receptors (NMDARs) are responsible for excitatory synaptic transmission in the anterior cingulate cortex (ACC). ACC plasticity maintains masseter hyperalgesia caused by occlusal interference

There was significant heterogeneity in clinical designs, types of pain treated (several different forms of neuropathic and nociceptive oral and maxillofacial conditions), article types, and outcomes between all eight publications, alongside the small number of search results, meaningful data interruption was complex. Of the eight articles, three concluded that ketamine was ineffective at ameliorating pain,[222-224] another three provided support for the use of ketamine in treating painful conditions,[225-227] and two concluded mixed data on ketamine's ability to combat pain.[228,229] Five of the articles mentioned ketamine as a study on the drug's acute pain relief effects (immediately following initiation of therapy

and for up to 3 days post-treatment),[222-225,229] while two focused on ketamine's long-term therapeutic effects on pain (up to three months post initial treatment).[226,227] One of the articles mentioned the use of ketamine relative to both acute and long-term effects of treating both acute and chronic pain but failed to follow up on the treatment's effectiveness on chronic conditions for more than three days after therapy initiation.[228] The majority of the articles reported pain scores using the visual analog scale (VAS) or numeric rating scale (NRS), tested for pain responses using a standardized quantitative sensory test (QST), and reported outcomes results using analysis of variance (ANOVA). Most of the articles were randomized, double-blinded, placebo-controlled cross-over studies. The study by Mathisen et al.[228] was the only study that came close in an attempt to report the long-term benefits of ketamine infusion therapy for the treatment of chronic oral and maxillofacial pain but failed to be double-blinded, lacked a placebo control, lacked longer-term follow-up after treatment initiation, and lacked any consistency in ketamine treatment protocols between participants (intramuscular injection vs. intravenous injection, single intravenous bolus dose injection vs. multiple intravenous bolus doses injections, single intravenous transfusion vs. repeated intravenous transfusions, and use of racemic ketamine vs. (R)-ketamine vs. (S)-ketamine with a wide variety of dose ranges). The study by Baad-Hansen et al.[223] reported results of intravenously administered ketamine on chronic pain but only recorded pain scores during the first 15 minutes of a 30-minute transfusion protocol and again once after removal of painful stimuli (capsaicin) and 30 minutes post-transfusion. In this study, the ketamine dose used was less (0.05 mg/kg and 0.07 mg/kg), and the infusion period (10

minutes and 20 minutes, respectively) was shorter than those proposed by current consensus guidelines.[161] Other studies administered ketamine either via a single intramuscular injection (doses ranging from 0.45 mg to 2 mg, or weight-based at 0.4 mg/kg to 1.80 mg/kg with one study[229] co-administrating 0.05 mg/kg midazolam), and another study[222] injected ketamine into the TMJ intra-articular space (0.55mg). Additionally, one case series,[226] provided a minimal explanation of methods, making exact replication of the study impossible. This is unfortunate as the reported results favored ketamine when co-administered as a nerve block in the trigeminal region (10mg ketamine with 1mg morphine in 2mL of bupivacaine), with patients reporting continued relief up to 3 months later. Finally, one case report by Shiiba et al.[227] demonstrated that after a series of ketamine infusions (0.4 mg/kg for 1 hour), complete relief after three months of treatment was received in a patient presenting with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). In addition to these eight clinical studies, 15 pre-clinical studies[230-244] came up during the search. All 15 of these articles provided support for either the use of ketamine for treatment specifically related to oral and maxillofacial pain conditions or alluded to the role of the NMDAR in oral and maxillofacial pain conditions and their potential as possible treatment targets.

Review of Results from Published Reviews.

Due to the lack of clinical trials relating to intravenous ketamine therapy for chronic oral maxillofacial pain disorders, two recently published systematic reviews of

intravenous ketamine for chronic pain without the classification of pain coming from oral and maxillofacial origins are discussed here. Orhurhu et al.[245] published in 2019 a systemic review and meta-analysis of randomized controlled trials. This review included seven studies of randomized controlled trials of intravenous ketamine infusions compared to a placebo for relieving chronic pain. A wide range of infusion protocols was reported in the studies (treatment duration ranged of 0.5 to 100 hours, with a median duration of 5 hours; the number of days of consecutive or intermittent infusions was 1 – 10 days, with a median of 1 day; the dose of ketamine during transfusion using a 70-kg patient as reference was 0.23 – 0.6 mg/kg with a median of 0.35 mg/kg). Participants included human subjects of at least 18 years of age who had chronic pain for at least three months with a pain intensity of at least four or greater on an NRS or at least 40 or greater on a VAS. The intervention was defined as intravenous ketamine given either as bolus or infusion, with control being the administration of a placebo. The primary outcome was defined as the lowest intensity pain score recorded at least 48 hours or more post completion of treatment. The seven studies included 211 participants (108 receiving intravenous ketamine and 103 receiving placebo. One trial was reported as a cross-over study). Samples ranged from 19 – 60, with a mean of 24 participants. Participant ages ranged from 41.9 – 71 years of age with a mean of 48 years. There was significant heterogenicity when it came to defining chronic pain. The predominant form studied was neuropathic pain, but also included nociceptive, nociplastic, and mixed chronic pain conditions. Six of seven studies reported the lowest pain scores between 48 hours and two weeks using an NRS. Meta-analysis of the data from these trials revealed a

significant reduction in pain scores favoring ketamine over control treatments (mean difference, -1.83 points; 95% CI, -2.35 to -1.31 points; P <.0001; I^2 = 48.5%).[245] Subgroup analysis was performed to determine if the primary outcome depended on the dose of ketamine received (high dose vs. low dose, with high dose defined as cumulative dose over 400mg. Meta-analysis of the data from high dose ketamine trials demonstrated a significant reduction in pain scores compared to control (mean difference, -2.11 points; 95% CI, -2.87 to -1.35 points; P <.0001; I^2 = 69.2%).[245] Meta-analysis of the data from low dose ketamine trails revealed an analgesic benefit of ketamine compared to control (mean difference, -1.30 points; 95% CI, -2.01 to -0.59 points; P = .0001; I^2 = 0.0%).[245] For participants with pain of neuropathic and mixed neuropathic pain syndromes, a meta-analysis showed a significant reduction in pain scores with ketamine compared to control (mean difference, -1.75 points; 95% CI, -2.08 to -1.43 points; P < .00001; I^2 = 0.0%).[245] Nociceptive or nociplastic pain syndromes also lowered pain scores favoring ketamine. Meta-analysis of the data revealed a significant reduction in pain scores with intravenous ketamine over control (mean difference, -1.97 points; 95% CI, -3.04 to -0.90 points; P < .00001; I^2 = 69.5%).[245] Pain scores reported at two weeks post-treatment found lower pain scores in the ketamine group compared to control. Meta-analysis of this data revealed a significant reduction in pain scores favoring intravenous ketamine (mean difference, -2.23 points; 95% CI, -2.59 to -1.87 points; P < .001; I^2 = 0.0%).[245] Reported pain scores four weeks after treatment, found lower pain scores in the ketamine group. Meta-analysis of the data revealed a nonsignificant reduction in pain scores with IV ketamine compared to control (mean difference, -0.74 points; 95% CI, -1.88 to 0.41

points; P =.208; I^2 = 58.6%).[245] Reported pain scores at eight weeks post-treatment reported lower pain scores in the IV ketamine group. Meta-analysis revealed a nonsignificant reduction in pain scores with ketamine compared to control (mean difference, -0.68 points; 95% CI, -1.75 to -0.40 points; P =.174; I^2 = 48.2%).[245] Reported pain scores at 12 weeks after treatment showed no lowering of pain scores in either intravenous ketamine or control. Meta-analysis of the data showed no significant reduction in pain scores with ketamine compared to control (mean difference, -0.55 points; 95% CI, -1.50 to 0.39 points; P =.251; I^2 = 0.0%).[245]

The second systematic review was published in 2021 by Chitneni et al.[246] and included 14 studies related to ketamine infusions to treat complex regional pain syndrome (CRPS). Although not common, there have been arguments made for CRPS related to changes in the orofacial region.[247] Of the 14 double-blinded, placebo-controlled studies reviewed by Chitneni et al., there were 455 participants. Sample sizes ranged from 4 to 114 human subjects aged between 12 and 68. Follow-up periods ranged from 3 hours to 5 years. Ketamine infusion regimens ranged from 0.15 mg/kg to 7 mg/kg. In 13 out of the 14 studies, ketamine infusion therapy decreased pain scores and provided relief of symptoms.

