PainWeek®

You're Using WHAT for Pain Management? Psilocybin, Ecstasy, and Ketamine!

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Disclosure

Learning Objectives

- List five potential therapeutic uses for psilocybin
- Explain the pros and cons of MDMA (ecstasy) in the management of total pain
- Describe the mechanism of action, efficacy, adverse effects and role in therapy of ketamine

Psilocybin: History

- Classic psychedelics have been used as sacraments in religious and/or healing contexts since ancient times.
- Attracted great interest within the psychiatry and neuroscience fields in the 1950s and 1960s.
- Promising results reported for both psychological distress at end-of-life and addiction.
- Research came to a halt in the 1970s.

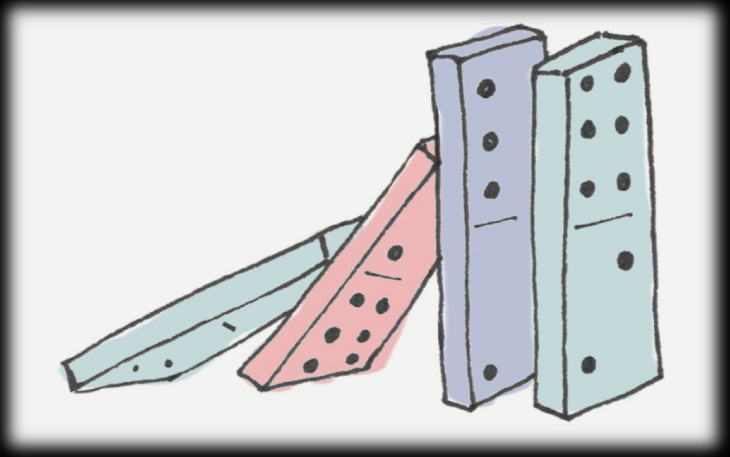
Johnson MW, et al. Pharmacol Therapeut 2019;197:83:102.

Psilocybin: The Science

- Naturally occurring pro-drug that is produced by >100 species of mushrooms
- Once ingested, psilocybin is rapidly metabolized to psilocin
  - Psilocin – agonist at $5HT_{3\text{-}2A}$ receptors in the brain
- Experts think this is what triggers “neuronal avalanching”

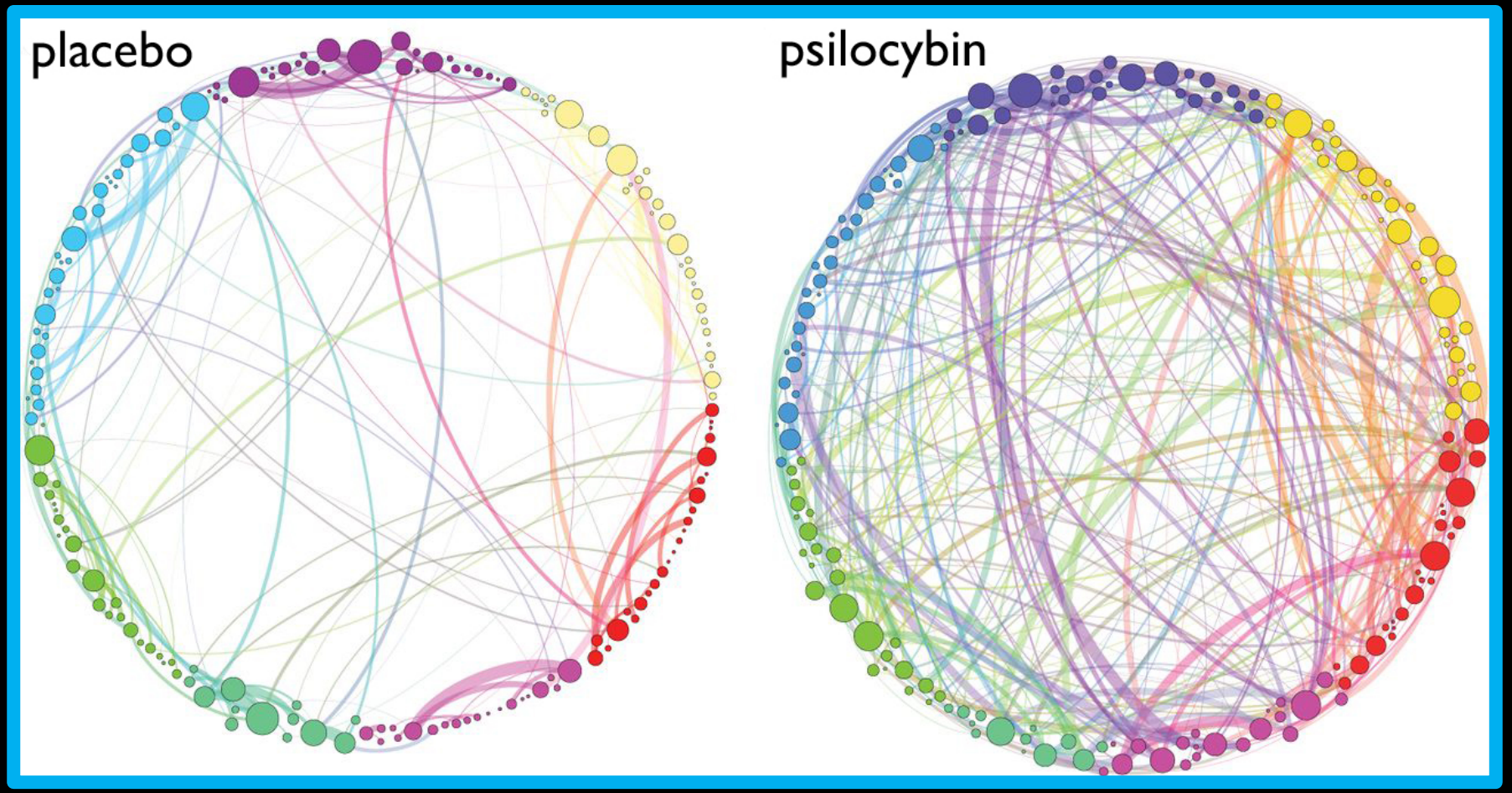
Psilocybin: The Science (cont'd)

