New Agents and Approaches for Migraine Treatment

Carol Redillas, MD

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Carol Redillas, M.D.
Crescent City Headache and Neurology
New Orleans, Louisiana

ICHD-3 Criteria for Migraine

(A) At least five attacks fulfilling criteria B–D

(B) Headache attacks lasting 4–72 h (when untreated or unsuccessfully treated)

(C) Headache has at least two of the following four characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

(D) During headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

(E) Not better accounted for by another diagnosis

:

ICHD-3 Criteria for Chronic Migraine

(A) Migraine-like or tension-type-like headache on ≥15 days/month for >3 months that fulfill criteria B and C

(B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura

(C) On ≥8 days/month for >3 months, fulfilling any of the following:

1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D) Not better accounted for by another diagnosis

Migraine

- One year period prevalence is 18% in women and 6% in men
- Significantly impairs functional ability at work, in school, at home and in social situations
- Among neurologic conditions, it ranks second in terms of years lost to disability
- Associated with considerable financial burden, annual total costs estimated to be ~ $27B in the US

Migraine Pathophysiology

Disease of the brain – hypothalamus and trigeminal system

Vasoactive neuropeptide (such as CGRP, Substance P, and PACAP-38) release from trigeminal C fibers and activation of trigeminal A delta fibers leads to afferent stimulation of the central pathways

Serotonin inhibits the trigeminal nerve (5HT1D and F) and vasoconstricts blood vessel (5HT1B)

Acute Treatment of Migraines

Goals of Acute Treatment

- Rapid and consistent freedom from pain and associated symptoms, especially the most bothersome symptom, without recurrence.
- Restore ability to function.
- Minimal need for repeat dosing or rescue medications.
- Optimal self- care and reduced subsequent use of resources (e.g., ER visits, diagnostic imaging, clinician and ambulatory infusion center visits).
- Minimal or no adverse events (AEs).
- Cost considerations.

Acute treatments with evidence of efficacy in migraine

- **Established efficacy**
  - *Migraine specific*
    - Triptans
    - Ergotamine derivatives
    - Gepants
    - Lasmiditan
  - *Non-specific*
    - Nsaids- ASA, celecoxib oral solution, diclofenac, ibuprofen naproxen
    - Combination analgesic- ASA/acetaminophen/caffeine

Acute treatments with evidence of efficacy in migraine

- **Probably effective**
  - *Migraine specific*
    - Ergotamine
    - Other forms of dihydroergotamine
  - *Non-specific*
    - Nsads- Flurbiprofen, ketoprofen, IV and IM ketorolac
    - IV Magnesium
    - Isometheptene
    - Antiemetics- chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine

Triptans

Triptans

- Binds to serotonin (5 HT1B and 5 HT1 D) receptors
- Reduces release of CGRP
- Vasoconstrictors --- thus, can cause chest pain/tightness/pressure and neck/throat/jaw tightness and pressure
- Effective, considered the standard of care

Triptans

- About 30% of patients have an insufficient response to triptans, resulting in significantly higher healthcare utilization and costs
- Patients who do not respond to initial therapy with a triptan, or those with side effects or contraindications may benefit from a second triptan or a different therapy

Triptans

- Sumatriptan---oral, nasal, injectable
- Sumatriptan/Naproxen--oral
- Rizatriptan---oral, MLT
- Zolmitriptan--- oral, ZMT, nasal
- Frovatriptan---oral
- Almotriptan---oral
- Naratriptan---oral
- Eletriptan---oral

Criteria in initiating treatment with gepants, ditans or neuromodulatory devices

- Use is appropriate when ALL the following are met:
  - > Prescribed/recommended by a licensed clinician
  - > Patient is at least 18 years of age
  - > Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine

Criteria in initiating treatment with gepants, ditans or neuromodulatory devices

Either of the following:

- > Contraindications to or inability to tolerate triptans
- > Inadequate response to two or more oral triptans, as determined by EITHER of the following
  - - Validated acute treatment patient-reported outcome questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC)
  - -Clinician attestation

- *Abbreviations: FIS, Functional Impairment Scale; ICHD-3, International Classification of Headache Disorders, 3rd edition; Migraine- ACT, Migraine Assessment of Current Therapy; mTOQ, Migraine Treatment Optimization Questionnaire; PGIC, Patient Global Impression of Change; PPMQ-R, Patient Perception of Migraine Questionnaire-Revised.*

Meet the GEPANTS

CGRP receptor antagonists ("gepants")

- Blocks the CGRP receptor or binds to CGRP
- No vasoconstrictor activity
- Minimal side effects
- No evidence of medication overuse headaches

UBROGEPANT

- FDA approved in December 2019
- Only gepant with an optional second dose
- Most common S/E– nausea, somnolence

Ubrogepant– Pain Freedom

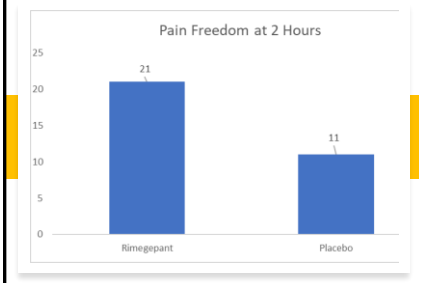
Ubrogepant– Return to Function

RIMEGEPANT

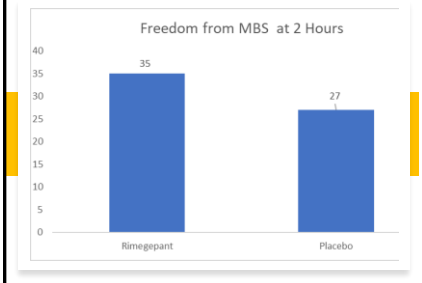
FDA approved in February 2020 (for acute treatment) and in May 2021 (for prevention of migraines)

Comes as an ODT tablet

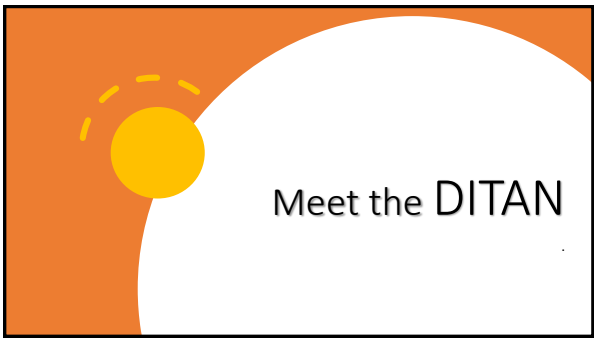
Most common S/E- nausea



Rimegepant --- Pain Freedom at 2 Hours

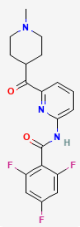


Rimegepant– Freedom from Most Bothersome Symptom at 2 Hours



LASMIDITAN

- FDA approved in October 2019
- First and only FDA-approved ditan
- Presumably exerts its therapeutic effects by activating the 5-HT1F receptor; however, the exact mechanism of action is unknown.



LASMIDITAN

- Associated with driving impairment and sleepiness
- Schedule V drug
- Caution patients not to drive or operate heavy machinery within 8 hours of intake
- Frequent use can potentially cause medication overuse headaches

Lasmiditan– Pain Freedom at 2 Hours

Lasmiditan–Elimination of Most Bothersome Symptom at 2 Hours

Meet the COX-2 Inhibitor

Celecoxib Oral Solution

- FDA approved in May 2020
- Reaches peak plasma concentration in 60 minutes with greater bioavailability at a lower dose compared with celecoxib capsules
- Blocks prostaglandin synthesis, which reduces pain and inflammation

Celecoxib Oral Solution

- Contraindicated in patients with coronary artery bypass graft (CABG) surgery
- Can cause an increased risk of serious GI S/E including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.
- Boxed warning about risk of serious cardiovascular thrombotic events

Celecoxib Oral Solution

Migraine Prevention

Goals of migraine prevention

- Reduce attack frequency, severity, duration, and disability.
- Improve responsiveness to and avoid escalation in use of acute treatment.
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments

Goals of migraine prevention

- Reduce overall cost associated with migraine treatment.
- Enable patients to manage their own disease to enhance a sense of personal control.
- Improve health-related quality of life (HRQoL).
- Reduce headache-related distress and psychological symptoms.

Indications For Preventive Treatment

- Attacks significantly interfere with patients' daily routines despite acute treatment.
- Frequent attacks
- Contraindication to, failure, or overuse of acute treatments
- AEs with acute treatments
- Patient preference

Medications with evidence of efficacy in migraine prevention

Established efficacy

- *Oral*
  - Candesartan
  - Divalproex/valproate sodium
  - Topiramate
  - Frovatriptan
  - Metoprolol
  - Propranolol
  - Timolol
- .
- *Parenteral*
  - Erenumab
  - Fremanezumab
  - Galcanezumab
  - Eptinezumab
  - Onabotulinum toxin A

Medications with evidence of efficacy in migraine prevention

Probably effective

- *Oral*
  - Amitriptyline
  - Nadolol
  - Atenolol
  - Lisinopril
  - Memantine
  - Venlafaxine
- .
- *Parenteral*
  - Onabotulinum A + CGRP Mab

Meet the Monoclonal Antibodies

Monoclonal Antibodies

- Very large molecules, > 500 x larger than smaller molecules
- Eliminated by the reticuloendothelial system, thus, no renal or hepatic toxicity
- Does not cross the BBB
- Low side effect profile
- Studied in both episodic and chronic migraines

Erenumab

- FDA approved in May 2018 for adults 18 years and above with migraine
- Targets the CGRP receptor
- Fully humanized
- 70 mg or 140 mg SQ monthly

Erenumab– Change in Mean Monthly Migraine Days

EPISODIC MIGRAINE

Erenumab–Change in Mean Monthly Migraine Days

CHRONIC MIGRAINE

Erenumab vs Topiramate

- FDA approved for migraine in September 2018 and for cluster headaches in June 2019
- Targets the CGRP ligand
- 90% humanized

Galcanezumab

Galcanezumab–Reduction in Mean Monthly Migraine Days Over 6 Months

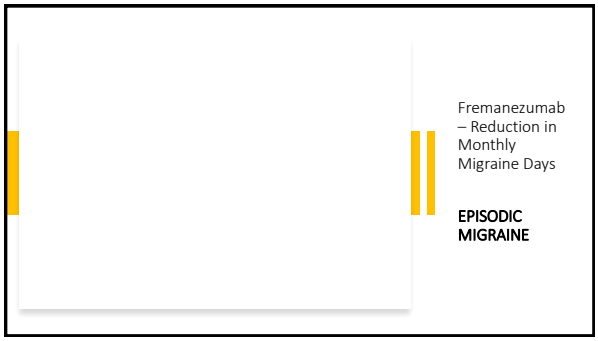
EPISODIC MIGRAINE

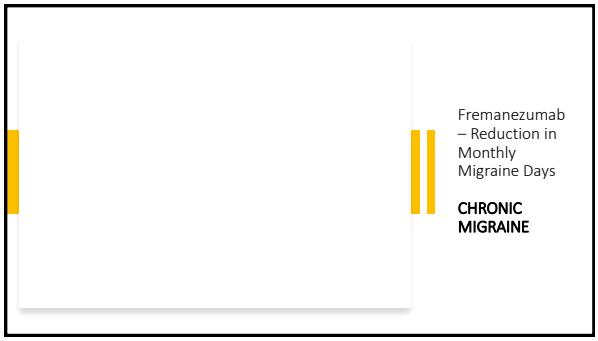
Galcanezumab–Reduction in Mean Monthly Headache Days

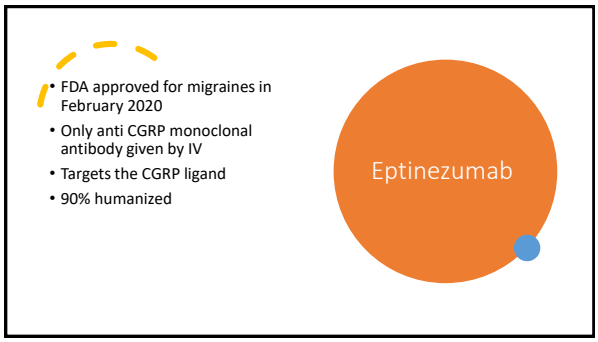
CHRONIC MIGRAINE

Fremanezumab

- FDA approved for migraine in September 2018
- Targets the CGRP ligand
- 95% humanized
- Can be dosed monthly or quarterly