Chapter 4. Discussion

The most critical discussion point is the near absolute lack of clinical research on the prolonged benefits of intravenous ketamine infusion therapy with any of the chronic oral and maxillofacial pain conditions. None of the studies included for review analyze the effects of such treatment on the long-term outcomes of treating chronic pain in a meaningful scientific manner. This is in stark contrast to what is being done with ketamine infusion therapy for a wide variety of other chronic pain conditions. As mentioned in the National Academies of Sciences, Temporomandibular Disorders: Priorities for Research and Care, we must bridge these gaps between the dental and medical professions to provide patients with needed care.

In addition to several pre-clinical animal studies, the data in these reviews overwhelming points to the effectiveness of intravenous ketamine for treating a myriad of chronic pain conditions (neuropathic, nociceptive, nociplastic, and mixed). [245] Results from Orhurhu et al. show that intravenous ketamine reduced pain scores between 48 hours and two and eight weeks after infusion. Evidence was also found that supported a dose-response effect of ketamine (higher doses are associated with more significant and more prolonged pain relief but also carry a higher incidence of nausea and vomiting). Chitneni et al. reported lasting benefits after infusion of up to one to two months in CRPS patients. Some conclusions from this author's systematized review provided results suggesting ketamine as ineffective in treating chronic pain. However, the methods used

were not consistent with those widely accepted for treating chronic pain.[161] They also failed to mirror any similarity for the methods that have been reported in other papers relating to the use of ketamine for the treatment of chronic pain.

It is essential to realize that ketamine's primary analgesic effect remains ambiguous (either through dampening of CNS pain amplification via numerous pathways and reversal of central sensitization by NMDA receptor blockade.[102] Although pre-clinical data highlights ketamine's benefit in mainly treating neuropathic pain, there is growing evidence to support its benefits for inflammatory, nociceptive, and nociplastic pain conditions as well as headaches,[218,248] thus providing even more hope and promise for its use in chronic oral and maxillofacial pain conditions. Reviews have also shown that combination therapy is superior to single-agent treatment for chronic pain syndromes.[249] This has been upheld in treating acute pain, where the addition of ketamine alongside opioid treatment has been proven beneficial.[250] In the setting of chronic pain, as is seen with many other treatments in this category, ketamine does not offer a permanent solution. Instead, the goal of ketamine therapy should be the reduction of pain for a clinically meaningful length of time and correspond with improvements in functionality.[143]

The current state of research related to ketamine infusion therapy for chronic pain also presents many limitations. The number of patients enrolled in trials is small, and the lack of standardized infusion protocols, patient selection criteria, and follow-up periods prevent more robust analysis. Pain reporting is also subjective, which leads to a wide variety of responses and complicates the investigation. Also, ketamine is a generic

medication, so there is no substantial financial incentive driving further studies. It also closes doors to would-be industry grants to invest in research.[143,245]

In the United States, a significant barrier to ketamine infusion therapy is the lack of reimbursement by payers, which can severely limit access to care for lower-income patient populations. However, for many patients suffering from refractory pain, the relief afforded by a single infusion of ketamine justifies the allocation of resources.[143] It is recommended by Orhurhu et al. that intravenous ketamine be used, on a case-by-case basis, as a principal analgesic in patients with chronic pain refractory to traditional treatments. However, the analgesic effects are limited, and the actual impact of intravenous ketamine among chronic pain patients depends on each individual. Intravenous ketamine can ameliorate pain scores (observed during the transfusion, quantified as early as 48 hours post-transfusion, lasting for up to two weeks or more depending on the dosing regimen).

Chapter 5. Conclusion

Current data from several clinical studies, alongside several pre-clinical animal studies, favorably suggest that intravenous ketamine can provide relief of chronic pain that is refractory to traditional treatment. However, there appears to be a minimal attempt by the dental profession to explore such therapy for their chronic pain patients. Further, well-designed clinical research needs to be carried out in chronic oral and maxillofacial pain conditions to determine the utility of intravenous ketamine therapy. In heeding the call of the National Academies of Sciences[1] for expanding research in this area, now more than ever represents an excellent opportunity for a fundamental change to take place. With the addition of two new dental specialties (i.e., dental anesthesiology and orofacial pain), alongside those in dentistry (e.g., oral surgeons, general dentist, etc.) who have been diagnosing and treating these patients for years, there now exists a unique set of clinical knowledge and knowhow. Collectively, the dental profession has the opportunity to translate the current literature and research into evidence-based practices for chronic oral and maxillofacial pain conditions.

There is a call from many in the literature for further research in this arena. More needs to be done to pursue and determine ideal dosing regimens, ideal patient populations, ideal conditions for treatment, and to correct for substantial clinical design heterogeneity (e.g., variations in dosages, protocols, number of subjects, combinations of pharmacological agents) that exist in the field currently. Despite these pitfalls, ketamine

demonstrates excellent promise for treating chronic pain and provides a possible path forward for many who have exhausted current modalities to no avail.

References

1. National Academies of Sciences E, Medicine, Health, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: Yost O, Liverman CT, English R, Mackey S, Bond EC, eds. Temporomandibular Disorders: Priorities for Research and Care. Washington (DC): National Academies Press (US). Copyright 2020 by the National Academy of Sciences. All rights reserved.; 2020.
2. Chopra K, Arora V. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. Expert Opin Ther Targets 2014;18(2):159-76. (In eng). DOI: 10.1517/14728222.2014.855720.
3. Romero-Reyes M, Uyanik JM. Orofacial pain management: current perspectives. J Pain Res 2014;7:99-115. (In eng). DOI: 10.2147/jpr.S37593.
4. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743-800. (In eng). DOI: 10.1016/s0140-6736(15)60692-4.
5. Okeson JP. The classification of orofacial pains. Oral Maxillofac Surg Clin North Am 2008;20(2):133-44, v. (In eng). DOI: 10.1016/j.coms.2007.12.009.
6. Okeson JP. Bell's Orofacial Pains. The Clinical Management of Orofacial Pain. 2005(6th ed.).
7. Gureje O, Von Korff M, Kola L, et al. The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. Pain 2008;135(1-2):82-91. (In eng). DOI: 10.1016/j.pain.2007.05.005.
8. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry 2003;60(1):39-47. (In eng). DOI: 10.1001/archpsyc.60.1.39.
9. Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. Ann Intern Med 2001;134(9 Pt 2):917-25. (In eng). DOI: 10.7326/0003-4819-134-9_part_2-200105011-00017.
10. Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. J Affect Disord 2001;63(1-3):35-41. (In eng). DOI: 10.1016/s0165-0327(00)00186-5.
11. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. Int J Methods Psychiatr Res 2003;12(1):34-43. (In eng). DOI: 10.1002/mpr.140.

12. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. Jama 1998;280(2):147-51. (In eng). DOI: 10.1001/jama.280.2.147.
13. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163(20):2433-45. (In eng). DOI: 10.1001/archinte.163.20.2433.
14. Greco T, Eckert G, Kroenke K. The outcome of physical symptoms with treatment of depression. J Gen Intern Med 2004;19(8):813-8. (In eng). DOI: 10.1111/j.1525-1497.2004.30531.x.
15. Jackson KC, 2nd, St Onge EL. Antidepressant pharmacotherapy: considerations for the pain clinician. Pain Pract 2003;3(2):135-43. (In eng). DOI: 10.1046/j.1533-2500.2003.03020.x.
16. Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care. Psychosom Med 2006;68(2):262-8. (In eng). DOI: 10.1097/01.psy.0000204851.15499.fc.
17. Bair MJ, Kroenke K, Sutherland JM, McCoy KD, Harris H, McHorney CA. Effects of depression and pain severity on satisfaction in medical outpatients: analysis of the Medical Outcomes Study. J Rehabil Res Dev 2007;44(2):143-52. (In eng). DOI: 10.1682/jrrd.2006.06.0061.
18. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. Psychosom Med 2004;66(1):17-22. (In eng). DOI: 10.1097/01.psy.0000106883.94059.c5.
19. Karp JF, Scott J, Houck P, Reynolds CF, 3rd, Kupfer DJ, Frank E. Pain predicts longer time to remission during treatment of recurrent depression. J Clin Psychiatry 2005;66(5):591-7. (In eng). DOI: 10.4088/jcp.v66n0508.
20. Mossey JM, Gallagher RM. The longitudinal occurrence and impact of comorbid chronic pain and chronic depression over two years in continuing care retirement community residents. Pain Med 2004;5(4):335-48. (In eng). DOI: 10.1111/j.1526-4637.2004.04041.x.
21. Ohayon MM. Specific characteristics of the pain/depression association in the general population. J Clin Psychiatry 2004;65 Suppl 12:5-9. (In eng).
22. Williams LS, Jones WJ, Shen J, Robinson RL, Kroenke K. Outcomes of newly referred neurology outpatients with depression and pain. Neurology 2004;63(4):674-7. (In eng). DOI: 10.1212/01.wnl.0000134669.05005.95.
23. Lindsay PG, Wyckoff M. The depression-pain syndrome and its response to antidepressants. Psychosomatics 1981;22(7):571-3, 576-7. (In eng). DOI: 10.1016/s0033-3182(81)73478-9.
24. Goldenberg DL. Pain/Depression dyad: a key to a better understanding and treatment of functional somatic syndromes. Am J Med 2010;123(8):675-82. (In eng). DOI: 10.1016/j.amjmed.2010.01.014.
25. Gallagher RM, Verma S. Managing pain and comorbid depression: A public health challenge. Semin Clin Neuropsychiatry 1999;4(3):203-20. (In eng). DOI: 10.153/scnp00400203.