- **Neuronal avalanching**
  - Increased activity in the visual cortex → changes in perception
  - Decreased blood flow to regions of the brain collectively known as the "default mode network" → unconstrained cognition and loss of ego
  - Increased connectivity among different regions of the brain, resulting in synchronization



Nichols DE, et al. Clin Pharmacol Ther 2017;101(2):209-219.

Brain on Psilocybin



https://www.telegraph.co.uk/news/science/science-news/11207979/What-your-brain-looks-like-on-magic-mushrooms.html

Psilocybin: Administration

Psilocybin: Potential Therapeutic Uses

- Cancer-related psychological distress
- Treatment-resistant depression
- Addiction
  - Smoking cessation
  - Alcohol dependence
- Obsessive compulsive disorder
- Cluster headaches

Johnson MW, et al. Neurotherapeutics 2017;14:734-740.

Psilocybin: Cancer-Related Psychological Distress

Objective	• To explore the safety and efficacy of psilocybin in patients with advanced-stage cancer and reactive anxiety
Design	• Randomized, double-blind, placebo-controlled crossover trial
Patient Population	• 12 patients with advanced-stage cancer who were diagnosed with one of multiple possible DSM-IV anxiety-related disorders
Intervention	• Moderate-dose psilocybin (0.2 mg/kg) vs. Niacin (active control) in separate sessions ("several weeks apart")
Results	• At 1- and 3-month follow-ups, anxiety outcomes significantly reduced • At 6-month follow-up, depression outcomes significantly reduced • No clinically significant adverse events

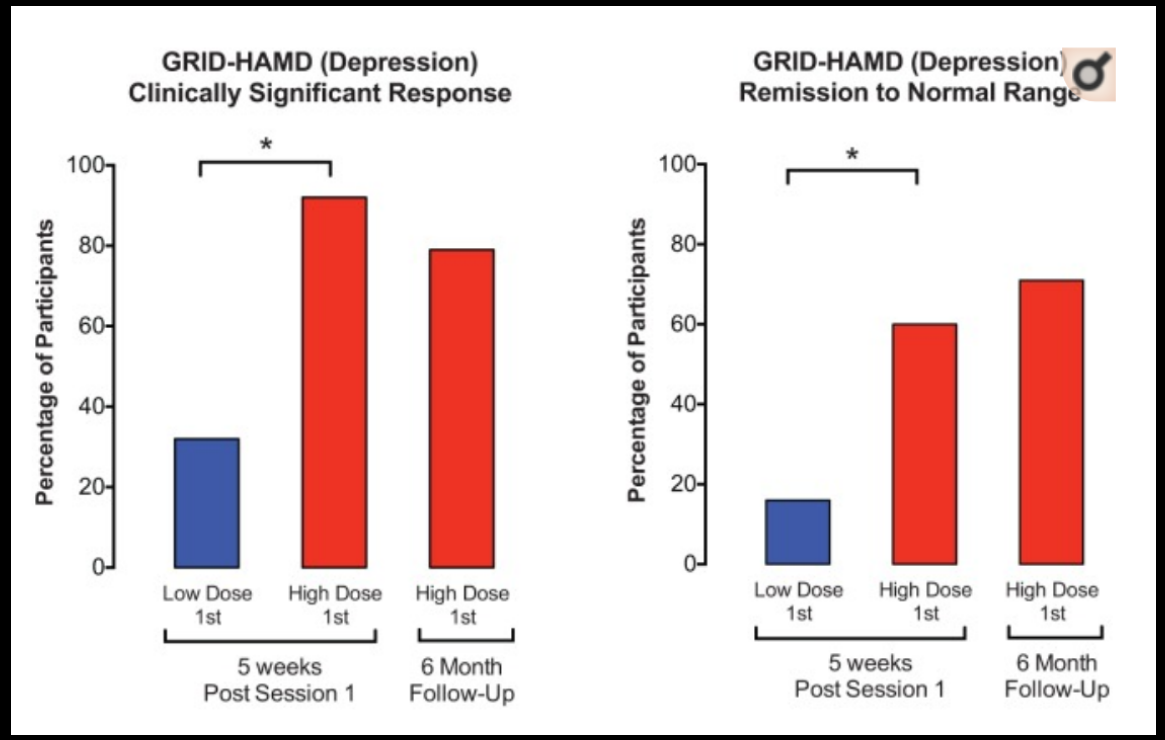
Grob CS, et al. Arch Gen Psychiatry 2011;68:71-78.