Fremanezumab – Reduction in Monthly Migraine Days
EPISODIC MIGRAINE


Fremanezumab – Reduction in Monthly Migraine Days
CHRONIC MIGRAINE


• FDA approved for migraines in February 2020
• Only anti CGRP monoclonal antibody given by IV
• Targets the CGRP ligand
• 90% humanized
Eptinezumab

Eptinezumab—Reduction in Monthly Migraine Days Months 1-3

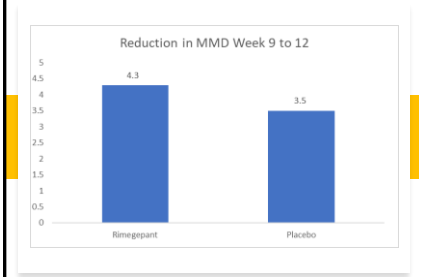
EPISODIC MIGRAINE

Eptinezumab—Reduction in Monthly Migraine Days Months 1-3

CHRONIC MIGRAINE

Rimegepant

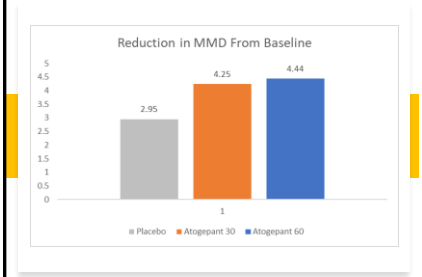
- FDA approved for migraine prevention in May 2021
- Binds to the CGRP receptors
- Dosed every other day



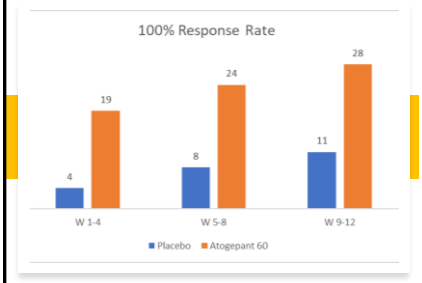
Rimegepant– Reduction in Monthly Migraine Days at Weeks 9 to 12

Atogepant

- FDA approved in September 2021
- Indicated for episodic migraine in adults
- Most common S/E -- nausea, constipation, fatigue
- Avoid use in patients with severe hepatic impairment



Atogepant– Reduction in Monthly Migraine Days Weeks 9-12



Atogepant– 100% Response Rate

Criteria for initiating treatment with monoclonal antibodies (episodic migraines)

- Prescribed by a licensed clinician
- Patient is at least 18 years of age
- Diagnosis of ICHD-3 migraine with or without aura and both of the following:
  - > Inability to tolerate or inadequate response to an 8-week trial to two or more of the following: topiramate, divalproex/valproate sodium, beta blockers, tricyclic antidepressants, SNRI
  - > At least moderate disability (MIDAS ≥ 11 or HIT-6 > 50)

Criteria for initiating treatment with monoclonal antibodies (Chronic migraines)

- Prescribed by a licensed clinician
- Patient is at least 18 years of age
- Diagnosis of ICHD-3 migraine with or without aura and both of the following:
- > Inability to tolerate or inadequate response to an 8-week trial to two or more of the following: topiramate, divalproex/valproate sodium, beta blockers, tricyclic antidepressants, SNRI
  - > Inability to tolerate or inadequate response to a minimum of 2 quarterly injections (6 months) of onabotulinum toxin A

Criteria for continuation of monoclonal antibodies

- Reduction in mean MHDs or headache days of at least moderate severity of ≥50% relative to the pretreatment baseline (diary documentation or medical professional attestation)
- A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:
  - MIDAS - Reduction of ≥5 points when baseline score is 11–20
    Reduction of ≥30% when baseline score is >20
  - MPFID Reduction of ≥5 points
  - H I T-6 Reduction of ≥5 points

HIT, Headache Impact Test; MHD, monthly headache day; MIDAS, Migraine Disability Assessment; MPFID, Migraine Physical Function Impact Diary

Neuromodulation in migraines

NEUROMODULATORY DEVICES

- Theoretically, there are targets in the central and peripheral nervous systems that can be manipulated using electrical or magnetic pulses on nerves that are directly or indirectly involved in pain processing
- Can be used with prescribed drug treatment
- Can reduce reliance on medications

NEUROMODULATORY DEVICES

Different devices target different nerves!

NEUROMODULATORY DEVICES

- Vagus nerve stimulation (VNS) targets the vagus nerve, which extends from the brainstem to the abdomen
- Occipital nerve stimulation (ONS) targets the occipital nerves
- Remote electrical neuromodulation (REN) stimulates peripheral nerves in the arm, with the goal of blocking pain signals from reaching the brain.
- Single-pulse transcranial magnetic stimulation (sTMS) is not aimed at any particular nerve but rather at the brain more generally
- Supraorbital stimulation targets the trigeminal nerve that innervates the forehead, upper eyelid, and scalp.

Vagus Nerve Stimulator (VNS)

- Handheld device
- FDA cleared in 2015 preventative and abortive treatment for migraine and cluster headache in adults
- In 2021, also FDA cleared for preventative and abortive treatment of migraine in adolescents between ages 12 to 17

Vagus Nerve Stimulator (VNS)

• Stimulates the vagus nerve blocks pain signals causing migraine pain

Vagus Nerve Stimulator for migraine prevention

• First daily treatment should be applied within 1 hour of waking and the second treatment should be applied at night.

Vagus Nerve Stimulator for migraine prevention

• **A Randomized, Multicenter, Double-blind, Parallel, Sham-controlled Study of Non-invasive Vagus Nerve Stimulation for the Prevention of Migraines. (Premium II)**

>> Showed a mean reduction in monthly migraine days for the active group compared to the sham group

>> Responder rate was greater in the active group than the sham group (26.81%; p = 0.0481)

>> Subgroup analysis suggested that participants with aura responded preferentially

Vagus Nerve Stimulator for acute migraine treatment

- Use at the earliest sign of pain
- Can repeat if pain persists
- Some patients have relief within 30 minutes
- Almost half of patients had little to no migraine pain within 2 hours after first use
- Majority of patients who were pain-free at 2 hours remained pain-free for 48 hours

Vagus Nerve Stimulator for acute migraine treatment

- **The PRospectivE Study of nVNS for the Acute Treatment Of Migraine PRESTO**

>> Almost half of patients had little or no migraine pain within 2 hours of first use

>> Majority of patients who were pain were at 2 hours remained pain free at 48 hours

Vagus Nerve Stimulator

- Contraindications

>> Presence of an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device

>> Presence of a metallic device, such as a stent, bone plate, or bone screw, implanted at or near the neck

>> Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device (e.g., mobile phone)

Implantable Occipital Nerve Stimulator

- Involves the surgical implantation of a device that sends electrical impulses to the occipital nerve
- Can be reversible
- Considered investigational for headaches but is used off label

Implantable Occipital Nerve Stimulator

Implantable Occipital Nerve Stimulation

- ONSTIM trial

>> at 3 months 39% of patients reported at least 50% reduction in headache days per month or a 3-point reduction in pain intensity with adjustable stimulation, compared with 0% in the medically managed group

Silberstein et al, 2012

>> Trial did not meet primary endpoint of responder rate but showed a significant reduction in the number of headache days and migraine related disability in the active vs the control group

Implantable Occipital Nerve Stimulator

Mekhail et al, 2016

>> 60% and 35% of patients reported a 30% and 50% reduction in headache days and/or pain intensity, respectively.

Miller, et al, 2016

>> 45.3 % of patients showed a more than 30 % reduction of monthly moderate-to-severe headache days

>> Significant improvements were also seen in pain intensity, daily pain duration and headache related disability

Implantable Occipital Nerve Stimulation

- Complications
  - >> Lead migration or fracture
  - >> Surgical site infection
  - >> Hardware malfunction
  - >> Battery failures
  - >> Seromas
  - >> Hematomas
  - >> Pain and numbness at lead sites

Implantable Occipital Nerve Stimulator

- Contrainidications
  - >> No improvement in the quality of life after a trial period
  - >> Local infection
  - >> Bleeding abnormalities
  - >> Arnold-Chiari malformation
  - >> Presence of an implanted electrical device (e.g., pacemaker, spinal cord stimulator) that may interfere with therapy
  - >> Pregnancy

Remote Electrical Neuromodulation (REN)

- Sub-threshold conditioning stimulation of the median and musculocutaneous nerves inhibits pain in remote body regions by activating pain control centers in the brainstem
- To be used at the first sign of a migraine

Remote Electrical Neuromodulation

- Wireless remote electrical neuromodulation device for the acute treatment of migraine with or without aura in patients 12 years of age or older
- Self-applied to the upper-arm
- Controlled by a user-friendly app
- FDA cleared for adults and adolescents 12 years old and above

Remote Electrical Neuromodulation

Remote Electrical Neuromodulation

- Grosberg et al, 2021- 60% experienced relief of pain at 2 hours, and approximately 65% had sustained pain relief at 24hours.
- Hershey et al, 2020- 71% and 35% of adolescent participants had pain relief and pain-free at 2 hours, respectively. At 2 hours, 69% experienced improvement in functional ability.

Remote Electrical Neuromodulation

- Contraindications

>> Patients with congestive heart failure, severe cardiac or cerebrovascular disease, uncontrolled epilepsy, or in those with an active implantable medical device (ie, pacemaker, hearing aid implant).

Single-Pulse Transcranial Magnetic Stimulation (sTMS)

- FDA cleared for both prevention and acute treatment in adolescents (12 y/o and above) and adults
- Battery powered and handheld
- Blocks cortical spreading depression by suppressing cortical neuronal firing and by increasing the threshold of activation of the occipital cortex

Single Pulse Transcranial Magnetic Stimulation (sTMS)

Single-Pulse Transcranial Magnetic Stimulation (sTMS)

- For acute treatment -- treat with up to 4 sequential pulses at the earliest indication of an attack; if no relief, can treat again as needed
- For prevention- treat with up to 4 pulses twice daily
- As with most migraine therapy, efficacy builds over time. Patients should adhere to a treatment protocol for at least 3 months before adjusting therapy.

Single-Pulse Transcranial Magnetic Stimulation (sTMS)

Adverse effects -- resolve immediately after treatment

>>> lightheadedness

>>> tingling

>>> tinnitus

Contraindications

>>> presence of conductive metal implants in the head and neck

Single-Pulse Transcranial Magnetic Stimulation (sTMS)

- Starling et al, 2019 (ESPOUSE study) - showed reduction of headache days, acute medication days and Headache Impact Test (HIT-6) score

External concurrent occipital and trigeminal neurostimulation (eCOM)

- FDA cleared in March 2021
- Worn as a headset delivering stimulation to 6 branches of the occipital and trigeminal nerves
- For the acute treatment of migraine with or without aura in patients 18 years of age or older.

