Medications Used During Ketamine Infusion Therapy Designed to Improve Outcomes in Patients with CRPS
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“CHRONIC PAIN IS NO JOKE. AND IT’S EVERY DAY WAKING UP NOT KNOWING HOW YOU’RE GOING TO FEEL.”

— LADY GAGA
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
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
“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)
• 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
• 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
• **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)
• 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

![HALOPERIDOL Tablets 5mg](image)
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
• 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)

- Promethazinе (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 Heart 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)
• Medication used to manage headache in ketamine infusion therapy
  – Fioricet (butalbital 50 mg/ acetaminophen 300 mg vs 325 mg/caffeine 40 mg)
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)
– 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
– Dextromethorphan
  • Formulation
    – Oral
  • Mechanism of action
    – Binds to the NMDA receptor (implicated in reducing pain)
• 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
• 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 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!
Nothing is impossible.
The word itself says, “I’m possible”!

– Audrey Hepburn
Thank you!