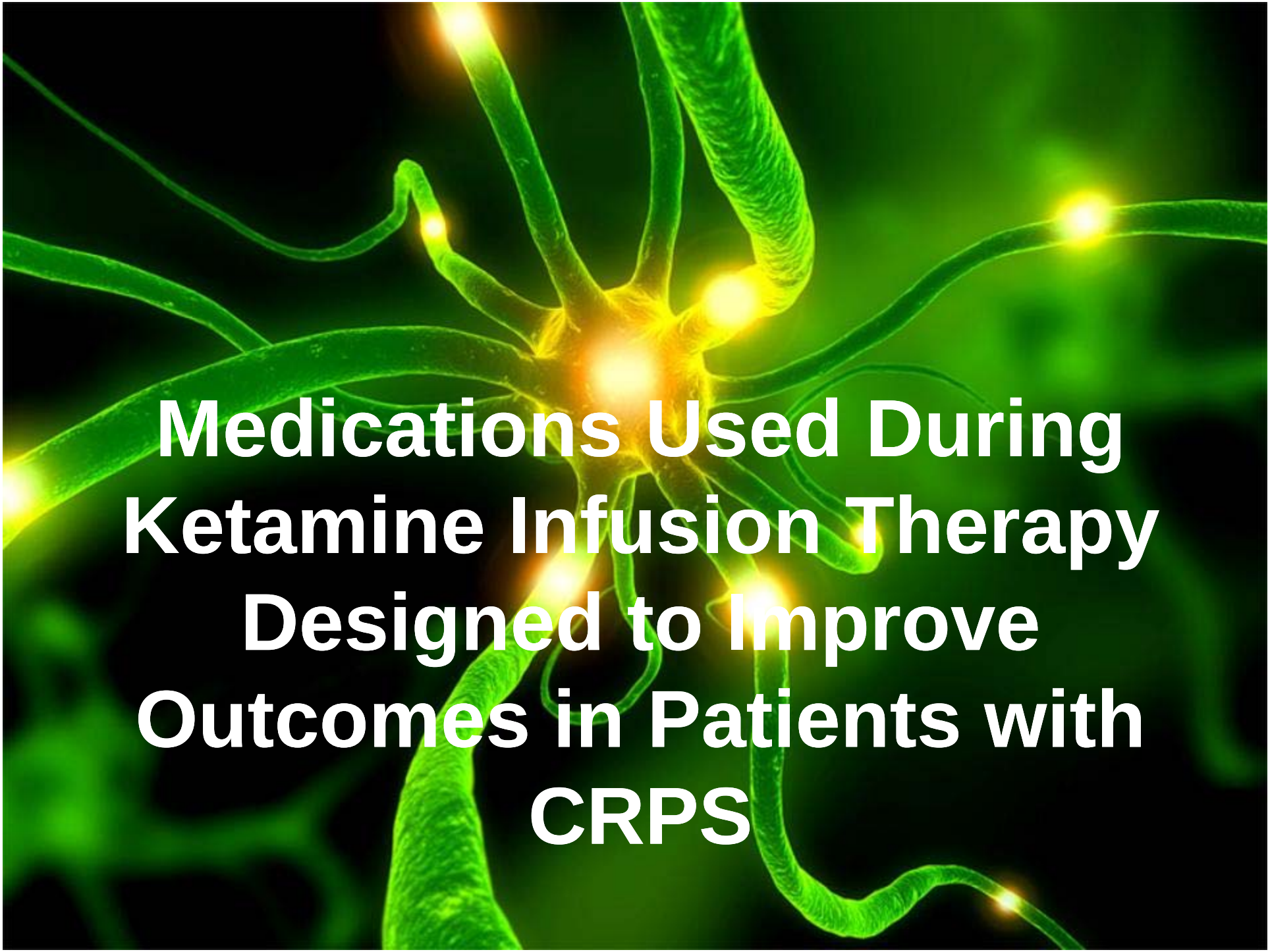
Medications Used During Ketamine Infusion Therapy Designed to Improve Outcomes in Patients with CRPS

Alpine Health & Wellness

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Adjuvant Medications in Ketamine Infusion Therapy

- Adjuvant – A substance that helps and enhances the effect of a drug, treatment, or biological system
- Debate persists regarding ketamine dosing protocols

Adjuvant Medications in Ketamine Infusion Therapy

- Many medications may be used during ketamine infusion therapy that
  - Mitigate or eliminate associated side effects
  - Improve pain
  - Optimize overall outcomes
  - Are often used off-label

Side Effects Associated with Ketamine Infusion Therapy

- “May be present during administration, but rapidly dissipate upon termination of treatment”

Jonkerman K. et al. (September 2017)