26. Blier P, Abbott FV. Putative mechanisms of action of antidepressant drugs in affective and anxiety disorders and pain. J Psychiatry Neurosci 2001;26(1):37-43. (In eng).
27. McNeill C. Temporomandibular Disorders: Guidelines for Classification, Assessment, and Management. Chicago, IL: Quintessence Publishing Co, Inc, 1993.
28. Zakrzewska JM. Differential diagnosis of facial pain and guidelines for management. Br J Anaesth 2013;111(1):95-104. (In eng). DOI: 10.1093/bja/aet125.
29. Scrivani SJ, Keith DA, Kaban LB. Temporomandibular disorders. N Engl J Med 2008;359(25):2693-705. (In eng). DOI: 10.1056/NEJMra0802472.
30. Schiffman EL, Velly AM, Look JO, et al. Effects of four treatment strategies for temporomandibular joint closed lock. Int J Oral Maxillofac Surg 2014;43(2):217-26. (In eng). DOI: 10.1016/j.ijom.2013.07.744.
31. Ohrbach R, Dworkin SF. The Evolution of TMD Diagnosis: Past, Present, Future. J Dent Res 2016;95(10):1093-101. (In eng). DOI: 10.1177/0022034516653922.
32. Simons, Travel, Simons. Myofascial Pain and Dysfunction: The Trigger Point Manual. Upper Half of Body. 2nd ed. ed. Atlanta, GA: Lippincott Williams & Wilkins, 1998.
33. Benoliel R, Sharav Y. Chronic orofacial pain. Curr Pain Headache Rep 2010;14(1):33-40. (In eng). DOI: 10.1007/s11916-009-0085-y.
34. Farella M, Michelotti A, Iodice G, Milani S, Martina R. Unilateral posterior crossbite is not associated with TMJ clicking in young adolescents. J Dent Res 2007;86(2):137-41. (In eng). DOI: 10.1177/154405910708600206.
35. Lee YH, Lee KM, Auh QS, Hong JP. Magnetic Resonance Imaging-Based Prediction of the Relationship between Whiplash Injury and Temporomandibular Disorders. Front Neurol 2017;8:725. (In eng). DOI: 10.3389/fneur.2017.00725.
36. Scapino RP. Histopathology associated with malposition of the human temporomandibular joint disc. Oral Surg Oral Med Oral Pathol 1983;55(4):382-97. (In eng). DOI: 10.1016/0030-4220(83)90193-7.
37. Summers MN, Haley WE, Reveille JD, Alarcón GS. Radiographic assessment and psychologic variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. Arthritis Rheum 1988;31(2):204-9. (In eng). DOI: 10.1002/art.1780310208.
38. Salaffi F, Cavalieri F, Nolli M, Ferraccioli G. Analysis of disability in knee osteoarthritis. Relationship with age and psychological variables but not with radiographic score. J Rheumatol 1991;18(10):1581-6. (In eng).
39. Dekker J, Tola P, Aufdemkampe G, Winckers M. Negative affect, pain and disability in osteoarthritis patients: the mediating role of muscle weakness. Behav Res Ther 1993;31(2):203-6. (In eng). DOI: 10.1016/0005-7967(93)90073-4.
40. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis 1993;52(4):258-62. (In eng). DOI: 10.1136/ard.52.4.258.

41. Fernandez-Sanroman J. Surgical treatment of recurrent mandibular dislocation by augmentation of the articular eminence with cranial bone. J Oral Maxillofac Surg 1997;55(4):333-8; discussion 338-9. (In eng). DOI: 10.1016/s0278-2391(97)90119-1.
42. Moore AP, Wood GD. Medical treatment of recurrent temporomandibular joint dislocation using botulinum toxin A. Br Dent J 1997;183(11-12):415-7. (In eng). DOI: 10.1038/sj.bdj.4809523.
43. Undt G, Kermer C, Rasse M. Treatment of recurrent mandibular dislocation, Part II: Eminectomy. Int J Oral Maxillofac Surg 1997;26(2):98-102. (In eng). DOI: 10.1016/s0901-5027(05)80825-2.
44. Caminiti MF, Weinberg S. Chronic mandibular dislocation: the role of non-surgical and surgical treatment. J Can Dent Assoc 1998;64(7):484-91. (In eng).
45. International Classification of Orofacial Pain, 1st edition (ICOP). Cephalalgia 2020;40(2):129-221. (In eng). DOI: 10.1177/0333102419893823.
46. Romero-Reyes M, Graff-Radford S. Is there hope for chronic pain and headache? Headache 2007;47(8):1262-71. (In eng). DOI: 10.1111/j.1526-4610.2007.00909.x.
47. De Leeuw. The American Academy of Orofacial Pain. 4th ed. ed. Hanover Park, IL: Quintessence Publishing Co, Inc, 2008.
48. Sarlani E, Balciunas BA, Grace EG. Orofacial pain--Part I: Assessment and management of musculoskeletal and neuropathic causes. AACN Clin Issues 2005;16(3):333-46. (In eng). DOI: 10.1097/00044067-200507000-00007.
49. Sarlani E, Balciunas BA, Grace EG. Orofacial Pain--Part II: Assessment and management of vascular, neurovascular, idiopathic, secondary, and psychogenic causes. AACN Clin Issues 2005;16(3):347-58. (In eng). DOI: 10.1097/00044067-200507000-00008.
50. Kitt CA, Gruber K, Davis M, Woolf CJ, Levine JD. Trigeminal neuralgia: opportunities for research and treatment. Pain 2000;85(1-2):3-7. (In eng). DOI: 10.1016/s0304-3959(99)00310-3.
51. Merrill RL, Graff-Radford SB. Trigeminal neuralgia: how to rule out the wrong treatment. J Am Dent Assoc 1992;123(2):63-8. (In eng). DOI: 10.14219/jada.archive.1992.0047.
52. Lutz J, Linn J, Mehrkens JH, et al. Trigeminal neuralgia due to neurovascular compression: high-spatial-resolution diffusion-tensor imaging reveals microstructural neural changes. Radiology 2011;258(2):524-30. (In eng). DOI: 10.1148/radiol.10100477.
53. Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. 1967. J Neurosurg 2007;107(1):216-9. (In eng). DOI: 10.3171/jns-07/07/0216.
54. Bakshi R, Lerner A, Fritz JV, Sambuchi GD. Vascular compression in trigeminal neuralgia shown by magnetic resonance imaging and magnetic resonance angiography image registration. Arch Neurol 2001;58(8):1290-1. (In eng). DOI: 10.1001/archneur.58.8.1290.