External concurrent occipital and trigeminal neurostimulation (eCOM)

External concurrent occipital and trigeminal neurostimulation (eCOM)

- Tepper, et al 2021-- 78% of patients with pain freedom at 2 hours had sustained pain freedom at 24 hours
- Daniel, et al 2019- 76% of patients achieved headache relief at 2 hours

External concurrent occipital and trigeminal neurostimulation (eCOM)

- Contraindications:
  - > Presence of metal implant or shrapnel in the head, except for dental implants
  - > Recent brain or facial trauma (less than 3 months)

- Contraindications
  - > Presence of skin abrasions at the contact area of the device
  - > Presence of implanted neurostimulators or any implanted metallic or electronic device in the head, cardiac pacemaker or implanted or wearable defibrillator

External concurrent occipital and trigeminal neurostimulation (eCOM)

- Adverse effects
  - > Unpleasant sensations, scalp numbness
  - > Persistent tingling sensation
  - > Pain

External concurrent occipital and trigeminal neurostimulation (eCOM)

- Adverse effects
  - > Skin reaction or redness beneath or around the electrodes
  - > Sleepiness, dizziness, fatigue, or disruption in sleep patterns
  - > Tension-type headache after treatment

External concurrent occipital and trigeminal neurostimulation (eCOM)

Future of migraine

- Acute treatments
  - > Zavegepant
  - > AXS-07 (Meloxicam/Rizatriptan) –open label
  - > Dihydroergotamine nasal powder- open label, Phase 3

Future of Migraine

- Preventive
  - > Oral Zavegepant – Phase 2/3
  - > Cabergoline (Denmark)
  - > LY3451838– monoclonal antibody vs the PACAP 38 receptor , Phase 2
  - > Lu AG09222- monoclonal antibody vs PACAP, Phase 2
  - > ABP-450 (prabotulinumtoxinA)- Phase 2

THANK YOU!

Atypical Facial Pain and TMJ

Marcela Romero-Reyes, DDS, PhD

UNIVERSITY of MARYLAND
SCHOOL OF DENTISTRY

Atypical Facial Pain and TMJ

Marcela Romero Reyes DDS, PhD,FAHS

Diplomate, American Board of Orofacial Pain
Fellow, American Academy of Orofacial Pain
Fellow, American Headache Society

Clinical Professor
Director, Brotman Facial Pain Clinic
Department of Neural and Pain Sciences
University of Maryland, Baltimore
School of Dentistry

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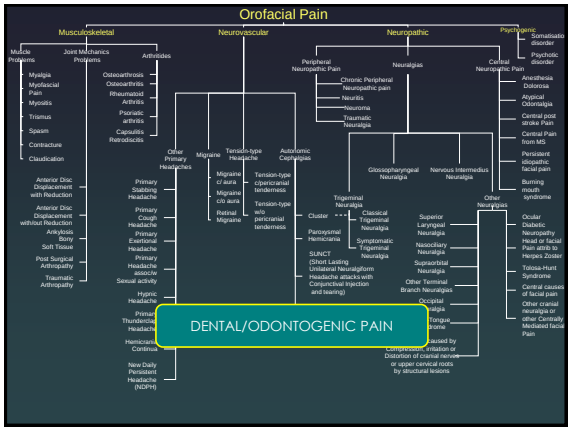
- Immediate past Chair, Special Section -TMD, Cervical Spine and Orofacial Pain- American Headache Society

WHAT IS OROFACIAL PAIN?

- **HEAD**
- **FACE**
- **NECK**
- **INTRAORAL STRUCTURES**

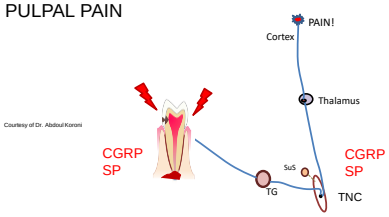


Visceral/Vascular/Neurovascular

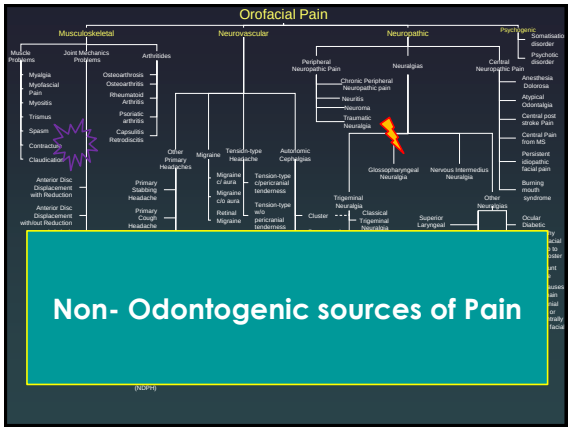
Visceral pains: Odontogenic Pains

- Dull, aching, throbbing sensation
- From mild tenderness/soreness to violent, intolerable intensity

PULPAL PAIN



Courtesy of Dr. Abdoul Koroni



TEMPOROMANDIBULAR DISORDERS

TMD or TMJ?

Important…A note about the lingo…

- "Doctor, I have TMJ"; " My patient has TMJ"
  - Temporomandibular Joint = TMJ
  - Anatomic part of the jaw joint!

- Temporomandibular disorders =TMD
- A heterogeneous group of disorders that affect the TMJ, muscles of mastication and associated structures.

Marcela Romero DDS, PhD, FAHS

Musculoskeletal Pains **Temporomandibular disorders (TMD)**

- Constellation of clinical problems involving the masticatory musculature and/or TMJ and associated structures. *(Romero-Reyes and Uyanik, 2014, J Pain Res; Okeson, 2014, Bell's Oral and Facial Pain)*
- Symptoms: Pain with mastication, headache, earache, jaw ache or pre auricular pain or joint pain, joint sounds and limitation of opening.
- Most common reason for patients to seek treatment after dental pain *(Dworkin, 2011; JEBDP; Dworkin et al, 1990, JADA)*
- More prevalent in women *(Johansson A et-al, 2003; Zakrzewska JM, 2013)*
- 5-12% prevalence of TMD (NIDCR) with incidence 3.9% per annum (Slade GD et-al, 2013 OPERRA study)
- Exerts a considerable burden on the population. *(Dworkin SF, LeResche L, 1993)*
- Headache, lower back pain, fibromyalgia and functional disorders such as IBS are strongly associated with TMD *(Ohrbach R et-al, 2011; Bair E et-al 2013, OPPERA)*

Marcela Romero DDS, PhD, FAHS

IMPORTANT!

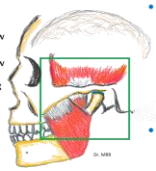
Not only in TMD the source of pain is the TMJ!

OROFACIAL PAIN DISORDERS

NEUROPATHIC | MUSCULOSKELETAL | NEUROVASCULAR

TEMPOROMANDIBULAR DISORDERS

- **TMJ Disorders**
  - Arthralgia
  - Disc displacement w reduction
  - Disc displacement w reduction w intermittent locking
  - Disc displacement w/o reduction w limited opening
  - Disc displacement w/o reduction w/o limited opening
  - Degenerative Joint Disease (DJD)
  - Systemic Arthritides
  - Subluxation



- **Masticatory muscle disorders**
  - Myalgia
    - Local myalgia
  - Myofascial pain
    - Myofascial pain with referral
- **Headache Disorders**
  - Headache attributed to TMD

Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group† J. Oral Facial Pain Headache (2014)

Marcela Romero DDS, PhD

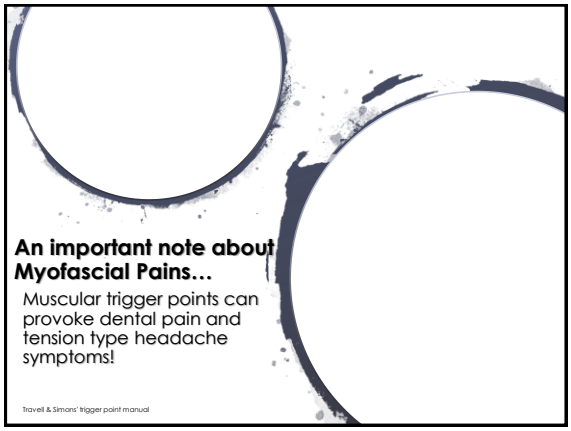
MUSCLE DISORDERS

MYALGIA

- Dull aching pain
- Continuous pain associated with muscle function
- Confirmed by palpation and looking for replication of the pain complaint.
- The palpation induced pain **DOES NOT** radiate!

MYOFASCIAL PAIN

- Regional, dull, aching pain and presence of localized trigger points in muscle, tendons or fascia that reproduce pain when palpated and produce a pattern of regional pain spreading beyond the location of the palpating fingertips within the muscle palpated or referred pain beyond the boundary of the muscle palpated *(Travell & Simons, 1998; Romero-Reyes & Uyanik, 2014; Orofacial Pain Guidelines, AAOP 2018)*



Orofacial Pain Prospective Evaluation and Risk Assessment Study – The OPPERA Study

OPPERA Chronic TMD Model

Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Knott C, Ohrbach R, Weir B, Slade GD. Orofacial Pain Prospective Evaluation and Risk Assessment Study – The OPPERA Study. The Journal of Pain 2011;12(11, Supplement):T4-T11.e12

What have we learned from OPPERA about chronic TMD?

Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Knott C, Ohrbach R, Weir B, Slade GD. Orofacial Pain Prospective Evaluation and Risk Assessment Study – The OPPERA Study. The Journal of Pain 2011;12(11, Supplement):T4-T11.e12

- **Psychological variables** Psychological stress, affective disorders, maladaptive pain coping, somatic awareness may contribute and increase the risk of TMD and exacerbate symptomatology *(Fillingim RB, et-al, 2011; 2013)*
- **TRAUMA:** Jaw injury (extrinsic or intrinsic injuries) is strongly associated with the development of TMD *(Sharma, S et-al 2019).*
- **MICROTRAUMA:** Parafunction (clenching) may be a cause and consequence of the pain experienced in TMD *(Ohrbach R et-al, 2011)*
- **Pain amplification/perception:** Patients with TMD are more sensitive to many experimental noxious stimuli and present an increase extracephalic pain sensitivity *(Greenspan JD, et-al 2011)*
- **Genetics:** Impaired catabolism of cathecholamines due to low activity of COMT haplotypes *(Slade GD et-al, 2015)* and association HTR2A (serotonin receptor gene) *(Smith SB et-al, 2011)*

TMD

- **The natural history of TMD…**
- TMD has been reported to have a tendency to remit or improve symptoms over 5 and 7.6 year follow up in an observational study accompanied with improvements in pain symptomatology as well as psychological domains *(Ohrbach R, Dworkin SF, 1998; Fillingim et-al, 2018 OPPERA study)*
- **TMD management should be conservative, reversible and based in evidence based therapeutic modalities!** *(Greene, CS, 2010)*

TMD Guidelines of Care

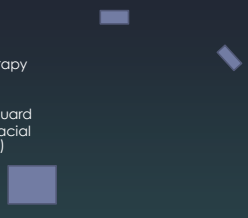
- **What we have learned**
- TMD should be managed within a biopsychosocial framework, in which behavioral approaches supplement conservative medical care *(Green CS, JADA 2010)*
- A minority of TMD patients will demonstrate resistant to therapy and become patients with chronic pain problems…Research focus!
- **Management**
- Evidence based
- Differential diagnosis: Patient history, clinical examination, imaging when indicated.
- **Conservative and reversable management** unless there are specific and justifiable indications to the contrary.

From Statement of temporomandibular disorders approved by AADR, JADA 2010

TMD Management

Decision is based case by case!