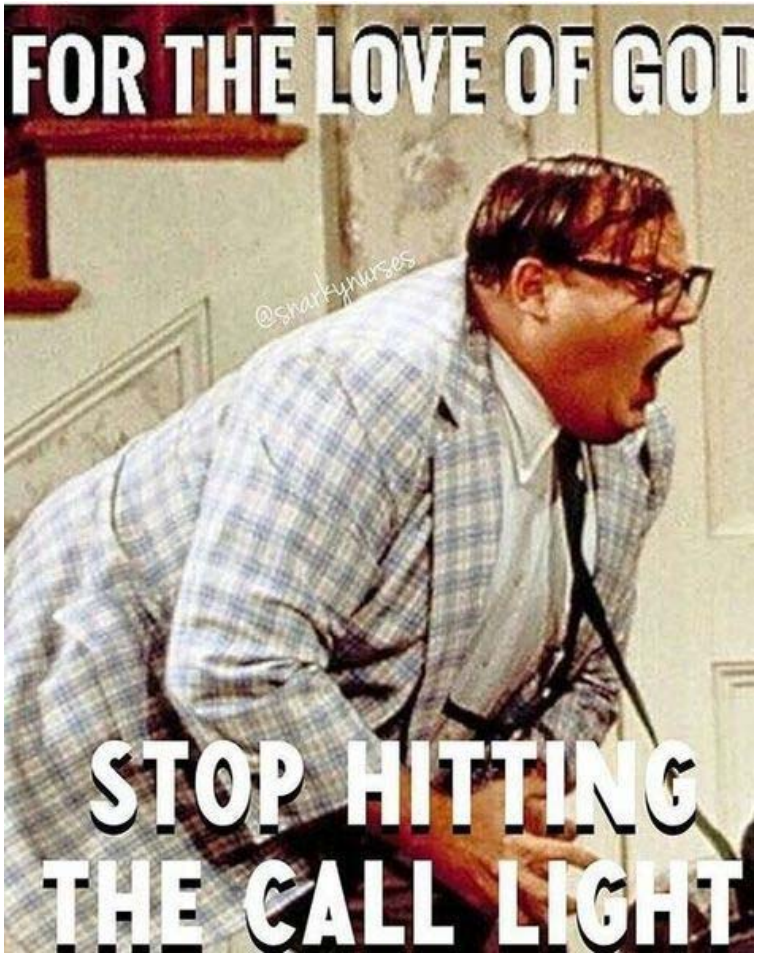
Adjuvant Medications in Ketamine Infusion Therapy

- It is critical that the patient's overall experience to ketamine infusion therapy be as safe and comfortable as possible to ensure optimal outcomes
- Treatment options for patients with CRPS are often limited and suboptimally effective in managing their symptoms

Adjuvant Medications in Ketamine Infusion Therapy

- An optimal and customized environment in which patients undergo ketamine infusion therapy is necessary for patients to achieve the best outcomes possible
- Mindful customization of patients' adjunctive medications in ketamine infusion therapy is a critical consideration in this process

Adjuvant Medications in Ketamine Infusion Therapy




Conditions that May Be Managed by Adjuvant Medications During Ketamine Infusion Therapy

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"The Burning Man people took all our ketamine, so we'll have to settle for this herbal crap."

Conditions Managed by Adjuvant Medications During KIT

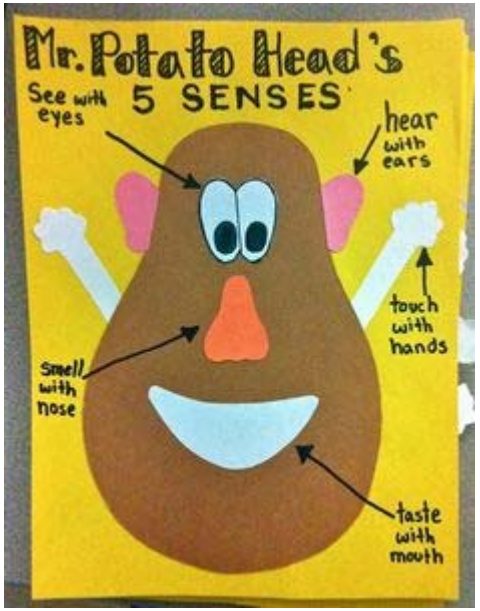
- Psychological effects
- Euphoria (“drug high”)
- Nausea, vomiting, and dyspepsia (upset stomach)
- Hypertension (high blood pressure)
- Tachycardia (fast heart rate)
- Headache

Psychological Effects

- Hallucinations/synesthesias
- Paranoia
- Derealization/depersonalization
- Anxiety
- Panic attacks
- Emergence agitation