55. Matsuka Y, Fort ET, Merrill RL. Trigeminal neuralgia due to an acoustic neuroma in the cerebellopontine angle. J Orofac Pain 2000;14(2):147-51. (In eng).
56. Feinerman DM, Goldberg MH. Acoustic neuroma appearing as trigeminal neuralgia. J Am Dent Assoc 1994;125(8):1122-5. (In eng). DOI: 10.14219/jada.archive.1994.0124.
57. Singh PM, Kaur M, Trikha A. An uncommonly common: Glossopharyngeal neuralgia. Ann Indian Acad Neurol 2013;16(1):1-8. (In eng). DOI: 10.4103/0972-2327.107662.
58. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl 1986;3:S1-226. (In eng).
59. Marks PV, Purchas SH. Life-threatening glossopharyngeal neuralgia. Aust N Z J Surg 1992;62(8):660-1. (In eng).
60. Merrill R. L. Head and Neck Pain. Seminars in Anesthesia, Perioperative Medicine, and Pain 1997;16(4):280-291.
61. Mathews GJ, Osterholm JL. Painful traumatic neuromas. Surg Clin North Am 1972;52(5):1313-24. (In eng). DOI: 10.1016/s0039-6109(16)39843-7.
62. Lee EJ, Calcaterra TC, Zuckerbraun L. Traumatic neuromas of the head and neck. Ear Nose Throat J 1998;77(8):670-4, 676. (In eng).
63. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10(9):895-926. (In eng). DOI: 10.1016/j.jpain.2009.06.012.
64. Patel SB, Boros AL, Kumar SK. Atypical odontalgia--an update. J Calif Dent Assoc 2012;40(9):739-47. (In eng).
65. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629-808. (In eng). DOI: 10.1177/0333102413485658.
66. Woolf CJ, Ma Q. Nociceptors--noxious stimulus detectors. Neuron 2007;55(3):353-64. (In eng). DOI: 10.1016/j.neuron.2007.07.016.
67. Sherrington CS. Observations on the scratch-reflex in the spinal dog. J Physiol 1906;34(1-2):1-50. (In eng). DOI: 10.1113/jphysiol.1906.sp001139.
68. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci 2003;26(12):696-705. (In eng). DOI: 10.1016/j.tins.2003.09.017.
69. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288(5472):1765-9. (In eng). DOI: 10.1126/science.288.5472.1765.
70. Woolf CJ, Walters ET. Common patterns of plasticity contributing to nociceptive sensitization in mammals and Aplysia. Trends Neurosci 1991;14(2):74-8. (In eng). DOI: 10.1016/0166-2236(91)90024-o.
71. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306(5944):686-8. (In eng). DOI: 10.1038/306686a0.
72. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52(1):77-92. (In eng). DOI: 10.1016/j.neuron.2006.09.021.

73. Bliddal H, Danneskiold-Samsøe B. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol 2007;21(3):391-402. (In eng). DOI: 10.1016/j.berh.2007.03.005.
74. Schaible HG, Schmelz M, Tegeder I. Pathophysiology and treatment of pain in joint disease. Adv Drug Deliv Rev 2006;58(2):323-42. (In eng). DOI: 10.1016/j.addr.2006.01.011.
75. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol 2007;21(3):481-97. (In eng). DOI: 10.1016/j.berh.2007.03.006.
76. Burstein R, Jakubowski M. Analgesic triptan action in an animal model of intracranial pain: a race against the development of central sensitization. Ann Neurol 2004;55(1):27-36. (In eng). DOI: 10.1002/ana.10785.
77. Ablin J, Neumann L, Buskila D. Pathogenesis of fibromyalgia - a review. Joint Bone Spine 2008;75(3):273-9. (In eng). DOI: 10.1016/j.jbspin.2007.09.010.
78. Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48(5):1420-9. (In eng). DOI: 10.1002/art.10893.
79. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. Curr Rheumatol Rep 2002;4(4):299-305. (In eng). DOI: 10.1007/s11926-002-0038-5.
80. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. J Pain 2007;8(11):893-901. (In eng). DOI: 10.1016/j.jpain.2007.06.006.
81. Staud R, Bovee CE, Robinson ME, Price DD. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. Pain 2008;139(2):315-323. (In eng). DOI: 10.1016/j.pain.2008.04.024.
82. Woolf CJ, King AE. Subthreshold components of the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat lumbar spinal cord. J Neurophysiol 1989;62(4):907-16. (In eng). DOI: 10.1152/jn.1989.62.4.907.
83. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol 1984;356:443-58. (In eng). DOI: 10.1113/jphysiol.1984.sp015475.
84. Woolf CJ, King AE. Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord. J Neurosci 1990;10(8):2717-26. (In eng). DOI: 10.1523/jneurosci.10-08-02717.1990.
85. McNamara CR, Mandel-Brehm J, Bautista DM, et al. TRPA1 mediates formalin-induced pain. Proc Natl Acad Sci U S A 2007;104(33):13525-30. (In eng). DOI: 10.1073/pnas.0705924104.
86. LaMotte RH, Shain CN, Simone DA, Tsai EF. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1991;66(1):190-211. (In eng). DOI: 10.1152/jn.1991.66.1.190.

87. Jordt SE, Bautista DM, Chuang HH, et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 2004;427(6971):260-5. (In eng). DOI: 10.1038/nature02282.
88. Alvarez FJ, Villalba RM, Carr PA, Grandes P, Somohano PM. Differential distribution of metabotropic glutamate receptors 1a, 1b, and 5 in the rat spinal cord. J Comp Neurol 2000;422(3):464-87. (In eng). DOI: 10.1002/1096-9861(20000703)422:3<464::aid-cne11>3.0.co;2-#.
89. Antal M, Fukazawa Y, Eördögh M, et al. Numbers, densities, and colocalization of AMPA- and NMDA-type glutamate receptors at individual synapses in the superficial spinal dorsal horn of rats. J Neurosci 2008;28(39):9692-701. (In eng). DOI: 10.1523/jneurosci.1551-08.2008.
90. Azkue JJ, Mateos JM, Elezgarai I, et al. The metabotropic glutamate receptor subtype mGluR 2/3 is located at extrasynaptic loci in rat spinal dorsal horn synapses. Neurosci Lett 2000;287(3):236-8. (In eng). DOI: 10.1016/s0304-3940(00)01189-7.
91. Pitcher MH, Ribeiro-da-Silva A, Coderre TJ. Effects of inflammation on the ultrastructural localization of spinal cord dorsal horn group I metabotropic glutamate receptors. J Comp Neurol 2007;505(4):412-23. (In eng). DOI: 10.1002/cne.21506.
92. Brenner GJ, Ji RR, Shaffer S, Woolf CJ. Peripheral noxious stimulation induces phosphorylation of the NMDA receptor NR1 subunit at the PKC-dependent site, serine-896, in spinal cord dorsal horn neurons. Eur J Neurosci 2004;20(2):375-84. (In eng). DOI: 10.1111/j.1460-9568.2004.03506.x.
93. Fang L, Wu J, Lin Q, Willis WD. Calcium-calmodulin-dependent protein kinase II contributes to spinal cord central sensitization. J Neurosci 2002;22(10):4196-204. (In eng). DOI: 10.1523/jneurosci.22-10-04196.2002.
94. Fang L, Wu J, Zhang X, Lin Q, Willis WD. Increased phosphorylation of the GluR1 subunit of spinal cord alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor in rats following intradermal injection of capsaicin. Neuroscience 2003;122(1):237-45. (In eng). DOI: 10.1016/s0306-4522(03)00526-8.
95. Fang L, Wu J, Lin Q, Willis WD. Protein kinases regulate the phosphorylation of the GluR1 subunit of AMPA receptors of spinal cord in rats following noxious stimulation. Brain Res Mol Brain Res 2003;118(1-2):160-5. (In eng). DOI: 10.1016/j.molbrainres.2003.08.002.
96. Jones TL, Sorkin LS. Activated PKA and PKC, but not CaMKIIalpha, are required for AMPA/Kainate-mediated pain behavior in the thermal stimulus model. Pain 2005;117(3):259-270. (In eng). DOI: 10.1016/j.pain.2005.06.003.
97. Liu XJ, Gingrich JR, Vargas-Caballero M, et al. Treatment of inflammatory and neuropathic pain by uncoupling Src from the NMDA receptor complex. Nat Med 2008;14(12):1325-32. (In eng). DOI: 10.1038/nm.1883.
98. Ultenius C, Linderoth B, Meyerson BA, Wallin J. Spinal NMDA receptor phosphorylation correlates with the presence of neuropathic signs following