- Home care program (soft diet, PT modalities)
- Pharmacotherapy
  - NSAIDs
  - Muscle relaxants
  - Trigger point injection therapy
  - TMJ injection
- Non-pharmacological
  - Stabilization splint /night guard
  - Physical therapy (craniofacial and cervical therapeutics)
  - Behavioral therapy
  - Arthrocentesis (e.g. DD w/o reduction)



Trigger point injection

TMJ Injection

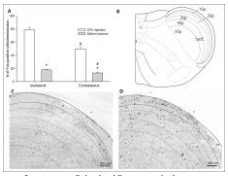
Stabilization splint

TMD and Headache Comorbidity

- TMD is a risk factor for increased prevalence of primary headaches, particularly migraine and chronic daily headache *(Goncalves et al, 2010, 2011)*
- **Migraine** has been shown to be the most prevalent primary headache observed in TMD patients *(Goncalves, et-al 2010; Goncalves, et-al 2011)*
- Patients that present migraine and TMD such as **myofascial pain** present a higher disability impact *(Mittiratanakul and Merrill, 2006; Goncalves et-al, 2010)*
- In some cases the presence of **TMD** more than doubles the likely prevalence of headache, it may exacerbate an existing headache disorder, and it also potentially accelerates the progression to **chronic migraine headache** *(Bevilaqua GD et-al, 2009)*
- The presence of **migraine** has shown to be a significant predictor of first onset **TMD** (Tchivileva IE et-al, Pain. 2017)
- Clinical experience suggests that **migraine** management may be more difficult in patients with **TMD** in comparison to those without the comorbidity (Magnusson,T et-al, 1978; Bevilaqua GD et-al, 2010)

At the bench side…

Orofacial Pain Model



Spontaneous Behavioral Responses in the Orofacial Region: A Model of Trigeminal Pain in Mouse. Romero-Reyes M et al. Headache: The Journal of Head and Face Pain. 2013; 53: 137-178

Headache Model

Sumatriptan alleviates nitroglycerin-induced mechanical and thermal allodynia in mice Bates E et al. Cephalalgia 2010;30:170-178

Trigeminal Nucleus Caudalis (TNC) Activation

Experimental Neurology

Regular Article

A potent and selective calcitonin gene-related peptide (CGRP) receptor antagonist, MK-8825, inhibits responses to nociceptive trigeminal activation: Role of CGRP in orofacial pain

Marcela Romero-Reyes, Vanessa Pardi, Simon Akerman

Calcitonin gene-related peptide (CGRP) y DTM

- Spontaneous nociceptive facial grooming behaviours and neuronal activation in the Sp5 mediated by masseteric-CFA are attenuated by a rodent specific CGRP receptor antagonist (Romero-Reyes et al, 2015 Exp Neurol)

CGRP HAS A ROLE IN TMD PATHOPHYSIOLOGY

Received: 27 May 2020 | Revised: 18 August 2020 | Accepted: 8 September 2020
DOI: 10.1111/bph.15263

RESEARCH PAPER

Preclinical studies investigating the neural mechanisms involved in the co-morbidity of migraine and temporomandibular disorders: the role of CGRP

Simon Akerman | Marcela Romero-Reyes

Department of Neural and Pain Sciences, University of Maryland Baltimore, Baltimore, MD, 21201, USA

Correspondence
Dr. Simon Akerman and Dr. Marcela Romero-Reyes, Department of Neural and Pain

Abstract

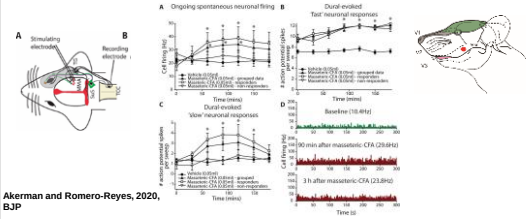
Background and Purpose: Temporomandibular disorders (TMD) and migraine can be co-morbid. This can be a significant factor in exacerbating and increasing the prevalence of migraine-like symptoms. However, the underlying mechanisms involved are

CGRP AS THE MODULATOR OF THE COMORBIDITY BETWEEN TMD AND MIGRAINE

Where orofacial Pain Meets Headache

Masseteric-CFA on dural-central trigeminovascular neurons

Complete Freund's adjuvant (CFA) injection in the masseter muscle (V3 trigeminal division) causes delayed activation and sensitization of trigeminovascular neurons (V1 trigeminal division TCC neurons) and potentiates dural-evoked TCC neuronal firing



Akerman and Romero-Reyes, 2020, BJP

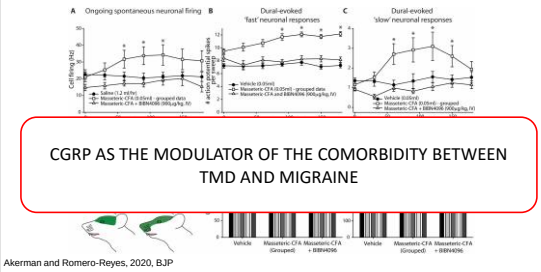
Where orofacial Pain Meets Headache

Masseteric-CFA injection (V3) induces expansion of cutaneous receptive field and delayed hypersensitive neuronal responses to innocuous and noxious extracranial cutaneous facial stimulation in the V1 regions – indicative of facial cutaneous allodynia and hyperalgesia.

Akerman and Romero-Reyes, 2020, BJP

Where orofacial Pain Meets Headache

CGRP receptor antagonist (BIBN4096-olcegepant) prevents these changes.



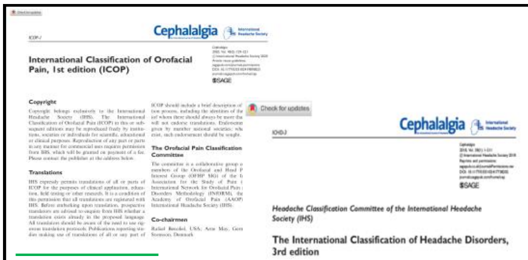
CGRP AS THE MODULATOR OF THE COMORBIDITY BETWEEN TMD AND MIGRAINE

Akerman and Romero-Reyes, 2020, BJP

Atypical Facial Pain

Persistent idiopathic facial pain

Marcela Romero Reyes DDS. PhD. FAAOP. FAHS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International Classification of Orofacial Pain, 1st edition (ICOP)

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Translations

The Orofacial Pain Classification Committee

Co-chairmen

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Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

Persistent idiopathic facial pain (ICHD-3 13.12; ICOP 6.2)

- Previously known as **atypical facial pain**.
- It is a term (now a diagnostic category/criteria in the ICHD-3 and ICOP-1) applied when any other source of pain has been ruled out and no absolute mechanism can be determined to be assigned into another diagnostic category.

Marcela Romero Reyes DDS, PhD, FAAOP, FAHS

Persistent Idiopathic Facial Pain (PIFP)

- Orofacial Pain that occurs in the absence of any neurological deficit or any other obvious etiology *(Clarkson E, Jung E. Dent. Clin. N. Am., 2020; Benoniel R, Gaul, C. Cephalalgia, 2017).*
- Often misdiagnosed with trigeminal neuralgia (*Weiss AL, Ehrhardt KP, Tolba R. Curr Pain Headache Rep. 2017)*
- IMPORTANT! The ICHD-3 and ICOP subdivides trigeminal neuralgia into classical, secondary and idiopathic.
  - Idiopathic trigeminal neuralgia purely paroxysmal or with concomitant continuous pain.
    - Idiopathic trigeminal neuralgia with concomitant continuous pain.
    - Diagnostic criteria:
  - Recurrent paroxysms of unilateral facial pain fulfilling criteria for Idiopathic trigeminal neuralgia
  - Concomitant continuous or near-continuous pain between attacks in the affected trigeminal distribution.

Persistent Idiopathic Facial Pain (PIFP)

- The incidence is estimated at 4.4 per 100,000 person-years, and lifetime prevalence is estimated at 0.03% with a predilection for presenting in older women.*(Forssell H, Jaaskelainen S, et-al. J Oral Rehabil; Koopman JS, Dieleman JP, et-al. Pain. 2009)*
- It can be described as a dull, aching, nagging in quality, deep or superficial diffuse orofacial pain, may not follow neuroanatomical distributions and may present slight subjective sensory disturbances *(Clarkson E, Jung E. Dent. Clin. N. Am., 2020; Forsell H, Tenovuo O, et-al. Neurology, 2007; ICOP-1. Cephalalgia 2020).*
- Its presentation has a wide variation but has been reported considerable overlap of neurophysiologic and sensory abnormalities in AFP and Trigeminal neuropathic pain (TNP) *(Forsell H, Tenovuo O, et-al. Neurology, 2007).*
- Few randomized controlled trials for the managament of PIFP. Management includes pharmacological modalities such as TCAs, SSNRIs, anticonvulsants (gabapentin, pregabalin) and nonpharmacological such as CBT *(List T et-al, JOFP 2003; Forssell H, Tasmuth T et-al JOFP, 2004)*

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International Headache Society

ICOP-I

International Classification of Orofacial Pain, 1st edition (ICOP)

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6. Idiopathic orofacial pain

6.1 Burning mouth syndrome (BMS)
- 6.1.1 Burning mouth syndrome without somatosensory changes
- 6.1.2 Burning mouth syndrome with somatosensory changes
- 6.1.3 Probable burning mouth syndrome

6.2 Persistent idiopathic facial pain (PIFP)
- 6.2.1 Persistent idiopathic facial pain without somatosensory changes
- 6.2.2 Persistent idiopathic facial pain with somatosensory changes
- 6.2.3 Probable persistent idiopathic facial pain

6.3 Persistent idiopathic dentoalveolar pain
- 6.3.1 Persistent idiopathic dentoalveolar pain without somatosensory changes
- 6.3.2 Persistent idiopathic dentoalveolar pain with somatosensory changes
- 6.3.3 Probable persistent idiopathic dentoalveolar pain

6.4 Constant unilateral facial pain with additional attacks (CUFPA)

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Translations

The Orofacial Pain Classification Committee

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ICHD-3

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

Persistent idiopathic facial pain (ICHD-3 13.12; ICOP 6.2)

The ICOP and the ICHD-3 suggest that PIFP can only be diagnosed when:
- Pain is present for more than 3 months
- Occurring daily with episodes of pain lasting for greater than 2 hours
- Poorly localized, not following the distribution of a peripheral nerve
- Clinical/radiological examinations are normal. Excluded local causes.

The ICOP includes the classification with and without somatosensory changes on use of qualitative or quantitative sensory testing.

Courtesy of Dr. Tony Schwartz

Persistent Dentoalveolar Pain (PDAP)

- PDAP is a chronic pain condition that presents as a persistent tooth or teeth pain or pain over a dentoalveolar site formerly occupied by a tooth in the absence of any detectable pathology during a radiological and clinical exam.
- Unfortunately, patients may undergo several dental procedures in hopes to relieve their pain.
- PDAP is often comorbid with TMD symptomatology and chronic tension type headache (TTH) *(Baad-Hansen et-al,JOFP 2008).*
- PDAP sufferers present increase TMD disability, sleep disturbances, depression and other psychiatric conditions and poor quality of life *(Durham & Nixdorf, Int. Endod. J.I2014; Nixdorf D et-al,J Dent 2015; Ciaramella et-al, ISRN Neurosci, 2018)*
- PDAP may be considered a is chronic overlapping pain conditions (COPC). PDA is comorbid with COPC and presents several common characteristics attributed to COPCs.*(Babiloni AE, et-al Oral Dis 2020)*

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ICOP-1

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International Classification of Orofacial Pain, 1st edition (ICOP)

Persistent Idiopathic dentoalveolar pain ICOP 6.3

Previously known as Atypical odontalgia; phantom tooth pain, primary dentoalveolar pain disorder (PDAP)

- Persistent unilateral intraoral dentoalveolar pain, rarely occurring in multiple sites, with variable features, recurring daily for more than 2 hrs/day for more than 3 months, in the absence of any preceding causative event (surgery, dental procedure; >6 months since last dental procedure, if not Dx under 4.1.2.3 PTTNP/Post-traumatic Trigeminal Neuropathy)
- May be present with and without somatosensory changes as determined by qualitative and quantitative sensory testing

A. Intraoral dentoalveolar pain fulfilling criteria B and C
B. Recurring daily for >2 hours/day for >3 months[1]
C. Pain has both of the following characteristics:
   1. localized to a dentoalveolar site (tooth or alveolar bone)[2]
   2. deep, dull, pressure-like quality[3]
D. Clinical and radiographic examinations are normal,[4] and local causes have been excluded
E. Not better accounted for by another ICOP or ICHD-3 diagnosis.[5]

Idiopathic Facial and Dentoalveolar Pains

- Their diagnosis is of exclusion and should be made after other local, systemic or other sources of OFP have been ruled out
- It is not uncommon to receive referrals of "atypical Facial pain" in the Orofacial pain clinical setting.
-

The need of a thorough evaluation and history to rule out the possibility of other orofacial pain disorders is crucial!

The clinician needs to consider be aware of other OFP that may not had been considered into the differential diagnosis.