Psychological Effects

- Synesthesia
  - A medical condition in which one of the five senses stimulates another sense
    - Examples
      - Sound may produce the visualization of color
      - Letters of the alphabet may produce particular scents
      - Taste may present as a complex mixture of temperature and texture
  - Can be induced by ketamine
  - More common in females

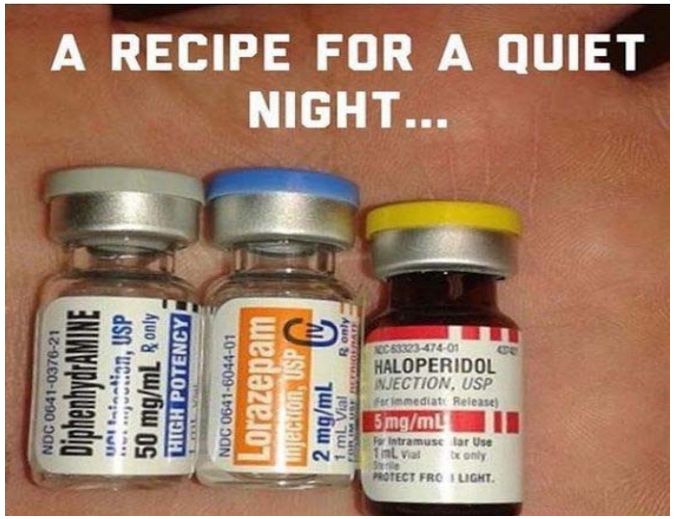


Psychological Effects

- Emergence agitation
  - A state of nonpurposeful restlessness, noncooperation, and inconsolability
  - Often accompanied by crying, screaming, thrashing, and disorientation

Psychological Effects

- Medication classes to be considered
  - Benzodiazepines
  - Alpha-2 receptor agonists
  - Antipsychotics (neuroleptics)
  - Antihistamines



Psychological Effects

- Benzodiazepines
  - Description
    - Primarily used for the treatment of anxiety and muscle spasm
    - May cause short-term amnesia
    - Varying potency and duration of action
  - Mechanism of action
    - Affects neurotransmitters in the brain, chemicals that nerves release in order to communicate with other nearby nerves
    - Modulates the GABA-A receptor
    - GABA-A receptor is a ligand-gated chloride-selective ion channel

Psychological Effects

- Benzodiazepines commonly used in ketamine infusion therapy
  - Diazepam (Valium)
  - Lorazepam (Ativan)
  - Midazolam (Versed)

Psychological Effects

- Diazepam (Valium)
  - Formulations
    - Oral, sublingual, intramuscular, and intravenous
  - Characteristics
    - Long-acting
  - Pharmacokinetics (what the body does to a medication)
    - Oral and intravenous onset of action within 15 minutes
    - Peak onset (oral) 1 hour
    - Half-life 20-50 hours
  - Side effects, warnings, and precautions
    - Drowsiness, dizziness, tiredness, blurred vision, and respiratory depression

Psychological Effects

- Lorazepam (Ativan)
  - Formulations
    - Oral, sublingual, intramuscular, and intravenous
  - Characteristics
    - Short-acting
  - Pharmacokinetics (what the body does to a medication)
    - Intermediate-acting
    - Intravenous onset of action within 15 minutes (rapid)
    - Half-life 1-4 hours
  - Side effects, warnings, and precautions
    - Drowsiness, dizziness, tiredness, blurred vision, and respiratory depression

Psychological Effects

- Midazolam (Versed)
  - Formulations
    - Intramuscular and intravenous
  - Characteristics
    - Short-acting
  - Pharmacokinetics (what the body does to a medication)
    - Intravenous onset of action within 15 minutes (most rapid)
    - Peak onset (intravenous) 0.5-1.5 hours
    - Half-life 1-4 hours
  - Side effects, warnings, and precautions
    - Drowsiness, dizziness, tiredness, blurred vision, and respiratory depression

Psychological Effects

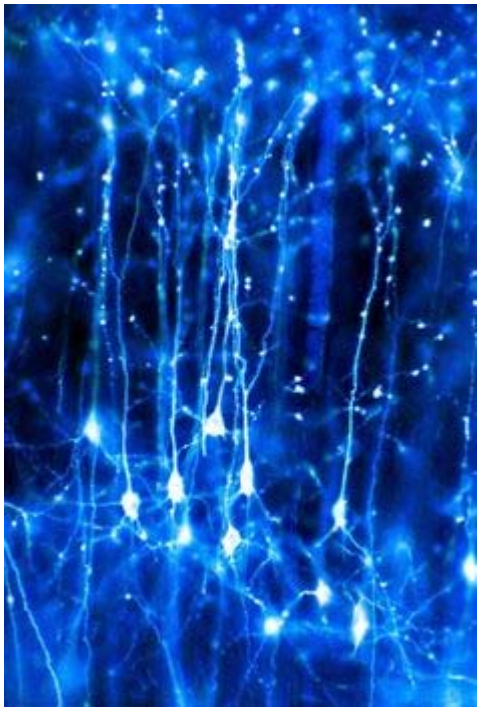
- Alpha-2 agonists
  - Description
    - Decreases norepinephrine (adrenaline) in the brain
    - Decreases arterial pressure
  - Mechanism of action
    - Selectively blocks the sympathetic nervous system
    - Decreases norepinephrine release in the brain
    - Decreases arterial pressure