peripheral nerve injury in the rat. Neurosci Lett 2006;399(1-2):85-90. (In eng). DOI: 10.1016/j.neulet.2006.01.018.
99. Yu XM, Salter MW. Src, a molecular switch governing gain control of synaptic transmission mediated by N-methyl-D-aspartate receptors. Proc Natl Acad Sci U S A 1999;96(14):7697-704. (In eng). DOI: 10.1073/pnas.96.14.7697.
100. Zou X, Lin Q, Willis WD. Effect of protein kinase C blockade on phosphorylation of NR1 in dorsal horn and spinothalamic tract cells caused by intradermal capsaicin injection in rats. Brain Res 2004;1020(1-2):95-105. (In eng). DOI: 10.1016/j.brainres.2004.06.017.
101. Zou X, Lin Q, Willis WD. Role of protein kinase A in phosphorylation of NMDA receptor 1 subunits in dorsal horn and spinothalamic tract neurons after intradermal injection of capsaicin in rats. Neuroscience 2002;115(3):775-86. (In eng). DOI: 10.1016/s0306-4522(02)00490-6.
102. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44(3):293-299. (In eng). DOI: 10.1016/0304-3959(91)90100-c.
103. Mendell LM, Wall PD. RESPONSES OF SINGLE DORSAL CORD CELLS TO PERIPHERAL CUTANEOUS UNMYELINATED FIBRES. Nature 1965;206:97-9. (In eng). DOI: 10.1038/206097a0.
104. Sivilotti LG, Thompson SW, Woolf CJ. Rate of rise of the cumulative depolarization evoked by repetitive stimulation of small-caliber afferents is a predictor of action potential windup in rat spinal neurons in vitro. J Neurophysiol 1993;69(5):1621-31. (In eng). DOI: 10.1152/jn.1993.69.5.1621.
105. Davies SN, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Res 1987;424(2):402-6. (In eng). DOI: 10.1016/0006-8993(87)91487-9.
106. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology 1987;26(8):1235-8. (In eng). DOI: 10.1016/0028-3908(87)90275-9.
107. Thompson SW, King AE, Woolf CJ. Activity-Dependent Changes in Rat Ventral Horn Neurons in vitro; Summation of Prolonged Afferent Evoked Postsynaptic Depolarizations Produce a d-2-Amino-5-Phosphonovaleric Acid Sensitive Windup. Eur J Neurosci 1990;2(7):638-49. (In eng). DOI: 10.1111/j.1460-9568.1990.tb00453.x.
108. Ma QP, Woolf CJ. Noxious stimuli induce an N-methyl-D-aspartate receptor-dependent hypersensitivity of the flexion withdrawal reflex to touch: implications for the treatment of mechanical allodynia. Pain 1995;61(3):383-390. (In eng). DOI: 10.1016/0304-3959(94)00195-k.
109. Abbadie C, Brown JL, Mantyh PW, Basbaum AI. Spinal cord substance P receptor immunoreactivity increases in both inflammatory and nerve injury models of persistent pain. Neuroscience 1996;70(1):201-9. (In eng). DOI: 10.1016/0306-4522(95)00343-h.

110. Abbadie C, Trafton J, Liu H, Mantyh PW, Basbaum AI. Inflammation increases the distribution of dorsal horn neurons that internalize the neurokinin-1 receptor in response to noxious and non-noxious stimulation. J Neurosci 1997;17(20):8049-60. (In eng). DOI: 10.1523/jneurosci.17-20-08049.1997.
111. Adwanikar H, Karim F, Gereau RWt. Inflammation persistently enhances nocifensive behaviors mediated by spinal group I mGluRs through sustained ERK activation. Pain 2004;111(1-2):125-35. (In eng). DOI: 10.1016/j.pain.2004.06.009.
112. Chen SR, Pan HL. Distinct roles of group III metabotropic glutamate receptors in control of nociception and dorsal horn neurons in normal and nerve-injured Rats. J Pharmacol Exp Ther 2005;312(1):120-6. (In eng). DOI: 10.1124/jpet.104.073817.
113. Cheng HT, Suzuki M, Hegarty DM, et al. Inflammatory pain-induced signaling events following a conditional deletion of the N-methyl-D-aspartate receptor in spinal cord dorsal horn. Neuroscience 2008;155(3):948-58. (In eng). DOI: 10.1016/j.neuroscience.2008.06.024.
114. Chu YC, Guan Y, Skinner J, Raja SN, Johns RA, Tao YX. Effect of genetic knockout or pharmacologic inhibition of neuronal nitric oxide synthase on complete Freund's adjuvant-induced persistent pain. Pain 2005;119(1-3):113-123. (In eng). DOI: 10.1016/j.pain.2005.09.024.
115. de Novellis V, Siniscalco D, Galderisi U, et al. Blockade of glutamate mGlu5 receptors in a rat model of neuropathic pain prevents early over-expression of pro-apoptotic genes and morphological changes in dorsal horn lamina II. Neuropharmacology 2004;46(4):468-79. (In eng). DOI: 10.1016/j.neuropharm.2003.10.014.
116. Dogrul A, Ossipov MH, Lai J, Malan TP, Jr., Porreca F. Peripheral and spinal antihyperalgesic activity of SIB-1757, a metabotropic glutamate receptor (mGLUR(5)) antagonist, in experimental neuropathic pain in rats. Neurosci Lett 2000;292(2):115-8. (In eng). DOI: 10.1016/s0304-3940(00)01458-0.
117. Fundytus ME, Osborne MG, Henry JL, Coderre TJ, Dray A. Antisense oligonucleotide knockdown of mGluR1 alleviates hyperalgesia and allodynia associated with chronic inflammation. Pharmacol Biochem Behav 2002;73(2):401-10. (In eng). DOI: 10.1016/s0091-3057(02)00831-6.
118. Giles PA, Trezise DJ, King AE. Differential activation of protein kinases in the dorsal horn in vitro of normal and inflamed rats by group I metabotropic glutamate receptor subtypes. Neuropharmacology 2007;53(1):58-70. (In eng). DOI: 10.1016/j.neuropharm.2007.04.003.
119. Goudet C, Chapuy E, Alloui A, Acher F, Pin JP, Eschalier A. Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. Pain 2008;137(1):112-124. (In eng). DOI: 10.1016/j.pain.2007.08.020.
120. Hu HJ, Alter BJ, Carrasquillo Y, Qiu CS, Gereau RWt. Metabotropic glutamate receptor 5 modulates nociceptive plasticity via extracellular signal-regulated

kinase-Kv4.2 signaling in spinal cord dorsal horn neurons. J Neurosci 2007;27(48):13181-91. (In eng). DOI: 10.1523/jneurosci.0269-07.2007.
121. Kerr BJ, Bradbury EJ, Bennett DL, et al. Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord. J Neurosci 1999;19(12):5138-48. (In eng). DOI: 10.1523/jneurosci.19-12-05138.1999.
122. Lee SE, Kim JH. Involvement of substance P and calcitonin gene-related peptide in development and maintenance of neuropathic pain from spinal nerve injury model of rat. Neurosci Res 2007;58(3):245-9. (In eng). DOI: 10.1016/j.neures.2007.03.004.
123. Lu VB, Biggs JE, Stebbing MJ, et al. Brain-derived neurotrophic factor drives the changes in excitatory synaptic transmission in the rat superficial dorsal horn that follow sciatic nerve injury. J Physiol 2009;587(Pt 5):1013-32. (In eng). DOI: 10.1113/jphysiol.2008.166306.
124. Lu Y, Sun YN, Wu X, et al. Role of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor subunit GluR1 in spinal dorsal horn in inflammatory nociception and neuropathic nociception in rat. Brain Res 2008;1200:19-26. (In eng). DOI: 10.1016/j.brainres.2008.01.012.
125. Mannion RJ, Costigan M, Decosterd I, et al. Neurotrophins: peripherally and centrally acting modulators of tactile stimulus-induced inflammatory pain hypersensitivity. Proc Natl Acad Sci U S A 1999;96(16):9385-90. (In eng). DOI: 10.1073/pnas.96.16.9385.
126. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ, Frenk H. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. Brain Res 1993;605(1):164-8. (In eng). DOI: 10.1016/0006-8993(93)91368-3.
127. Marabese I, de Novellis V, Palazzo E, et al. Effects of (S)-3,4-DCPG, an mGlu8 receptor agonist, on inflammatory and neuropathic pain in mice. Neuropharmacology 2007;52(2):253-62. (In eng). DOI: 10.1016/j.neuropharm.2006.04.006.
128. Minami T, Nishihara I, Uda R, Ito S, Hyodo M, Hayaishi O. Involvement of glutamate receptors in allodynia induced by prostaglandins E2 and F2 alpha injected into conscious mice. Pain 1994;57(2):225-231. (In eng). DOI: 10.1016/0304-3959(94)90227-5.
129. Neugebauer V, Lücke T, Schaible HG. Requirement of metabotropic glutamate receptors for the generation of inflammation-evoked hyperexcitability in rat spinal cord neurons. Eur J Neurosci 1994;6(7):1179-86. (In eng). DOI: 10.1111/j.1460-9568.1994.tb00616.x.
130. Obata K, Noguchi K. BDNF in sensory neurons and chronic pain. Neurosci Res 2006;55(1):1-10. (In eng). DOI: 10.1016/j.neures.2006.01.005.
131. Park JS, Yaster M, Guan X, et al. Role of spinal cord alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors in complete Freund's adjuvant-induced inflammatory pain. Mol Pain 2008;4:67. (In eng). DOI: 10.1186/1744-8069-4-67.