Suspicious dental and facial pains in where no other source has been detected…

- During interview, medical history and evaluation, it needs to be considered…
- Musculoskeletal sources:
- Myofascial pain (MFP) sources:
  - Masticatory and cervical spine muscles can refer to teeth and craniofacial structures!
- Headache or facial pain attributed to inflammation or calcification of the stylohyoid ligament/process.

An important note about Myofascial Pains…

Muscular trigger points can provoke dental pain!

Some MFP trigger points associated with facial pain and headache

- Temporalis
- Masseter
- Trapezius (upper)
- Suboccipital muscles (Splenius capitis, cervicis)
- Occipito frontalis

Travell & Simmon

Eagle Syndrome

- Musculoskeletal disorder.
- Elongated styloid process or calcified stylohyoid ligament.
- The styloid process lies in the area of the palatine process just behind the pharyngeal wall and it is close to the internal and external carotid arteries and CN. IX
- Pain can be a dull ache experienced during swallowing, chewing, ear pain a persistent sore throat or feeling of something caught in the throat…

IMAGING

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Cephalalgia

ICHD-3

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

11.8 Headache or facial pain attributed to inflammation of the stylohyoid ligament

Previously used term:
Eagle's syndrome.

Description:
Unilateral headache, with neck, pharyngeal and/or facial pain, caused by inflammation of the stylohyoid ligament and usually provoked or exacerbated by head turning.

Diagnostic criteria:
1.Any head, neck, pharyngeal and/or facial pain fulfilling criterion C[1]
2.Radiological evidence of calcified or elongated stylohyoid ligament
3.Evidence of causation demonstrated by at least two of the following:
   1.pain is provoked or exacerbated by digital palpation of the stylohyoid ligament
   2.pain is provoked or exacerbated by head turning
   3.pain is significantly improved by injection of local anaesthetic agent into the stylohyoid ligament, or by styloidectomy
   4.pain is ipsilateral to the inflamed stylohyoid ligament

Suspicious dental and facial pains in where no other source has been detected…

- During interview, medical history and evaluation, it needs to be considered…

Orofacial Pain resembling Primary Headache Disorders

Orofacial Pain resembling Primary Headache Disorders

The neurovascular link between headache and OFP

The International Classification of Orofacial Pain (ICOP) tells us…

- **Type 1:** Headache patients who report additional facial pain during, and usually ipsilateral to their headache.
- **Type 2:** Headache patients whose headache attacks have stopped and been replaced by facial pain attacks of the same characteristics of the former headache.
- **Type 3:** Headache naïve patients who develop new OFP attacks that resemble one of the primary headache types in pain character, duration and intensity, with or without the associated symptoms of these headache types.

Can I have a "headache" on my face or teeth?!

- V1 innervates extracranial structures : Pain in the periorbital region *(Akerman 2011).*
- **What about V2?**
- V2 gives the nervus meningeus medius, which supplies innervation to the dura of the anterior floor of the middle fossa *(Larrier and Lee, 2003).*
- Migraine localized in the area of V2 has been reported *(Silberstein, 2001; Oberman et-al,.2007: Campbell, 1990; Dauda and Jones, 2002; Bradley 2000)*
- **What about V3?**
- Stimulation of the dura (humans and animals) induces pain in any of the 3 divisions of the trigeminal nerve *(Daudia and Jones 2002)*
- Some patients only present pain in the V3 territory *(Silberstein, 2001)*

ICOP-I

Cephalalgia International Headache Society

International Classification of Orofacial Pain, 1st edition (ICOP)

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Establishing a differential diagnosis for OFPs resembling presentations of primary headaches is **ESSENTIAL!**

An incorrect diagnosis may lead to a misdiagnosis of idiopathic facial or dentoalveolar pains (atypical facial or dental pain) or may lead to irreversible dental procedures and a delay in appropriate management!

To whom I should refer for consultation/management?

OROFACIAL PAIN SPECIALIST


Cephalalgia

International Classification of Orofacial Pain, 1st edition (ICOP)

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Author manuscript

Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group


Cephalalgia

Headache Classification Committee of the International Headache Society (IHS)

The International Classification of Headache Disorders, 3rd edition

Orofacial Pain, a dental specialty

- Multiple efforts had been made for over the past 40 years to make Orofacial Pain a Dental Specialty.
- **On March 31st 2020, the ADA recognized Orofacial Pain (OFP) as a new dental specialty.**
- 12 OFP CODA approved programs in the US.
- The **American Board of Orofacial Pain** is recognized by the National Commission on Recognition of Dental Specialties and Certifying Boards as the national certifying Board for the Orofacial Pain (OFP) specialty.

AMERICAN ACADEMY OF OROFACIAL PAIN

AMERICAN BOARD OF OROFACIAL PAIN ABOP

Important considerations and final remarks

- Most of the time, patients present symptomatology in both, the TMJ and muscles of mastication.
- In TMD…It is not only the masseter, the temporalis and the TMJ! Temporomandibular mechanics are complex, and they also involve other muscles including the lateral pterygoids and the medial pterygoids which can also produce symptomatology.
- The cervical musculature and their associated structures can refer to facial structures and therefore, they need to be considered in the plan of management if during examination they elicited pain and referral (cranio-cervico-mandibular complex!).
- Trigeminal neuralgia is not TMD! These are two disorders of different etiologies and different characteristics (trigeminal neuralgia is neuropathic, TMD is musculoskeletal). Sometimes, the patient with trigeminal neuralgia may present muscle pain in the area of trigger but as a form of muscle guarding (e.g. secondary muscle co-contraction/protective muscle co-contraction).

Marcela Romero DDS, PhD, FAHS

Final Remarks

- Atypical facial Pains (PIFP and PDAP) can be devastating for the quality of life of the patient and require a careful differential diagnosis and management.
- The pain experience is very subjective. For some patients may be very difficult to describe their pain
- It is essential to emphasize the avoidance of unnecessary dental procedures
- In doubt…Ask for advice to a board-certified orofacial pain trained dentist and never underestimate second opinions!
- It is crucial to manage the pain in a multidisciplinary manner and provide understanding, and compassionate care and support for the patient.

Multidisciplinary care!

Building an integrative multidisciplinary team will deliver better outcomes for our patients!

AKNOWLEDGEMENTS

UNIVERSITY of MARYLAND CENTER TO ADVANCE CHRONIC PAIN RESEARCH

Clinical Research Team

Collaborators

Dr. Simon Akerman (UMB)

Lab members:

Dr. Ana Belen Salinas Abarca

Archana Vasanth-Kumar BDS MPH Michael Keaser BS

Hannah Rosen

Rodents

Jane L. Phillips, RDH, MS, CPT

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ClinicalTrials.gov: NCT05162027

ClinicalTrials.gov: NCT05142228

THANK YOU!

Ketamine: The Good, The Bad and the Ugly

Jijun (G-Jun) Xu, MD, PhD

IV Ketamine Infusion for Chronic Pain: *the Good, the Bad and the Ugly*

Jijun Xu, MD, PhD

Assistant Professor
Department of Pain Management, Anesthesiology Institute
Department of Inflammation and Immunity, Lerner Research Institute
Cleveland Clinic
Cleveland, OH

Disclosure

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  - FAER, ASRA, Mallinkrodt, Nevro
  - NIH/NCI, RSDSA, Cleveland Clinic Anesthesiology Institute and Lerner Research Institute, The Steve and Melody Golding Foundation

Outline

- Pharmacology of ketamine
- Ketamine for management of chronic refractory pain
- Development of a consensus protocol of ketamine infusion for CRPS
- Clinical considerations in use of ketamine for pain management

PHARMACOLOGY OF KETAMINE

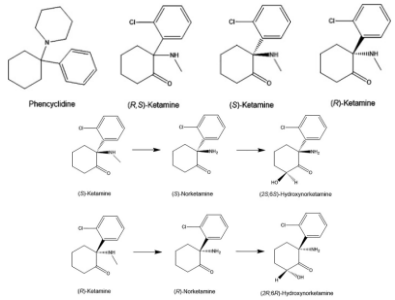
History of Ketamine

- 1962 First synthesized as replacement for phencyclidine
- 1964 First used in human subjects (U Michigan, Drs. Domino and Corssen)

"dissociative anesthetic"

- 1970 FDA approved ketamine for human use. Introduced into the Vietnam war as battlefield anesthetic
- 1981 DEA classified ketamine as Schedule **III** substance (moderate to low potential for physical and psychological dependence)

Chemical structure of phencyclidine, (*R,S*)-ketamine, enantiomers of ketamine, and their metabolites



Hashimoto K. Psychiatry Clin Neurosci. 2019 Oct; 73(10): 613–627.

S-Ketamine (Esketamine) vs R-Ketamine (Arketamine)

- Ketamine (or *RS*-ketamine) is a racemic mixture containing equal parts of *R*-ketamine and *S*-ketamine.
- *S*-ketamine has an approximately **fourfold greater affinity** for the NMDA receptor than the *R*-ketamine.
- *S*-ketamine shows an approximately **three- to fourfold greater anesthetic** potency and **greater undesirable psychotomimetic** side effects, compared with *R*-ketamine.
- In 2019, the FDA approved S-Ketamine (Esketamine, SPRAVATO™) spray for treatment-resistant depression
- *In Jan 2022, The FDA has given Investigational New Drug clearance for a clinical drug-drug interaction study of R-ketamine (PCN-101).*

Yang, C., Shirayama, Y., Zhang, Jc. *et al. Transl Psychiatry* **5**, e632 (2015). https://doi.org/10.1038/tp.2015.136

Basic pharmacological profiles of ketamine for different routs of administration

Route of Administration	Typical Dosing	Bioavailability, %	Time of Onset	Duration of Action After Dosing
Intravenous	1–4.5 mg/kg for general anesthesia induction; 1–6 mg/kg per hour for anesthesia maintenance; 0.5–2 mg/kg for 1-d outpatient or 3- to 5-d inpatient awake ketamine infusions in chronic pain (higher dosages titrated to effect from lower doses); 0.2–0.75 mg/kg for procedural analgesia, can be repeated; 0.1 mg/kg for IV infusion test; 5- to 35-mg/h continuous infusion for acute traumatic or postoperative pain, 1–7 mg/demand dose mixed with opioids in patient-controlled analgesia	N/A	30 s	5–10 min for bolus doses
Intramuscular	2–4 times IV dosing; 5–10 mg/ kg for surgical anesthesia; 0.4–2 mg/kg for procedural analgesia; bolus and treatment dosing 0.10–0.5 mg/kg for chronic pain	75–95	2–5 min	30–75 min
Intranasal	0.2–1 mg/kg for chronic pain and sedation; 3–6 mg/kg for procedural analgesia and anesthetic premedication	25–50	5–10 min	45–120 min
Subcutaneous	0.1–1.2 mg/kg per hour for chronic pain; bolus and treatment dosing 0.10–0.6 mg/kg	75–95	10–30 min	45–120 min
Oral	0.3–1.25 mg/kg for chronic pain; up to 3 mg/kg for procedural analgesia and anesthetic premedication	10–20	5–20 min	2–4 h
Rectal	5–10 mg/kg for anesthesia premedication and procedural analgesia	25–30	5–15 min	2–3 h
Topical	1%–10% cream for chronic pain	<5	<2 d	NA

Cohen Sp et al., Reg Anesth Pain Med. 2018 Jul; 43(5): 521–546

Ketamine: Mechanism of Action

Antagonism/Inhibition	
NMDA receptors	• Dissociative anesthesia, amnesia (Oye et al., 1992) • Inhibited sensory perception (Oye et al., 1992) • Analgesia (Oye et al., 1992)
HCN channels	• Hypnosis (Chen et al., 2009; Zhou C. et al., 2013)
Calcium channels (L-type voltage-dependent)	• Negative cardiac inotropy (Baum and Tecson, 1991) • Airway smooth muscle relaxation (Yamakage et al., 1995)
Voltage-gated sodium channels	• Decreased parasympathetic activity (Imaten et al., 2002) • Local anesthetic effect (Frenkel and Urban, 1992; Haeseler et al., 2003)
BK channels	• Analgesic effects on neuropathic pain (Hayashi et al., 2011)
Agonism/Activation	
Opioid receptors (particularly μ, δ)	• Central antinociception (Finck and Ngai, 1982; Pacheco Dda et al., 2014)
AMPA receptors	• Rapid antidepressant effects (Zanos et al., 2016)
$GABA_A$ receptors	• Anesthetic properties (Irifune et al., 2000)

Li, L. et al. Ketamine: 50 Years of Modulating the Mind. *Front. Hum. Neurosci.*, 29 November 2016

Clinical use of ketamine

Anesthesia	Analgesia and sedation		Psychiatry and neuroscience
Advantageous settings: • Hemodynamic instability • Pediatric patients • Uncooperative patients • Traumatic brain injury • Bronchospasm • Battlefield/Mass casualty	*Acute settings:* • Procedures • Burns • ED Agitation/Pain • Post-operative pain	*Chronic settings:* • Cancer pain • CRPS • Phantom limb pain • Fibromyalgia • Ischemic pain • Migraines	*Emerging use:* • Depression • Suicidal ideation • PTSD *Modeling:* • Schizophrenia • Consciousness

ED, emergency department; CPRS, complex regional pain syndrome; PTSD, post-traumatic stress disorder. Please see text ("Clinical Uses in Medicine" Section) fo associated references.