Psychological Effects

- Clonidine
  - Formulations
    - Oral and transdermal (topical)
  - Characteristics
    - Sedative and anti-anxiety actions
    - Reinforces the pain-alleviating effects of morphine
    - Acts rapidly with blood pressure declines in 30-60 minutes after an oral dose, the maximum decrease occurring within 2-4 hours
  - Side effects, warnings, and precautions
    - Dry mouth, drowsiness, dizziness, constipation, and sedation

Psychological Effects

- Alpha-2 agonists commonly used in ketamine infusion therapy
  - Clonidine (Catapres)
  - Dexmedetomidine (Precedex)
  - Tizanidine (Zanaflex)



Psychological Effects

- Dexmedetomidine (Precedex)
  - Formulation
    - Intravenous
  - Characteristics
    - Among the most active in this medication class
    - Slow infusion
    - Sedatives/hypnotics (e.g. midazolam) and opioids can enhance the sedating effects of dexmedetomidine
    - Anti-anxiety properties
    - Analgesic (pain-reducing) characteristics

Psychological Effects

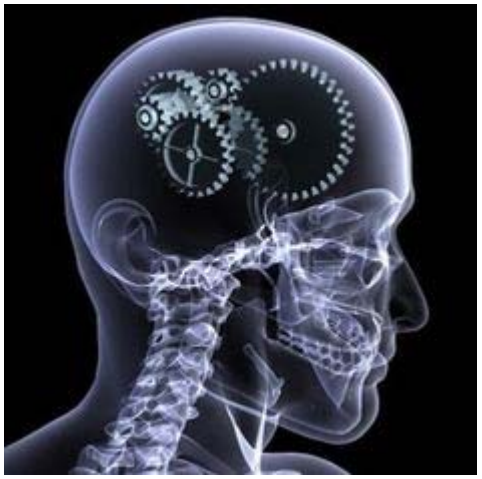
- Dexmedetomidine (Precedex)
  - Side effects, warnings, and precautions
    - Slow heart rate and cardiac arrest
    - Increased risk – Elderly, advanced heart block, dehydration, chronic high blood pressure (hypertension), and diabetes mellitus
    - Respiratory depression
    - Low blood pressure (hypotension)
    - Short-term high blood pressure (hypertension)

Psychological Effects

- Antipsychotics (neuroleptics)
  - Description
    - Antipsychotic medication used to treat schizophrenia
    - Particularly effective in managing hyperactivity, agitation, and mania
    - Possess anti-nausea properties
    - Tendency to provoke certain movement disorders (i.e. extrapyramidal effects)
  - Mechanism of action
    - Primarily blocks dopamine receptors
    - Secondarily, it blocks certain serotonin receptors

Psychological Effects

- Antipsychotics (neuroleptics) used in ketamine infusion therapy
  - Haloperidol (Haldol)
  - Aripiprazole (Abilify)



Psychological Effects

- Haloperidol (Haldol)
  - Formulations
    - Oral, intramuscular, and intravenous
  - Characteristics
    - Mechanism of action not clearly established
    - Indicated for the treatment of schizophrenia and Tourette's disorder
    - Associated with a particular movement disorder (i.e. tardive dyskinesia)
      - Potentially irreversible
      - Incidence increases as duration of treatment and cumulative exposure increases
      - Although uncommon, can develop after brief periods at low doses

Psychological Effects

- Haloperidol (Haldol)
  - Side effects, warnings, and precautions
    - Irregular heartbeat
    - Movement disorders (i.e. tardive dyskinesia)
    - Severe cardiovascular disease
      - Possibility of transient low blood pressure (hypotension)
      - Chest pain (angina pectoris)
    - May lower seizure threshold

Psychological Effects

- Aripiprazole (Abilify)
  - Formulations
    - Oral and sublingual
  - Characteristics
    - Mechanism of action is unclear
    - May work on specific dopamine and serotonin receptors

Psychological Effects

- Aripiprazole (Abilify)
  - Side effects, warnings, and precautions
    - Stroke in elderly people
    - Movement disorders (i.e. tardive dyskinesia)
    - Increased blood sugar
    - Lowers seizure threshold
    - Low blood pressure
    - Neuroleptic malignant syndrome (NMS)
      - Characterized by high fever, stiff muscles, confusion, sweating, and/or changes in heart rate and blood pressure