132. Petcu M, Dias JP, Ongali B, Thibault G, Neugebauer W, Couture R. Role of kinin B1 and B2 receptors in a rat model of neuropathic pain. Int Immunopharmacol 2008;8(2):188-96. (In eng). DOI: 10.1016/j.intimp.2007.09.009.
133. Qu XX, Cai J, Li MJ, et al. Role of the spinal cord NR2B-containing NMDA receptors in the development of neuropathic pain. Exp Neurol 2009;215(2):298-307. (In eng). DOI: 10.1016/j.expneurol.2008.10.018.
134. Seltzer Z, Cohn S, Ginzburg R, Beilin B. Modulation of neuropathic pain behavior in rats by spinal disinhibition and NMDA receptor blockade of injury discharge. Pain 1991;45(1):69-75. (In eng). DOI: 10.1016/0304-3959(91)90166-u.
135. Simmons RM, Webster AA, Kalra AB, Iyengar S. Group II mGluR receptor agonists are effective in persistent and neuropathic pain models in rats. Pharmacol Biochem Behav 2002;73(2):419-27. (In eng). DOI: 10.1016/s0091-3057(02)00849-3.
136. Siniscalco D, Giordano C, Fuccio C, et al. Involvement of subtype 1 metabotropic glutamate receptors in apoptosis and caspase-7 over-expression in spinal cord of neuropathic rats. Pharmacol Res 2008;57(3):223-33. (In eng). DOI: 10.1016/j.phrs.2008.01.007.
137. Tal M, Bennett GJ. Neuropathic pain sensations are differentially sensitive to dextrorphan. Neuroreport 1994;5(12):1438-40. (In eng). DOI: 10.1097/00001756-199407000-00008.
138. Tanabe M, Nagatani Y, Saitoh K, Takasu K, Ono H. Pharmacological assessments of nitric oxide synthase isoforms and downstream diversity of NO signaling in the maintenance of thermal and mechanical hypersensitivity after peripheral nerve injury in mice. Neuropharmacology 2009;56(3):702-8. (In eng). DOI: 10.1016/j.neuropharm.2008.12.003.
139. Young MR, Fleetwood-Walker SM, Dickinson T, et al. Behavioural and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. Brain Res 1997;777(1-2):161-9. (In eng).
140. Zhang HM, Chen SR, Pan HL. Effects of activation of group III metabotropic glutamate receptors on spinal synaptic transmission in a rat model of neuropathic pain. Neuroscience 2009;158(2):875-84. (In eng). DOI: 10.1016/j.neuroscience.2008.10.042.
141. Zhu CZ, Wilson SG, Mikusa JP, et al. Assessing the role of metabotropic glutamate receptor 5 in multiple nociceptive modalities. Eur J Pharmacol 2004;506(2):107-18. (In eng). DOI: 10.1016/j.ejphar.2004.11.005.
142. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016;157(8):1599-1606. (In eng). DOI: 10.1097/j.pain.0000000000000492.
143. Yang Y, Maher DP, Cohen SP. Emerging concepts on the use of ketamine for chronic pain. Expert Review of Clinical Pharmacology 2020;13(2):135-146. DOI: 10.1080/17512433.2020.1717947.

144. Johnson MI. The Landscape of Chronic Pain: Broader Perspectives. Medicina (Kaunas) 2019;55(5) (In eng). DOI: 10.3390/medicina55050182.
145. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 2016;338:114-129. (In eng). DOI: 10.1016/j.neuroscience.2016.06.006.
146. Melzack R, Casey KL. Sensory motivational and central control determinants of pain a new conceptual model. 1968:423-443.
147. Randolph CS, Greene CS, Moretti R, Forbes D, Perry HT. Conservative management of temporomandibular disorders: a posttreatment comparison between patients from a university clinic and from private practice. Am J Orthod Dentofacial Orthop 1990;98(1):77-82. (In eng). DOI: 10.1016/0889-5406(90)70035-b.
148. Danzig WN, Van Dyke AR. Physical therapy as an adjunct to temporomandibular joint therapy. J Prosthet Dent 1983;49(1):96-9. (In eng). DOI: 10.1016/0022-3913(83)90247-0.
149. Kirk WS, Jr., Calabrese DK. Clinical evaluation of physical therapy in the management of internal derangement of the temporomandibular joint. J Oral Maxillofac Surg 1989;47(2):113-9. (In eng). DOI: 10.1016/s0278-2391(89)80099-0.
150. Clark GT, Adachi NY, Dornan MR. Physical medicine procedures affect temporomandibular disorders: a review. J Am Dent Assoc 1990;121(1):151-62. (In eng). DOI: 10.14219/jada.archive.1990.0140.
151. Gangarosa L, Mahan PE. Pharmacologic Management of TMD-MPDS. Ear Nose Throat J 1982;61:670-678.
152. Gregg JM, Rugh JD. A textbook of Occlusion. Chicago, IL: Quintessence, 1983.
153. Song PC, Schwartz J, Blitzer A. The emerging role of botulinum toxin in the treatment of temporomandibular disorders. Oral Dis 2007;13(3):253-60. (In eng). DOI: 10.1111/j.1601-0825.2007.01352.x.
154. Clark GT. A critical evaluation of orthopedic interocclusal appliance therapy: effectiveness for specific symptoms. J Am Dent Assoc 1984;108(3):364-8. (In eng). DOI: 10.14219/jada.archive.1984.0002.
155. Tsuga K, Akagawa Y, Sakaguchi R, Tsuru H. A short-term evaluation of the effectiveness of stabilization-type occlusal splint therapy for specific symptoms of temporomandibular joint dysfunction syndrome. J Prosthet Dent 1989;61(5):610-3. (In eng). DOI: 10.1016/0022-3913(89)90286-2.
156. Kreiner M, Betancor E, Clark GT. Occlusal stabilization appliances. Evidence of their efficacy. J Am Dent Assoc 2001;132(6):770-7. (In eng). DOI: 10.14219/jada.archive.2001.0274.
157. Fricton J, Look JO, Wright E, et al. Systematic review and meta-analysis of randomized controlled trials evaluating intraoral orthopedic appliances for temporomandibular disorders. J Orofac Pain 2010;24(3):237-54. (In eng).
158. Parameters of care for oral and maxillofacial surgery. A guide for practice, monitoring and evaluation (AAOMS Parameters of Care-92). American

Association of Oral and Maxillofacial Surgeons. J Oral Maxillofac Surg 1992;50(7 Suppl 2):i-xvi, 1-174. (In eng).
159. Olds MJ, Woods CI, Winfield JA. Microvascular decompression in glossopharyngeal neuralgia. Am J Otol 1995;16(3):326-30. (In eng).
160. Administration UFaD. KETALAR (ketamine hydrochloride) Injection. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf).
161. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional Anesthesia and Pain Medicine 2018;43(5):1. DOI: 10.1097/aap.0000000000000808.
162. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol 2008(182):313-33. (In eng). DOI: 10.1007/978-3-540-74806-9_15.
163. Himmelseher S, Pfenninger E. [The clinical use of S-(+)-ketamine--a determination of its place]. Anasthesiol Intensivmed Notfallmed Schmerzther 1998;33(12):764-70. (In ger). DOI: 10.1055/s-2007-994851.
164. Singh NS, Zarate CA, Jr., Moaddel R, Bernier M, Wainer IW. What is hydroxynorketamine and what can it bring to neurotherapeutics? Expert Rev Neurother 2014;14(11):1239-42. (In eng). DOI: 10.1586/14737175.2014.971760.
165. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 2016;533(7604):481-6. (In eng). DOI: 10.1038/nature17998.
166. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. Anesth Essays Res 2014;8(3):283-90. (In eng). DOI: 10.4103/0259-1162.143110.
167. Cohen SP, Liao W, Gupta A, Plunkett A. Ketamine in pain management. Adv Psychosom Med 2011;30:139-161. (In eng). DOI: 10.1159/000324071.
168. Sprung J, Schuetz SM, Stewart RW, Moravec CS. Effects of ketamine on the contractility of failing and nonfailing human heart muscles in vitro. Anesthesiology 1998;88(5):1202-10. (In eng). DOI: 10.1097/00000542-199805000-00010.
169. MacPherson RD, Woods D, Penfold J. Ketamine and midazolam delivered by patient-controlled analgesia in relieving pain associated with burns dressings. Clin J Pain 2008;24(7):568-71. (In eng). DOI: 10.1097/AJP.0b013e31816cdb20.
170. Lenze EJ, Farber NB, Kharasch E, et al. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: A pilot randomised controlled trial. World J Biol Psychiatry 2016;17(3):230-8. (In eng). DOI: 10.3109/15622975.2016.1142607.
171. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology 1997;86(4):903-17. (In eng). DOI: 10.1097/00000542-199704000-00021.
172. Chang CH, Hsiao YH, Chen YW, Yu YJ, Gean PW. Social isolation-induced increase in NMDA receptors in the hippocampus exacerbates emotional