Li, L. et al. Ketamine: 50 Years of Modulating the Mind. *Front. Hum. Neurosci.*, 29 November 2016

KETAMINE INFUSION FOR MANAGEMENT OF CHRONIC REFRACTORY PAIN

Evidence and Recommendation Grades

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

UpToDate®

Ketamine for Refractory **Headache**: A Retrospective Analysis.

Schwenk ES, et al. Reg Anesth Pain Med. 2018. PMID: 29923953

- Retrospective study, 61 patients, **inpatient** 5 days of intravenous continuous ketamine infusion
- An **immediate responder** was a patient with decrease of 2 points or greater in the numerical rating scale (0–10) from start to final pain in the hospital. **Sustained response** at office visits 1 and 2 was determined based on maintaining the 2-point improvement at those visits. Patients were assessed daily for pain and adverse events (AEs).
- Forty-eight (77%) of the 61 patients were immediate responders. There were no differences regarding demographics, opioid use, or fibromyalgia between immediate responders and nonresponders.
- **Maximum improvement occurred 4.56 days (mean) into treatment**. Sustained response occurred in 40% of patients at visit 1 (mean, **38.1 days**) and 39% of patients at visit 2 (mean, **101.3 days**). The mean maximum ketamine rate was **65.2 ± 2.8 mg/h** (**0.76 mg/kg per hour**). Ketamine rates did not differ between groups. Adverse events occurred equally in responders and nonresponders and were mild.
- Ketamine was associated with short-term analgesia in many refractory headache patients with tolerable adverse events. A prospective study is warranted to confirm this and elucidate responder characteristics.

TABLE 3. Adverse Events From Ketamine Infusions

Adverse Events	Immediate Responders (n = 48)	Nonresponders (n = 13)	*P*
Nystagmus	36 (75)	7 (54)	0.141
Sedation	23 (48)	8 (62)	0.319
Nausea/vomiting	19 (40)	4 (31)	0.564
Blurry vision	17 (35)	6 (46)	0.482
Hallucinations	13 (27)	4 (31)	0.794
Vivid dreams	5 (10)	3 (23)	0.234

Data are presented as n (%).

Schwenk ES, *et al.* Reg Anesth Pain Med 2018;43: 875–879.

Intravenous Lidocaine and Ketamine Infusions for **Headache** Disorders: A Retrospective Cohort Study.

Ray JC, et al., Front Neurol. 2022 Mar 9;13:842082. doi: 10.3389/fneur.2022.842082

- 83 infusions (33 ketamine) for a headache disorder (77 migraine, three NDPH, two SUNCT, one cluster headache).
- 68.9% were semi-electively admitted to the hospital for infusion, the remainder through the emergency department
- The mean maximum tolerated dose of ketamine was **16.3 mg/h** (SD 6.5 mg)
- Ketamine infusion was associated with a ≥50% reduction in pain in 34.4% over a mean **5.1 days** (SD 1.5). No longer follow up reported.
- The overall rate of any adverse effect of intravenous infusion was 42.4% in the ketamine cohort. The majority of adverse events reported were minor. 12.1% (4/33) of patients who received a ketamine infusion had an adverse event that led to cessation of the infusion.
- The strengths: sample size, outcome data was available for every case, and each case was reviewed by a specialist neurologist.

Recommendation	Evidence
2	C

Ketamine for **cancer pain**: what is the evidence?

Jonkman K, van de Donk T, Dahan A.Curr Opin Support Palliat Care. 2017 Jun;11(2):88-92.

- Mercadante et al. (2000) studied **10** cancer patients with moderate to severe pain (numerical rating 5.9-6.6) resistant to morphine treatment.
  - Randomized, controlled, double-blind, crossover, double-dose
  - All patients received **three treatments at least 2 days apart**: ketamine **0.25 mg/kg**, ketamine **0.5 mg/kg** and saline infused intravenously **over 30 min**. Evaluations were restricted to 180 min. A **dose-dependent ketamine-induced analgesic effect** was observed (peak effect at t = 120 min) with no effect of placebo treatment. Central adverse events were observed in 4 patients during ketamine treatment and in none of the patients during placebo treatment
- Salas et al. (2012) studied **20** patients with cancer pain (pain score 5.8 +/- 1.8), refractory to treatment with opioids. Patients receiving intravenous morphine treatment were randomized to receive ketamine (n = 11; **dose on day 1: 0.5 mg/kg** by continuous intravenous infusion over 24 h that could be increased after one day to an infusion of **1 mg/kg over 24 h**) or placebo (n = 9). Patients were evaluated for 48 h.
  - Self-reported pain did **not** differ between treatment groups during the 48 h of the study. After 24 h, about 30% of patients in both groups experienced a 30% reduction in pain rating in both groups; after 48 h responder rates were 25% (placebo) and 50% (ketamine; not significantly different from placebo). Opioid consumption did not differ between groups. Side effects were not different between study groups.

Recommendation	Evidence
2	C

Chronic Neuropathic Conditions

- Neuropathic pain
  - Mixed neuropathic pain diagnoses
  - Traumatic spinal cord injury
  - Phantom limb pain
  - Post-herpetic neuralgia
- Conditions with chronic neuropathic pain features
  - Fibromyalgia
  - Complex regional pain syndrome
  - Ischemic pain
  - Chronic migraine
  - Chronic low back pain

Mixed Neuropathic Diagnoses

- 7 double-blind RCTs (n=78)
- 4 of 7 studies demonstrated significant reductions in pain compared to placebo
- Ketamine infusion ranged from 0.006 to 0.075 mg/kg/h
- Duration of infusions ranged from 5 minutes to 2 hours
- Possible dose-response relationship observed in 1 study (Leung, 2001)
- Duration of pain relief assessed in 1 of 7 studies (pain relief resolved 2-3 hours following infusion)

Recommendation	Evidence
2	C

Kvarnstrom A et al., Acta Anaesthesiol Scand. 2003; 47:868-877
Leung A, et al., Pain 2001; 91: 177-187
Max MB, et al., Clin Neuropharmacol. 1995; 18:360-368
Gottrup H et al., Anesthesiology. 2006; 104:527-536
Backonja M, et al., Pain. 1994;56: 51-57
Felsby S et al., Pain. 1996; 64:283-291
Jorum E, et al., Pain. 2003; 101:229-235

Traumatic Spinal Cord Injury

- 3 double-blind RCTs (n=69)
- All studies demonstrated significant reductionin pain scores compared to placebo
- Ketamine infusions ranged from 0.42 mg/kg/h to 0.4 mg/kg
- Duration of infusions ranged from 17 minutes to 5 hours for 7 consecutive days
- Duration of pain relief observed for 2 weeks following infusion (Amr 2010)

Recommendation	Evidence
2	B/C

Kvarnstrom A et al., Acta Anaesthesiol Scand. 2004; 48:498-506
Eide PK., et al., Neurosurgery. 1995; 37:1080-1087
Amr YM. Pain Physician. 2010; 13:245-249

Phantom Limb Pain

- 2 double-blind RCTs (n=21)
- Both studies demonstrated significant reductions in pain scores compared to placebo
- 0.1 mg/kg bolus over five minutes, then 0.5 mg/kg/h (Nikolajsen, 1996)
- 0.4 mg/kg infusion over 1 hour (Eichenberger, 2008)
- Duration of pain relief ranged from 35 min to 48 hours

Recommendation	Evidence
2	C

Nikolajsen et al., Pain. 1996 Sep;67(1):69-77.
Eichenberger et al., Anesth Analg. 2008 Apr;106(4):1265-73

Postherpetic neuralgia

- 1 RCT (n=8)
- IV ketamine 0.15 mg/kg over 10 min
- Significant reductions in pain compared to placebo observed 15 to 45 min following the infusion

Recommendation	Evidence
2	C

Eide PK et al., Pain. 1994 Sep;58(3):347-54.

Fibromyalgia

- 4 double-blind RCTs (n=97)
- All studies demonstrated significant reduction in pain scores compared to placebo during infusion
- Infusion ranged from 0.3 mg/kg to 0.5 mg/kg over 10 to 30 min
- Duration of infusion ranged from 17 min to 5 hours for 7 consecutive days
- Duration of pain relief observed for 2 hours in 1 study

Sörensen J, et al., Scand J Rheumatol. 1995;24(6):360-5
Sörensen J, et al., J Rheumatol. 1997 Aug;24(8):1615-21.
Noppers I, et al., Eur J Pain. 2011 Oct;15(9):942-9.
Graven-Nielsen T, et al., Pain. 2000 Apr;85(3):483-91.

Systematic Review of the Use of Intravenous Ketamine for **Fibromyalgia**.

Pastrak M, Abd-Elsayed A, Ma F, Vrooman B, Visnjevac O. Ochsner J. 2021 Winter;21(4):387-394. doi: 10.31486/toj.21.0038.

- Keywords used: "fibromyalgia," "chronic pain," "ketamine," "intravenous," and "infusion"
- 7 publications that included 118 patients with fibromyalgia who met inclusion criteria.
- Clinical studies revealed a **short-term reduction-only for a few hours** after the infusions-in self-reported pain intensity with single, low-dose, intravenous ketamine infusions. Case studies suggest that increases in the total dose of ketamine and longer, more frequent infusions may be associated with more effective pain relief and longer-lasting analgesia.
- This systematic review suggests a dose response, indicating potential efficacy of intravenous ketamine in the treatment of fibromyalgia.

Recommendation	Evidence
2	C

Ischemic Pain

- 2 double-blind RCTs (n=26)
- Mitchell, 2002
  - 0.6 mg/kg over four hours
  - Significant pain reduction compared to placebo at 1 and 5 days
- Persson, 1998
  - 0.15 mg/kg, 0.3 mg/kg, 0.45 mg/kg over 5 min
  - No significant pain reduction compared to IV morphine 10 mg

Recommendation	Evidence
2	C

Mitchell, et al., Pain. 2002 Jun;97(3):275-81.
Persson, et al., Acta Anaesthesiol Scand. 1998 Aug;42(7):750-8.

Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP. Anesth Analg. 2019 Jul;129(1):241-254.

- Database search through December 16, 2017 for randomized control trials comparing IV ketamine to placebo infusions for chronic pain that reported outcomes for ≥48 hours after the intervention
- 7 studies met inclusion criteria. All studies except one were at high risk of bias. These studies randomly assigned 211 patients with neuropathic (n = 2), mixed (n = 2), and nonneuropathic (nociplastic or nociceptive) (n = 3) pain.
- Evidence suggests that IV ketamine provides significant short-term (up to 2 weeks after the infusion) analgesic benefit in patients with refractory chronic pain, with **some evidence of a dose-response relationship**.
- Larger, multicenter studies with longer follow-ups are needed to better select patients and determine the optimal treatment protocol.

Perioperative intravenous low-dose ketamine for neuropathic pain after major lower back surgery: A randomized, placebo-controlled study.