Psychological Effects

- Antihistamines
  - Description
    - Compounds that oppose the effects of histamine
    - Often used to treat allergies
    - Sedative effects
  - Mechanism of action
    - Antihistamine
    - Anticholenergic

Psychological Effects

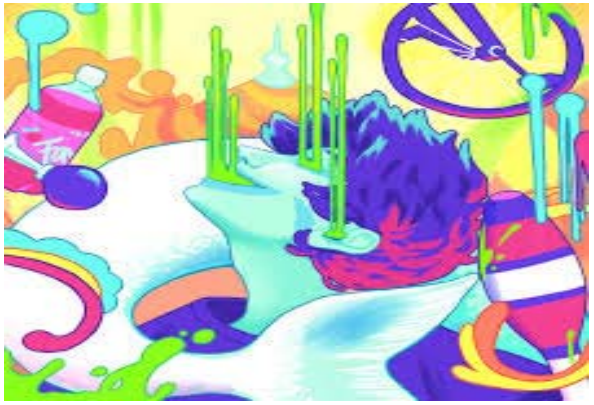
- Antihistamine used in ketamine infusion therapy
  - Diphenhydramine (Benadryl)

Psychological Effects

- Diphenhydramine (Benadryl)
  - Side effects, warnings and precautions
    - Generally safe
    - Can dose up to 400 mg
    - Dry mouth, nose, and throat
    - Drowsiness
    - Dizziness
    - Constipation
    - Stomach upset
    - Blurred vision

Euphoria

- Definition
  - A feeling or state of intense excitement and happiness
- Generally not problematic
- When uncomfortable, manage with similar medications used in treating psychological side effects



Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Description
  - Antiemetics are drugs that are effective in treating nausea and vomiting
  - Used to treat side effects of medications and motion sickness
  - Another class of medications is used to treat certain conditions of the stomach and intestines (increases muscle contractions in the upper digestive tract)

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Medications used to manage nausea, vomiting and dyspepsia (upset stomach) in ketamine infusion therapy
  - Ondansetron (Zofran)
  - Promethazine (Phenergan)
  - Metaclopramide (Reglan)

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Ondansetron (Zofran)
  - Formulations
    - Oral, sublingual, intramuscular, and intravenous
  - Mechanism of action
    - Blocks the action of serotonin, a natural substance that may cause nausea and vomiting

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Ondansetron (Zofran)
  - Side effects, warnings, and precautions
    - ECG changes (e.g. QT interval prolongation)
    - Serotonin syndrome
      - Mental status changes (e.g. agitation, hallucinations, delirium, and coma)
      - Problems with the autonomic nervous system (e.g. rapid heart rate, erratic blood pressure, dizziness, sweating, flushing, and fever)
      - Seizures
      - Neuromuscular symptoms (e.g. tremor, rigidity, overactive reflexes, and problems with coordination)
      - Gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhea)

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Ondansetron (Zofran)
  - Diarrhea
  - Headache
  - Fever
  - Lightheadedness/dizziness
  - Weakness
  - Tiredness/drowsiness
  - Constipation
  - Rash
  - Muscle Spasm

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Promethazine (Phenergan)
  - Formulations
    - Oral, rectal, intramuscular, and intravenous
  - Mechanism of action
    - Antipsychotic (phenothiazine) derivative
    - Antihistamine

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Promethazine (Phenergan)
  - Side effects, warnings, and precautions
    - Sedation
    - Respiratory depression
    - Lowers seizure threshold
    - Neuroleptic malignant syndrome (NMS)
      - Characterized by high fever, stiff muscles, confusion, sweating, and/or changes in heart rate and blood pressure

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Promethazine (Phenergan)
  - Side effects, warnings and precautions
    - Specific movement disorders (i.e. tardive dyskinesia and other extrapyramidal effects)
    - Neuroleptic malignant syndrome (NMS)
      - » Characterized by high fever, stiff muscles, confusion, sweating, and/or changes in heart rate and blood pressure
    - High blood pressure (hypertension)
    - Fluid retention
    - Lowers seizure threshold

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Metaclopramide (Reglan)
  - Formulations
    - Oral, sublingual, intramuscular, and intravenous
  - Mechanism of action
    - Blocks dopamine receptors
  - Warnings and precautions
    - Specific movement disorders (tardive dyskinesia and other extrapyramidal effects)
    - Neuroleptic malignant syndrome (NMS)
    - High blood pressure (hypertension)
    - Fluid retention
    - Lowers seizure threshold

Nausea, Vomiting, and Dyspepsia (Upset Stomach)