dysregulation in mice. Hippocampus 2015;25(4):474-85. (In eng). DOI: 10.1002/hipo.22384.
173. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology 2012;62(1):35-41. (In eng). DOI: 10.1016/j.neuropharm.2011.08.044.
174. Trujillo KA, Akil H. Inhibition of opiate tolerance by non-competitive N-methyl-D-aspartate receptor antagonists. Brain Res 1994;633(1-2):178-88. (In eng). DOI: 10.1016/0006-8993(94)91538-5.
175. Zhou HY, Chen SR, Pan HL. Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. Expert Rev Clin Pharmacol 2011;4(3):379-88. (In eng). DOI: 10.1586/ecp.11.17.
176. Sarton E, Teppema LJ, Olievier C, et al. The involvement of the mu-opioid receptor in ketamine-induced respiratory depression and antinociception. Anesth Analg 2001;93(6):1495-500, table of contents. (In eng). DOI: 10.1097/00000539-200112000-00031.
177. Smith DJ, Perrotti JM, Mansell AL, Monroe PJ. Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. Pain 1985;21(3):253-265. (In eng). DOI: 10.1016/0304-3959(85)90089-2.
178. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. Br J Anaesth 2013;110(6):1010-6. (In eng). DOI: 10.1093/bja/aes578.
179. Seeman P, Ko F, Tallerico T. Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Mol Psychiatry 2005;10(9):877-83. (In eng). DOI: 10.1038/sj.mp.4001682.
180. Sleigh J, Harvey M, Voss L, Denny B. Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care 2014;4(2):76-81. DOI: https://doi.org/10.1016/j.tacc.2014.03.002.
181. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Molecular Psychiatry 2018;23(4):801-811. DOI: 10.1038/mp.2017.255.
182. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47(4):351-4. (In eng). DOI: 10.1016/s0006-3223(99)00230-9.
183. Hu YD, Xiang YT, Fang JX, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. Psychol Med 2016;46(3):623-35. (In eng). DOI: 10.1017/s0033291715002159.
184. Ionescu DF, Swee MB, Pavone KJ, et al. Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study. J Clin Psychiatry 2016;77(6):e719-25. (In eng). DOI: 10.4088/JCP.15m10056.
185. Wilkinson ST, Ballard ED, Bloch MH, et al. The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual

Participant Data Meta-Analysis. Am J Psychiatry 2018;175(2):150-158. (In eng). DOI: 10.1176/appi.ajp.2017.17040472.
186. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res 2014;215(2):355-61. (In eng). DOI: 10.1016/j.psychres.2013.12.008.
187. López-Díaz Á, Fernández-González JL, Luján-Jiménez JE, Galiano-Rus S, Gutiérrez-Rojas L. Use of repeated intravenous ketamine therapy in treatment-resistant bipolar depression with suicidal behaviour: a case report from Spain. Ther Adv Psychopharmacol 2017;7(4):137-140. (In eng). DOI: 10.1177/2045125316675578.
188. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 2013;74(4):250-6. (In eng). DOI: 10.1016/j.biopsych.2012.06.022.
189. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. Bmj 2014;348:f7656. (In eng). DOI: 10.1136/bmj.f7656.
190. Ghasemi M, Phillips C, Trillo L, De Miguel Z, Das D, Salehi A. The role of NMDA receptors in the pathophysiology and treatment of mood disorders. Neurosci Biobehav Rev 2014;47:336-58. (In eng). DOI: 10.1016/j.neubiorev.2014.08.017.
191. Lin CH, Huang YJ, Lin CJ, Lane HY, Tsai GE. NMDA neurotransmission dysfunction in mild cognitive impairment and Alzheimer's disease. Curr Pharm Des 2014;20(32):5169-79. (In eng). DOI: 10.2174/1381612819666140110115603.
192. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. CNS Neurosci Ther 2013;19(6):403-10. (In eng). DOI: 10.1111/cns.12104.
193. Vranken JH. Elucidation of pathophysiology and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem 2012;12(4):304-14. (In eng). DOI: 10.2174/187152412803760645.
194. Kregel J, Vuijk PJ, Descheemaeker F, et al. The Dutch Central Sensitization Inventory (CSI): Factor Analysis, Discriminative Power, and Test-Retest Reliability. Clin J Pain 2016;32(7):624-30. (In eng). DOI: 10.1097/ajp.0000000000000306.
195. Tajerian M, Leu D, Yang P, Huang TT, Kingery WS, Clark JD. Differential Efficacy of Ketamine in the Acute versus Chronic Stages of Complex Regional Pain Syndrome in Mice. Anesthesiology 2015;123(6):1435-47. (In eng). DOI: 10.1097/aln.0000000000000889.
196. Zhang LM, Zhou WW, Ji YJ, et al. Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. Psychopharmacology (Berl) 2015;232(4):663-72. (In eng). DOI: 10.1007/s00213-014-3697-9.
197. Li CT, Chen MH, Lin WC, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: A randomized

controlled study. Hum Brain Mapp 2016;37(3):1080-90. (In eng). DOI: 10.1002/hbm.23085.
198. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29(10):1765-81. (In eng). DOI: 10.1038/sj.npp.1300506.
199. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain 2001;91(1-2):177-87. (In eng). DOI: 10.1016/s0304-3959(00)00433-4.
200. Eichenberger U, Neff F, Sveticic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. Anesth Analg 2008;106(4):1265-73, table of contents. (In eng). DOI: 10.1213/ane.0b013e3181685014.
201. Kvarnström A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand 2004;48(4):498-506. (In eng). DOI: 10.1111/j.1399-6576.2003.00330.x.
202. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 2009;147(1-3):107-15. (In eng). DOI: 10.1016/j.pain.2009.08.015.
203. Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. Clin Neuropharmacol 1995;18(4):360-8. (In eng). DOI: 10.1097/00002826-199508000-00008.
204. Gottrup H, Bach FW, Juhl G, Jensen TS. Differential effect of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. Anesthesiology 2006;104(3):527-36. (In eng). DOI: 10.1097/00000542-200603000-00021.
205. Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. Neurosurgery 1995;37(6):1080-7. (In eng). DOI: 10.1227/00006123-199512000-00007.
206. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician 2010;13(3):245-9. (In eng).
207. Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. Pain 1996;67(1):69-77. (In eng). DOI: 10.1016/0304-3959(96)03080-1.
208. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994;58(3):347-354. (In eng). DOI: 10.1016/0304-3959(94)90129-5.

209. Sörensen J, Bengtsson A, Bäckman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. Scand J Rheumatol 1995;24(6):360-5. (In eng). DOI: 10.3109/03009749509095181.
210. Sörensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. J Rheumatol 1997;24(8):1615-21. (In eng).
211. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain 2011;15(9):942-9. (In eng). DOI: 10.1016/j.ejpain.2011.03.008.
212. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009;145(3):304-311. (In eng). DOI: 10.1016/j.pain.2009.06.023.
213. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. Pain 2002;97(3):275-281. (In eng). DOI: 10.1016/s0304-3959(02)00033-7.
214. Persson J, Hasselström J, Wiklund B, Heller A, Svensson JO, Gustafsson LL. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Acta Anaesthesiol Scand 1998;42(7):750-8. (In eng). DOI: 10.1111/j.1399-6576.1998.tb05317.x.
215. Salas S, Frasca M, Planchet-Barraud B, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care. J Palliat Med 2012;15(3):287-93. (In eng). DOI: 10.1089/jpm.2011.0353.
216. Granata L, Niebergall H, Langner R, Agosti R, Sakellaris L. [Ketamine i. v. for the treatment of cluster headaches : An observational study]. Schmerz 2016;30(3):286-8. (In ger). DOI: 10.1007/s00482-016-0111-z.
217. Moisset X, Clavelou P, Lauxerois M, Dallel R, Picard P. Ketamine Infusion Combined With Magnesium as a Therapy for Intractable Chronic Cluster Headache: Report of Two Cases. Headache 2017;57(8):1261-1264. (In eng). DOI: 10.1111/head.13135.
218. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine Infusions for Treatment Refractory Headache. Headache 2017;57(2):276-282. (In eng). DOI: 10.1111/head.13013.
219. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: therapeutic and theoretic implications. Int J Clin Pharmacol Res 1995;15(5-6):181-9. (In eng).
220. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. Neurology 2013;80(7):642-7. (In eng). DOI: 10.1212/WNL.0b013e3182824e66.
221. The GRADE Working Group. GRADE. (http:// www.gradeworkinggroup.org.).