Czarnetzki C, et al., Eur J Pain. 2020 Mar;24(3):555-567. doi: 10.1002/ejp.1507. Epub 2019 Dec 9.

- Single-centre randomized trial, 80 patients received intravenous ketamine **0.25 mg/kg** preoperatively, followed by **0.25 mg/kg/hr** intraoperatively, and **0.1 mg/kg/hr** from 1 hr before the end of surgery until the end of recovery room stay; 80 controls received placebo.
- Preoperatively, 47.4% of patients in the ketamine group and 46.3% in the placebo group had neuropathic pain. At the end of the infusion, the median cumulative dose of ketamine was **84.8 mg** (IQR 67.4-106.7) and the median plasma level was 97 ng/ml (IQR 77.9-128.0).
- At 6 months, 28.8% of patients in the ketamine group and 23.5% in the placebo group had neuropathic pain (absolute difference, 5.2%; 95% CI -10.7 to 21.1; p = .607). At 12 months, 26.4% of patients in the ketamine group and 17.9% in the placebo group had neuropathic pain (absolute difference 8.5%; 95% CI -6.7 to 23.6; p = .319).
- In this patient population with a high prevalence of neuropathic lower back pain undergoing major lower back surgery, a perioperative intravenous low-dose ketamine infusion did **not** affect the prevalence of neuropathic lower back pain at 6 or 12 months postoperatively.

Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-blind, Crossover Trial.

Pickering G, et al., Anesthesiology. 2020 Jul;133(1):154-164.

- A randomized, double-blind, crossover, placebo-controlled study, **20** patients with neuropathic pain.
- Each ketamine-naïve patient received **one** infusion every 35 days in a random order: ketamine (**0.5 mg/kg**)/placebo or ketamine (0.5 mg/kg)/magnesium sulfate (3g) or placebo/placebo.
- The primary endpoint was the area under the curve of daily pain intensity for a period of 35 days after infusion. Secondary endpoints included pain (at 7, 15, 21 and 28 days) and health-related, emotional, sleep, and quality of life questionnaires.
- Daily pain intensity was **not** significantly different between the three groups (n = 20) over 35 days.
- There were **no** significant differences in emotional, sleep, and quality of life measures.
- During placebo, ketamine, and ketamine/magnesium infusions, 10%, 20%, and 35% of patients respectively reported at least one adverse event.

IV Ketamine infusion for CRPS

Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study.

Kiefer et al., Pain Med. 2008 Nov;9(8):1173-201.

- Twenty ASA I-III patients (USA, Germany), refractory CRPS, inpatient ketamine in anesthetic dosage over 5 days.
- *Anesthesia was induced by bolus injection of ketamine (1–1.5 mg/kg) and midazolam (2.5–7.5 mg). Tracheal intubation was facilitated by vecuronium (0.1 mg/kg). Treatment was maintained by infusions of ketamine over 5 days, starting at **3 mg/ kg/h**, followed by gradual daily titration up to a final dose of **7 mg/kg/h**. Midazolam was coadministered and adjusted as clinically required (0.15–0.4 mg/kg/h) to obtain a stable level of **deep sedation (Ramsay-Score 4–5)**, and to attenuate ketamine-specific side effects. The first three patients were not intubated and spontaneous ventilation was allowed. The remaining 17 patients were electively intubated, to limit the risk of aspiration. These 17 patients were mechanically ventilated. After 5 days, infusions were slowly tapered, first by reducing the ketamine dosage by 20% every four hours, followed by gradual reduction of midazolam in the same manner. Patients were then weaned from mechanical ventilation and extubated once adequate spontaneous ventilation, sufficient gas exchange, and the appropriate level of consciousness together with intact protective reflexes was attained.*
- Significant pain relief was observed at 1, 3, and 6 months following treatment (93.5 +/- 11.1%, 89.4 +/- 17.0%, 79.3 +/- 25.3%; P < 0.001). Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. If relapse occurred, significant pain relief was still attained at 3 and 6 months (59.0 +/- 14.7%, P < 0.004; 50.2 +/- 10.6%, P < 0.002). Quality of life, the associated movement disorder, and the ability to work significantly improved in the majority of patients at 3 and 6 months.
- This open-label trial suggests benefit in pain reduction, associated CRPS symptoms, improved quality of life and ability to work following anesthetic ketamine in previously refractory CRPS patients.

Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1.

Sigtermans et al., Pain. 2009 Oct;145(3):304-11.

Article history:
Received 1 April 2009
Received in revised form 20 May 2009
Accepted 18 June 2009

- Sixty CRPS-1 patients (48 females) (The Netherlands) with severe pain with a median (range) disease duration 7.4 (0.1–31.9) years. Patients were **admitted** to a short stay ward for 5 days.
- Double-blind randomized placebo-controlled parallel-group trial
- **4.2-day** intravenous infusion of low-dose ketamine (n = 30) or placebo (n = 30)
- *The drug infusion rate started at 1.2 µg/kg/min(or **5 mg/h** for a 70-kg patient) at 8 AM on day 1 and was titrated at regular intervals (max. thrice daily) to a maximum of 7.2 µg/kg/min (or **30 mg/h** for a 70-kg patient). The infusion rate was increased when pain relief was insufficient (based on reported visual analogue pain scores reported at 2 h (day)–8 h (night) intervals) and side effects were acceptable to the patients. At the end of infusion, the mean ketamine dose was **22.2 ± 2.0 mg/h/70 kg**.*
- Pain scores over the 12-week study period in patients receiving ketamine were significantly lower than those in patients receiving placebo (P < 0.001). The lowest pain score was at the end of week 1: ketamine 2.68 ± 0.51, placebo 5.45 ± 0.48. In week 12, significance in pain relief between groups was lost (P = 0.07). Treatment did not cause functional improvement.
- Patients receiving ketamine more often experienced mild to moderate psychomimetic side effects during drug infusion (76% versus 18%, P < 0.001).

Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study.

Schwartzman et al., Pain. 2009 Dec 15;147(1-3):107-15.

Article history:
Received 30 March 2009
Received in revised form 16 July 2009
Accepted 18 August 2009

- 19 subjects (Drexel University Neurology Pain Clinic, Philadelphia), CRPS, IASP criteria, duration of CRPS 0.8-20 years. Randomized, 9 ketamine, 10 placebo
- Pain questionnaires before infusion, activity watch, sensory and motor tests before and after infusion
- *Infusion protocol: 100 ml of normal saline with or without ketamine for 4 h (25 ml/h) daily for 10 days (5 days on, 2 days off, 5 days on). The maximum intravenous ketamine infusion rate for this study was **0.35 mg/kg/h**, not to exceed 25 mg/h (100 mg of ketamine over a 4 h period). On the first day, the intravenous ketamine infusion was set to 50% of the maximum rate. On the second day, the intravenous ketamine infusion was increased to 75% of the maximum rate. On the third day, the intravenous ketamine infusion was increased to the maximum rate and maintained at this level for the duration of the 10 day study.*
- Adjuvants: clonidine (0.1 mg p.o.) and midazolam (2 mg prior to and 2 mg following the 4 h infusion by i.v. push)
- Significant difference in the short-form McGill Pain Questionnaire scores was observed between the ketamine and placebo groups at 4 time points following the infusions (weeks 1–2, weeks 3 to 4, weeks 5–8, and weeks 9–12).
- Adverse effects: Six (4/9 in the ketamine group and 2/10 in the placebo group) nausea, headache, tiredness or dysphoria at some point during the trial. No agitation, blurred vision or any psychomimetic side effects.
- This trial failed to enroll the planned number of individuals, in part because the authors determined that higher dosages were necessary.

The Effect of Ketamine Infusion in the Treatment of CRPS: a Systemic Review and Meta-analysis.

- Database search of randomized clinical trials or cohort studies between Jan 1, 1950, and August 1, 2017 for meta-analyses.
- The primary outcome is pain relief using the 0-10 scale numerical rating pain score. The secondary outcome is the pain relief event rate, defined as the percentage of participants who achieved 30% or higher pain relief in each of the qualified studies.
- Ketamine treatment led to a decreased mean of pain score in comparison to the self-controlled baseline (p < 0.000001). The immediate pain relief event rate was 69% (95% confidence interval (CI) 53%, 84%). The pain relief event rate at the 1-3 months follow-ups was 58% (95% CI 41%, 75%).
- Limitations: there is a statistical significance of between-study heterogeneity.
- Author's notes: Additional random controlled trials and standardized multicenter studies are needed to confirm the short and long-term effect of ketamine for CRPS.

Recommendation	Evidence
2	B

Zhao J et al., The Effect of Ketamine Infusion in the Treatment of CRPS: a Systemic Review and Meta-analysis. Curr Pain Headache Rep. 2018 Feb 5;22(2):12. doi: 10.1007/s11916-018-0664-x

Consensus Guidelines on the Use
of Intravenous Ketamine Infusions for Chronic Pain From the ASRA, AAPM, & ASA.
Cohen SP, et al.,Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

- Evidence supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range.
- Most studies evaluating the efficacy of ketamine were small and uncontrolled and were either unblinded or ineffectively blinded.
- Adverse effects were few and the rate of serious adverse effects was similar to placebo in most studies, with higher dosages and more frequent infusions associated with greater risks.
- For spinal cord injury pain, there is weak evidence supporting ketamine infusions (0.42 mg/kg per hour to 0.4 mg/kg ranging from 17 minutes to 5 hours for 7 consecutive days) for short-term improvements in pain (grade C recommendation, low level of certainty).
- For CRPS, there is moderate evidence supporting ketamine infusions (22 mg/h for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty).
- For mixed neuropathic pain, PLP, PHN, fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty). **Excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.**

DEVELOPMENT OF A CONSENSUS PROTOCOL OF KETAMINE INFUSION FOR CRPS

The optimal protocol for IV ketamine infusion for CRPS hasn't really established!

- Huge variations in
  - Dose
  - Rate
  - Duration of infusion
  - Duration of pain improvement
- Lack of comprehensive adverse effects and clinical outcome measurements

Pain Medicine 2019; 20: 323–334
doi: 10.1093/pm/pny224

NEUROPATHIC PAIN SECTION

Review Article

Intravenous Ketamine Infusion for Complex Regional Pain Syndrome: Survey, Consensus, and a Reference Protocol

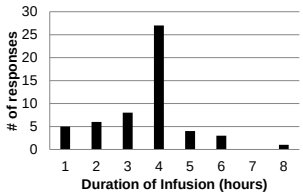
Jijun Xu, MD, PhD,[*,†] Christopher Herndon, PharmD,[‡,§] Samantha Anderson, BS,[¶] Philip Gelson, DO,[¶] Victor Foorsov, MD,[*,¶] Ronald E. Harbut, MD, PhD,[**] Peter Moskovitz, MD,[¶] and R. Norm Harden, MD[*,††]

- Survey of Ketamine Practitioners - Protocols, Efficacy, Adverse Effects
  - –323 responses internationally

rsdsa SUPPORTING THE CRPS COMMUNITY

Duration of Outpatient Infusion

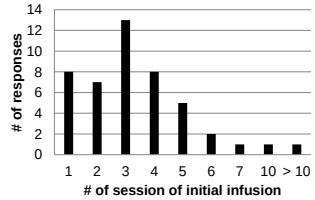
- –Range: 0.75 to 8 hours
- –Mode of infusion duration: **4 hrs/session**



Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Session of Outpatient Infusion

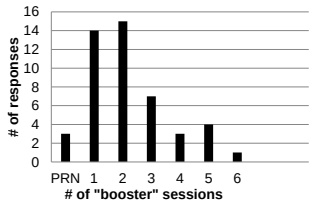
- –Range: 1 to > 10 initial sessions
- –Mode of initial infusion session: **3**
- –Average total initial infusion hours per round (hours/session * sessions) **: 16 ± 11 hours**



Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Outpatient "Booster" Sessions

- Range: 1 -6 Sessions
- Mode of "booster" session: **2**



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Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Interval of Subsequent Infusion – ADULT

- Range: 1 week – 1 year or PRN
- Mode of a +/- flat curve: **1 month**

Cleveland Clinic

Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Adjuvant Medications – Adult Outpatient

- Midazolam: Range 1 – 9+ mg
  - Mode: **2-4 mg**.
- Dexmedetomidine
  - Yes = 2
  - No = 14
- Clonidine
  - 0.1 mg: 4 responses

Cleveland Clinic

Adjuvant Medications

- Antiemetics
  - Ondensetron: **25** (dose range from unspecified to 4 -8 mg)
  - Metoclopramide: **8** (range 10 – 25 mg)
  - Promethazine: 2 (12.5 – 25 mg)
  - Aprepitant: 1
  - Ativan: 1 (1-2 mg)
  - Dexamethasone: 2 (range 4-8mg)

Cleveland Clinic

Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Adjuvant Medications

- Lidocaine: 2 (unspecified or 6 g/Kg)
- Diazepam: 1
- Alprazolam: 2
- Benadryl IV: 1 (25 -50 mg IV)
- Ketorlac: 3
- Magnesium/Magnesium sulfate: 2
- Zyprexa: 1
- Hydroxyzine: 1
- Propofol: 2
- Narcotic: 1

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Efficacy of infusion

- Pain metric:
  - **0-10 NRS** (19 of 33 answers)
- Definition of "Successful infusion using pain scale":
  - **50% or greater improvement in NRS** (15 of 30 answers)
- Duration of pain relief:
  - Range: 1 – 180 days
  - Mode: **7 – 90 days**
  - The median [25th, 75th percentiles] length of pain relief was **30** [14, 60] days in the ≤ 0.5, and **45** [21, 62] days in the > 0.5 mg/kg/hr group, respectively.