- Metaclopramide (Reglan)
  - Side effects, warnings, and precautions
  - Specific movement disorders (tardive dyskinesia and other extrapyramidal effects)
  - Neuroleptic malignant syndrome (NMS)
    - Characterized by high fever, stiff muscles, confusion, sweating, and/or changes in heart rate and blood pressure
  - High blood pressure (hypertension)
  - Fluid retention
  - Lowers seizure threshold

Hypertension (High Blood Pressure)

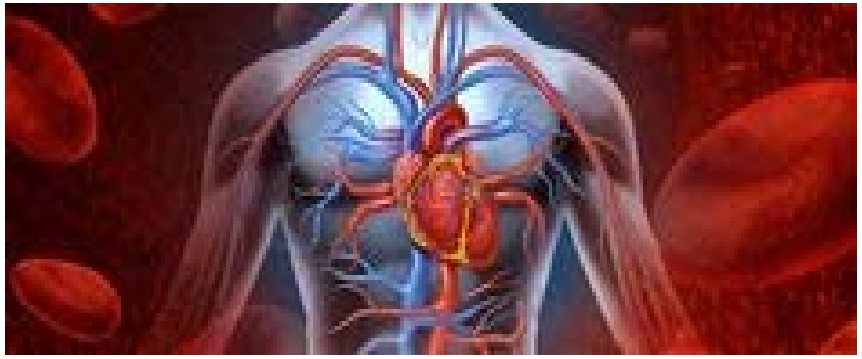
- Description
  - Not an uncommon side effect of ketamine infusion therapy
  - Medications include those specifically designed to lower blood pressure
  - High blood pressure in ketamine infusion therapy may be due to
    - Effects of ketamine
    - Anxiety and/or agitation
  - Other medications are helpful in managing high blood pressure by reducing anxiety and agitation

Hypertension (High Blood Pressure)

- Medications used to manage hypertension (high blood pressure) in ketamine infusion therapy
  - Clonidine (Catapres)
  - Labetalol
  - Dexmedetomidine (Precedex)
  - Benzodiazepines

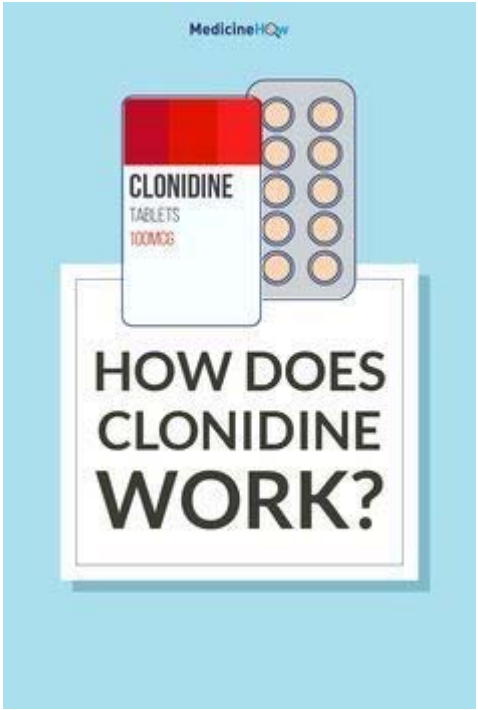
Hypertension (High Blood Pressure)

- Clonidine (Catapres)
  - Formulations
    - Oral and topical
  - Mechanism of action
    - Blocks the sympathetic nervous system



Hypertension (High Blood Pressure)

- Clonidine (Catapres)
  - Side effects, warnings, and precautions
    - Dry mouth
    - Tiredness
    - Weakness
    - Headache
    - Nervousness
    - Nausea and vomiting
    - Constipation
    - Hypotension (low blood pressure)
    - Slow heart rate



Hypertension (High Blood Pressure)

- Labetalol
  - Formulations
    - Oral and intravenous
  - Mechanism of action
    - Beta blocker

Hypertension (High Blood Pressure)

- Labetalol
  - Side effects, warnings, and precautions
    - Congestive heart failure
    - Irregular heart rate (i.e. arrhythmia)
    - Coronary artery disease/history of heart attack
    - Poorly-controlled diabetes mellitus
    - Hypotension (low blood pressure)

Hypertension (High Blood Pressure)

- Dexmedetomidine (Precedex)
  - Formulation
    - Intravenous
  - Mechanism of action
    - Stimulates the alpha-2 adrenergic receptors

Hypertension (High Blood Pressure)

- Dexmedetomidine (Precedex)
  - Side effects, warnings, and precautions
    - No contraindications
    - Slow heart rate
    - Hypotension (low blood pressure)
    - Cardiac arrest
    - Caution in patients with advanced heart block
    - Transient hypertension (high blood pressure)

Hypertension (High Blood Pressure)