222. Ayesh EE, Jensen TS, Svensson P. Effects of intra-articular ketamine on pain and somatosensory function in temporomandibular joint arthralgia patients. Pain 2008;137(2):286-294. (In eng). DOI: 10.1016/j.pain.2007.09.004.
223. Baad-Hansen L, Juhl GI, Jensen TS, Brandsborg B, Svensson P. Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. Pain 2007;129(1-2):46-54. (In eng). DOI: 10.1016/j.pain.2006.09.032.
224. Castrillon EE, Cairns BE, Ernberg M, et al. Effect of peripheral NMDA receptor blockade with ketamine on chronic myofascial pain in temporomandibular disorder patients: a randomized, double-blinded, placebo-controlled trial. J Orofac Pain 2008;22(2):122-30. (In eng).
225. Castrillon EE, Cairns BE, Wang K, Arendt-Nielsen L, Svensson P. Comparison of glutamate-evoked pain between the temporalis and masseter muscles in men and women. Pain 2012;153(4):823-829. (In eng). DOI: 10.1016/j.pain.2012.01.003.
226. Chang F-L, Huang G-S, Cherng C-H, Ho S-T, Wong C-S. Repeated peripheral nerve blocks by the co-administration of ketamine, morphine, and bupivacaine attenuate trigeminal neuralgia. Canadian Journal of Anesthesia/Journal canadien d'anesthésie 2003;50(2):201-202. DOI: 10.1007/bf03017860.
227. Shiiba S, Sago T, Kawabata K. Pain Relief in Short-Lasting Unilateral Neuralgiform Headache with Conjunctival inJection and Tearing Syndrome with Intravenous Ketamine: A Case Report. Acta Neurol Taiwan 2021;30(1):35-38. (In eng).
228. Mathisen LC, Skjelbred P, Skoglund LA, Øye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. Pain 1995;61(2):215-220. (In eng). DOI: 10.1016/0304-3959(94)00170-j.
229. Rabben T, Øye I. Interindividual differences in the analgesic response to ketamine in chronic orofacial pain. Eur J Pain 2001;5(3):233-40. (In eng). DOI: 10.1053/eujp.2001.0232.
230. Bereiter DA, Bereiter DF. Morphine and NMDA receptor antagonism reduce c-fos expression in spinal trigeminal nucleus produced by acute injury to the TMJ region. Pain 2000;85(1-2):65-77. (Article) (In English). DOI: 10.1016/s0304-3959(99)00246-8.
231. Brian, Shelly, Miguel, Peter. Tooth Pulp– and Facial Hair Mechanoreceptor–evoked Responses of Trigeminal Sensory Neurons Are Attenuated during Ketamine Anesthesia. Anesthesiology 1999;91(4):1025-1025. DOI: 10.1097/00000542-199910000-00023.
232. Cao Y, Xie QF, Li K, Light AR, Fu KY. Experimental occlusal interference induces long-term masticatory muscle hyperalgesia in rats. Pain 2009;144(3):287-293. (In eng). DOI: 10.1016/j.pain.2009.04.029.
233. Christensen D, Gautron M, Guilbaud G, Kayser V. Combined systemic administration of the glycine/NMDA receptor antagonist, (+)-HA966 and morphine attenuates pain-related behaviour in a rat model of trigeminal neuropathic pain. Pain 1999;83(3):433-440. (In eng). DOI: 10.1016/s0304-3959(99)00126-8.

234. Claudino R, Nones C, Araya E, Chichorro J. Analgesic Effects of Intranasal Ketamine in Rat Models of Facial Pain. J Oral Facial Pain Headache 2018;32(3):238-246. (Article) (In English). DOI: 10.11607/ofph.1973.
235. de Oliveira BA, Alves Rodrigues Santos SA, Menezes Pereira EW, et al. Orofacial Antinociceptive Effect of Nifedipine in Rodents Is Mediated by TRPM3, TRPA1, and NMDA Processes. J Oral Facial Pain Headache 2020;34(2):174-186. (In eng). DOI: 10.11607/ofph.2491.
236. Dong XD, Mann MK, Sessle BJ, Arendt-Nielsen L, Svensson P, Cairns BE. Sensitivity of rat temporalis muscle afferent fibers to peripheral N-methyl-D-aspartate receptor activation. Neuroscience 2006;141(2):939-945. (In eng). DOI: 10.1016/j.neuroscience.2006.04.024.
237. Fujimi Y, Takeda M, Tanimoto T, Matsumoto S. N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists suppress the superior sagittal sinus-evoked activity of C1 spinal neurons responding to tooth pulp electrical stimulation in rats. Odontology 2006;94(1):22-8. (In eng). DOI: 10.1007/s10266-006-0057-1.
238. Guo W, Wang H, Watanabe M, et al. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. J Neurosci 2007;27(22):6006-18. (In eng). DOI: 10.1523/jneurosci.0176-07.2007.
239. Kayser V, Latrémolière A, Hamon M, Bourgoin S. N-methyl-D-aspartate receptor-mediated modulations of the anti-allodynic effects of 5-HT1B/1D receptor stimulation in a rat model of trigeminal neuropathic pain. Eur J Pain 2011;15(5):451-8. (In eng). DOI: 10.1016/j.ejpain.2010.09.012.
240. Lee J, Saloman JL, Weiland G, Auh QS, Chung M-K, Ro JY. Functional interactions between NMDA receptors and TRPV1 in trigeminal sensory neurons mediate mechanical hyperalgesia in the rat masseter muscle. Pain 2012;153(7):1514-1524. DOI: 10.1016/j.pain.2012.04.015.
241. Li J-H, Yang J-L, Wei S-Q, et al. Contribution of central sensitization to stress-induced spreading hyperalgesia in rats with orofacial inflammation. Molecular Brain 2020;13(1). DOI: 10.1186/s13041-020-00645-x.
242. Piovesan EJ, Randunz V, Utiumi M, et al. Influence of NMDA and non-NMDA antagonists on acute and inflammatory pain in the trigeminal territory: a placebo control study. Arq Neuropsiquiatr 2008;66(4):837-43. (In eng). DOI: 10.1590/s0004-282x2008000600012.
243. Wong H, Kang I, Dong XD, et al. NGF-INDUCED MECHANICAL SENSITIZATION OF THE MASSETER MUSCLE IS MEDIATED THROUGH PERIPHERAL NMDA RECEPTORS. Neuroscience 2014;269:232-244. (Article) (In English). DOI: 10.1016/j.neuroscience.2014.03.054.
244. Xu XX, Cao Y, Mo SY, Liu Y, Xie QF. ACC Plasticity Maintains Masseter Hyperalgesia Caused by Occlusal Interference. Journal of Dental Research 2019;98(5):589-596. DOI: 10.1177/0022034519827590.
245. Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP. Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesth Analg 2019;129(1):241-254. (Review) (In English). DOI: 10.1213/ane.0000000000004185.

246. Chitneni A, Patil A, Dalal S, Ghorayeb JH, Pham YN, Grigoropoulos G. Use of Ketamine Infusions for Treatment of Complex Regional Pain Syndrome: A Systematic Review. Cureus 2021;13(10):10. (Review) (In English). DOI: 10.7759/cureus.18910.
247. Sakamoto E, Shiiba S, Noma N, et al. A possible case of complex regional pain syndrome in the orofacial region. Pain Med 2010;11(2):274-80. (In eng). DOI: 10.1111/j.1526-4637.2009.00777.x.
248. Schwenk ES, Dayan AC, Rangavajjula A, et al. Ketamine for Refractory Headache: A Retrospective Analysis. Reg Anesth Pain Med 2018;43(8):875-879. (In eng). DOI: 10.1097/aap.0000000000000827.
249. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev 2012;2012(7):Cd008943. (In eng). DOI: 10.1002/14651858.CD008943.pub2.
250. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43(5):456-466. (In eng). DOI: 10.1097/aap.0000000000000806.