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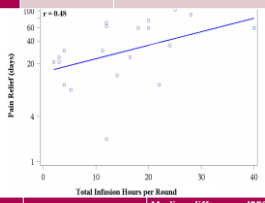
Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Correlation of total infusion hours per round (hours/day * days) or infusion rate with duration of pain relief

Exposure	unit	Ratio of geometric means (95% CI) of length of pain relief (days)	P value
Total infusion hours per round	Unit= 5hours	1.23 (1.03, 1.47)	0.028*



Exposure		Median difference (95% CI)	
Rates of IV ketamine infusion	> 0.5 vs ≤ 0.5 mg/kg/hr	2 (-28, 35)	0.47**

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A consensus reference protocol of IV ketamine infusion

- Inpatient
  - Initial rate: 10 mg/h (approximately 0.15 mg/kg/h based on ideal body weight), increased every two hours in 5– 10mg increments.
  - Maximum rate: 40 mg/h
  - Titrate to "drowsy to moderate sedation" (e.g., Richmond Agitation-Sedation Scale [RASS] score of –1 to –3) or pain reduction by 50% using numeric pain rating scale (verbal), whichever is achieved first.
  - Duration: 24 hours for three to five days.

RASS (Richmond Agitation Sedation Scale)			
4	Combative	Overtly combative, violent, immediate danger to staff	
3	Very agitated	Pulls or removes tubes or catheters; aggressive	
2	Agitated	Frequent non-purposeful mvmt, fights ventilator	
1	Restless	Anxious but movements not aggressive or vigorous	
0		Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥10sec)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)	
-3	Moderate sedation	Movement or eye opening to voice but no eye contact	
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation	Physical Stimulation
-5	Cannot be aroused	No response to voice or physical stimulation	

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A consensus reference protocol of IV ketamine infusion

- Outpatient
  - Initial rate on day 1: 0.4–0.7 mg/kg/h; then titrated to RASS score of –1 to –3 or pain reduction by 50% using numeric pain rating scale (verbal), whichever is achieved first.
  - If the patient becomes oversedated or dissociation is too great or not tolerated, then reduce infusion by 25%.
  - Maximum rate: 50 mg/h.
  - Total dose: 200 mg on day 1.
  - In subsequent sessions, dosing is 30% more than the prior day's maximum dose.
  - The routine target dose is 150 mg/h, or 600 mg over four hours (some participants suggested that carefully selected patients may receive up to 1200 mg over four hours).
  - Duration: Four hours for each of five to 10 sessions.

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A consensus reference protocol of IV ketamine infusion

- Co-administered Adjuvant Medications
  - Inpatient adjuvant medications include routine clonidine (or dexmedetomidine) titrated to cardiorespiratory parameters, optional ondansetron or other anti-emetic, optional magnesium (4 g per liter over each 24 hours), optional ephedrine for hypotension, optional nonsteroidal anti-inflammatory drug of choice.
  - Multiple other medications were endorsed by less than 14% of participants (e.g., barbiturates, Propofol, diphenhydramine).
  - Outpatient adjuvant medications differ from the inpatient reference protocol only in that clonidine and dexmedetomidine are considered optional.
- Tapering
  - Optional at 10 mg per hour for inpatients.
  - There was no tapering recommended for outpatients.

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A consensus reference protocol of IV ketamine infusion

- Subsequent ("Booster") Therapy
  - Inpatient booster sessions are considered optional, with a starting dose of 25% of the maximum dose during the previous inpatient therapy.
  - For outpatients, 25% of the maximum previous dose takes place for one or two days every one or two weeks.
- Outcomes Assessment
  - The participants of the consensus process agree that pain is the pivotal measure in assessing the infusion pace and impact. A variety of measures were mentioned, but the verbal numeric pain score is probably the most efficient in the context of the infusion session.
  - The "COMPACT" core data set for CRPS may be used in the infusion suite, and the full COMPACT is strongly recommended in the research context.

Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Recommended ketamine screening and peri-administration adverse effect prevention and monitoring

Sequence	Recommendation
Pre-administration screenings	• Substance abuse disorder risk screening • Airway and respiratory history • Psychiatric evaluation and/or clearance for those at risk of schizophrenia, bipolar, PTSD • Cardiac history • Medication history (ideally opioids should be discontinued) • Washout of other NMDA active agents (e.g., memantine, amantadine, methadone, levorphanol, dextromethorphan) • Drug interaction evaluation (CYP active drugs) • Baseline LFTs, pregnancy test, urine analysis, and urine toxicology screen
Peri-administration	• ECG (continuous) • Oxygen saturation (continuous) • Vitals (Q15 X 4, Q30 X 2, and then hourly) • Supplemental O2 and suction available • Standard crash cart including flumazenil and naloxone • IV site assessment (infection, patency)
Post-administration	• Postinfusion observation (minimum of 1 h) to include ability to perform certain ADLs • Released to family member or friend for observation for evening of infusion • Fall risk • Agitation, nightmares (take benzodiazepine)

ADLs = activities of daily living; CYP = ; ECG = ; LFTs = ; NMDA = N-methyl-d-aspartate; PTSD = post-traumatic stress disorder.

Xu J et al., *Pain Medicine*, 2019; 20: 323–334

Adverse effects of subanesthetic dose ketamine

Key Studies	Adverse Effects	Comments
Laskowski,[133] 2011; Bell,[134] 2005; Jouguelet-Lacoste,[135] 2015; Elia,[136] 2005; Drayna,[160] 2012	• Psychomimetic (dysphoria, hallucinations, nightmares, and vivid dreams)	• Unlikely to occur with intraoperative use alone; may occur if used postoperatively • If they occur, discontinuation of infusion often improves symptoms; benzodiazepines or α2 agonists may be effective
	• Blurry vision or diplopia	• Reported incidence 6.2% • Dose-response relationship unclear at subanesthetic doses • Incidence of intraocular pressure, a possible cause of visual symptoms, not known with subanesthetic dosages
Laskowski,[133] 2011; Bell,[134] 2005; Elia,[136] 2005	• Nausea and/or vomiting	• PONV no worse with ketamine than placebo and may be decreased
Wai,[183] 2012; Bell,[186] 2012; Wong,[188] 2014; Noppers,[189] 2011	• Hepatic toxicity	• Occurs mostly in ketamine abusers • Reported upper incidence 9.8% • Typically presents with elevated liver enzymes • Mechanism may be cholestatic • Resolves after ketamine cessation in most patients
Schwartzman,[133] 2009; Goldberg,[196] 2005;	• Headache	• Although reported at >10% in some studies, most report similar incidence to placebo • At higher doses, serious causes such as elevated intracranial pressure should be considered • Considered a treatment for headaches
Morgan,[190] 2011; Jhang,[191] 2015; Shaham,[192] 2007; Chen,[193] 2011	• Cystitis	• Occurs mostly in ketamine abusers • Typically presents with painful hematuria, dysuria, increased frequency, and pain postmicturition • Mechanism may involve direct toxic effect, bladder barrier dysfunction, neurogenic inflammation, immunoglobulin E–mediated inflammation, overexpression of carcinogenic genes, abnormal apoptosis, and nitric oxide synthase–mediated inflammation • First-line treatment is ketamine cessation; hyaluronic acid or anticholinergic agents may be helpful
Gomes,[178] 2011; Walker,[179] 2010; Vranken,[180] 2006; Rojas,[181] 2012; Errando,[182] 1999	• Spinal cord injury	• Reported only with intrathecal use • Weak evidence exists in animal studies; unknown effects in humans • Toxicity may be more likely if preservative used but may still occur with preservative-free formulation

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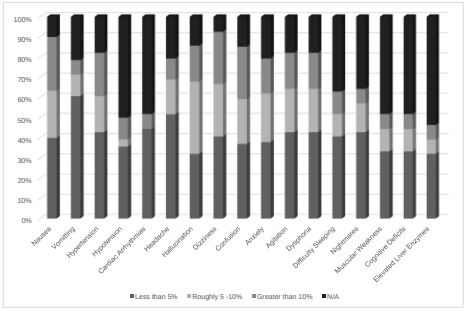
Cohen Sp et al., Reg Anesth Pain Med. 2018 Jul; 43(5): 521–546

Adverse effects of Ketamine infusion



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Possible Adverse Effects and their prevention

- Emergence phenomenon: Co-administration with a benzodiazepine often ameliorates emergence phenomenon sx
- NMDA antagonism → neuro-apoptosis. Many clinicians will co-administer clonidine with ketamine to reduce NMDA-mediated acetylcholine release in the posterior cingulate cortex.
- Long term frequent ketamine use (defined as treatment that lasted 6 months or more and "frequent use" was defined as two times or more per a month over the course of 3.82±1.3 mean years ± SD), resulted in significant impairment on digit span, digit symbol, Controlled Oral Word Association Test, and the trail Making Test, as compared to less long-term users (duration of ketamine treatment 1.86 ± 2.2 years) → Limit the use

Article

Dual action of ketamine confines addiction liability

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Linda D. Simmler[1,2], Yue Li[1,2], Lotfi C. Hadjas[1], Agnès Hiver[1], Ruud van Zessen[1] & Christian Lüscher[1,2]

- Cocaine: ↑the levels of dopamine in the nucleus accumbens → synaptic plasticity in the mesolimbic system → behavioral adaptations →addiction
- Ketamine: ↑the levels of dopamine in the nucleus accumbens, but with NMDAR antagonism, it reinforces the disinhibition of dopamine neurons in the ventral tegmental area (VTA) → rapid of-kinetics of the dopamine transients along with the NMDAR antagonism precluded the induction of synaptic plasticity in the VTA and the nucleus accumbens, and did not elicit locomotor sensitization or uncontrolled self-administration

Summary of Evidence

- Moderate evidence for relatively long-term pain reduction
  - CRPS
  - Ketamine infusion (22 mg/h for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) may provide pain reduction (≥ 30%) in more than 50% patient during the 1-3 month follow-up period
- Weak evidence for short-term pain reduction
  - Chronic non-cancer pain: up to 12 weeks pain relief
  - Spinal cord injury: up to 2 weeks pain improvement
  - Fibromyalgia
  - Migraine headaches
- Weak or no evidence for immediate pain reduction
  - Phantom limb pain
  - Post-herpetic neuralgia
  - Cancer-related pain
  - Ischemic pain

Dose
Duration

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Every Pain deserves world class care.