- Benzodiazepines
  - Formulations

    Oral, sublingual, intramuscular, and intravenous
  - Mechanism of action
    - Enhances the inhibitory actions of the neurotransmitter GABA

Hypertension (High Blood Pressure)

- Benzodiazepines
  - Side effects, warnings, and precautions
    - Drowsiness, dizziness, tiredness, blurred vision, and respiratory depression

Tachycardia (Fast Heart Rate)

- Description
  - Similar to managing high blood pressure in ketamine infusion therapy, medications used to manage tachycardia (fast heart rate) in ketamine infusion therapy include
    - Medications indicated to lower heart rate
    - Medications that may lower heart rate by reducing anxiety and agitation

Tachycardia (Fast Heart Rate)

- Medications used to manage tachycardia (fast heart rate) in ketamine infusion therapy
  - Clonidine (Catapres)
  - Labetalol
  - Dexmedetomidine (Precedex)
  - Benzodiazepines

Tachycardia (Fast Heart Rate)

- Clonidine (Catapres)
  - Formulations
    - Oral and topical
  - Mechanism of action
    - Blocks the sympathetic nervous system

Tachycardia (Fast Heat Rate)

- Clonidine (Catapres)
  - Side effects, warnings, and precautions
  - Dry mouth
  - Tiredness
  - Weakness
  - Headache
  - Nervousness
  - Nausea and vomiting
  - Constipation
  - Hypotension (low blood pressure)
  - Slow heart rate

Tachycardia (Fast Heart Rate)

- Labetolol
  - Formulations
    - Oral and intravenous
  - Mechanism of action
    - Beta blocker

Tachycardia (Fast Heart Rate)

- Labetalol
  - Side effects, warnings, and precautions
    - Congestive heart failure
    - Irregular heart rate (i.e. arrhythmia)
    - Coronary artery disease/history of heart attack
    - Poorly-controlled diabetes mellitus
    - Hypotension (low blood pressure)

Tachycardia (Fast Heart Rate)

- Dexmedetomidine (Precedex)
  - Formulation
    - Intravenous
  - Mechanism of action
    - Stimulates the alpha-2 adrenergic receptors

Tachycardia (Fast Heart Rate)

- Dexmedetomidine (Precedex)
  - Side effects, warnings, and precautions
    - Slow heart rate and cardiac arrest
    - Increased risk – Elderly, advanced heart block, dehydration, chronic high blood pressure (hypertension), and diabetes mellitus
    - Respiratory depression
    - Low blood pressure (hypotension)
    - Short-term high blood pressure (hypertension)

Tachycardia (Fast Heart Rate)

- Benzodiazepines
  - Formulations
    - Oral, sublingual, intramuscular, and intravenous
  - Mechanism of action
    - Enhances the inhibitory actions of the neurotransmitter GABA

Tachycardia (Fast Heart Rate)

- Benzodiazepines
  - Side effects, warnings, and precautions
    - Drowsiness, dizziness, tiredness, blurred vision, and respiratory depression

Headache

- Description
  - Not an uncommon side effect of ketamine infusion therapy
  - May persist after completion of ketamine infusion therapy (not uncommon the evening after undergoing KIT)
  - Characteristics
    - Involves the entire head
    - Dissimilar to migraine headache
    - Responds well to Fioricet (butalbital 50 mg/acetaminophen 300 vs 325 mg/caffeine 40 mg)

Headache

- Medication used to manage headache in ketamine infusion therapy
  - Fioricet (butalbital 50 mg/ acetaminophen 300 mg vs 325 mg/caffeine 40 mg)

Headache

- Fioricet (butalbital 50 mg/acetaminophen 300 mg vs 325 mg/caffeine 40 mg)
  - Formulation
    - Oral
  - Mechanism of action
    - Several mechanisms of action as this medication consists of combination of 3 distinct medications (multi-modal)
      - Barbiturate
      - Pain-reliever (analgesic)
      - Constricts blood vessel in the brain

Headache

- Fioricet
  - Constituents and mechanisms of action
    - Butalbital
      - Barbiturate
      - Nonselective depressant effect on the central nervous system
      - Sedative and hypnotic effects
    - Acetaminophen
      - Acts primarily in the central nervous system
      - Alleviates pain
    - Caffeine
      - Constricts blood vessels in the brain
      - Counteracts the sedative effects of butalbital

Headache

- Fioricet (butalbital 50 mg/acetaminophen 300 mg vs 325 mg/caffeine 40 mg)
  - Side effects, warnings, and precautions
    - Extended use is not recommended as it is habit-forming
    - Precautions for
      - Elderly
      - Debilitated
      - Severe kidney or liver disease
    - May cause increased central nervous system depression

Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Low-level evidence and often anecdotal
- Medications used to improve pain relief in ketamine infusion therapy
  - Dextromethorphan
  - Lidocaine
  - Magnesium
  - Ketorolac (Toradol)

Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Dextromethorphan
  - Formulation
    - Oral

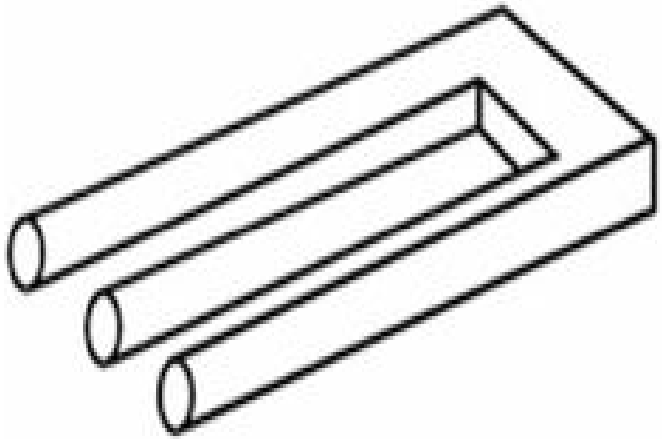
  Mechanism of action
    - Binds to the NMDA receptor (implicated in reducing pain)
  - May cause hallucinations, confusion, agitation, muscle twitching, overactive reflexes, shivering, and rapid heart rate

Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Dextromethorphan
  - Formulation
    - Oral
  - Mechanism of action
    - Binds to the NMDA receptor (implicated in reducing pain)

Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Dextromethorphan
  - Side effects, warnings and precautions
    - Hallucinations
    - Confusion
    - Agitation
    - Muscle twitching
    - Overactive reflexes
    - Shivering
    - Rapid heart rate

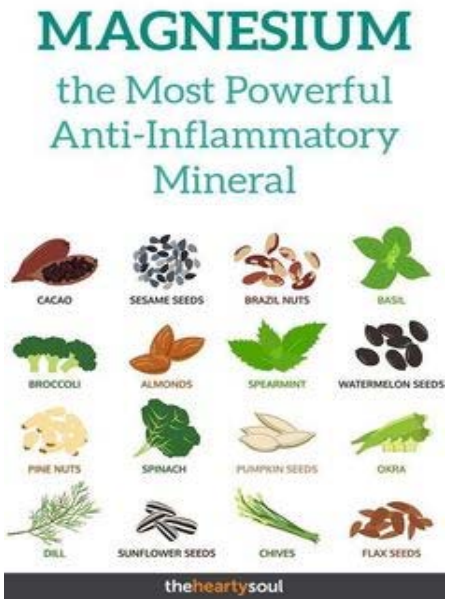


Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Magnesium
  - Formulation
    - Oral and intravenous
  - Mechanism of action
    - Binds to the NMDA receptor and may enhance the pain-relieving effects of ketamine
  - Side effects
    - May include heart disturbances, breathing difficulties, confusion, weakness, flushing, sweating, and low blood pressure

Miscellaneous Medication Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Magnesium
  - Side effects, warnings, and precautions
    - Heart disturbances
    - Breathing difficulties
    - Confusion
    - Weakness
    - Flushing
    - Sweating
    - Low blood pressure



Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Ketorolac (Toradol)
  - Formulation
    - Topical, oral, intramuscular, and intravenous
  - Mechanism of action
    - Non-steroidal anti-inflammatory drug

Miscellaneous Medications Purported to Improve Pain Relief in Ketamine Infusion Therapy

- Ketorolac (Toradol)
  - Side effects, warnings, and contraindications
    - History of peptic ulcer disease or gastrointestinal bleeding
    - Contraindicated in the setting of coronary artery bypass graft surgery including previous heart attack
    - Warning with heart failure or edema
    - Advanced kidney and/or liver disease
    - Hemorrhage
    - Consuming aspirin or other non-steroidal anti-inflammatory drugs
    - New high blood pressure or worsening of previous high blood pressure
    - Not to consume 5 days

The Big Picture

- Ketamine infusion therapy remains a promising treatment in managing CRPS symptoms
- In addition to non-pharmacologic considerations necessary to enhance ketamine infusion therapy outcomes, optimizing adjuvant medication therapy in ketamine infusion therapy is crucial in improving pain relief and limiting side effects
- There is hope!

The Bottom Line

- Everyone is unique when it comes to finding the right infusion “cocktail”

- Interview your ketamine infusion center first and see what they are or are not willing to offer

The Bottom Line

- Be patient – Sometimes it a takes a few infusions to find out what works best for you!
- Make sure your infusion center is familiar with CRPS and uses a CRPS protocol and not a depression protocol. Don’t waste your time or money!

The Bottom Line

Nothing is impossible.
The word itself *says*, "I'm possible"!

– Audrey Hepburn


Thank you!