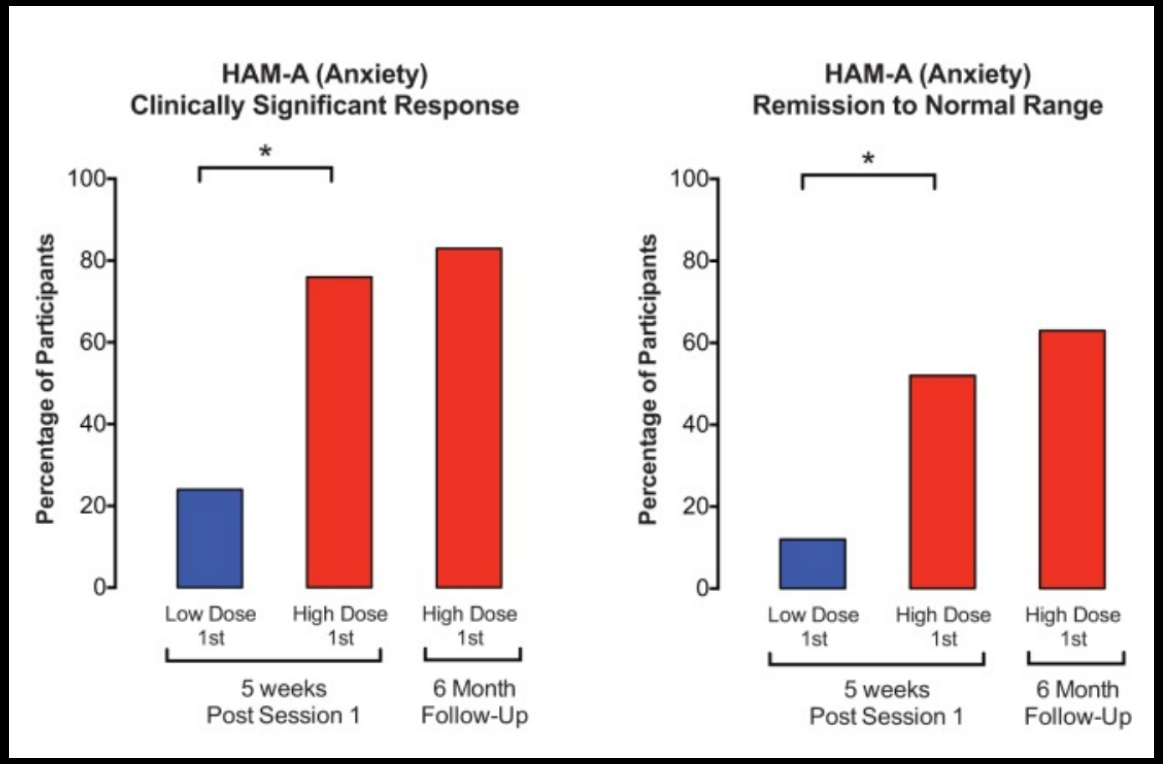
Psilocybin: Cancer-Related Psychological Distress

Objective	• To evaluate the efficacy of psilocybin for treatment of depressed mood and anxiety in psychologically distressed cancer patients
Design	• Randomized, double-blind, crossover trial
Patient Population	• 51 patients who were diagnosed with one of multiple possible DSM-IV mood or anxiety-related disorders in relation to a life-threatening cancer diagnosis
Intervention	• High dose (0.31 or 0.43 mg/kg, 22 mg/70 kg) vs. very low dose (0.014 or 0.043 mg/kg, 1-3 mg/70 kg) of psilocybin administered 5 weeks apart
Results	• High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety • At 6-month follow-up, 80% of participants continued to show clinically significant decreases in depressed mood and anxiety; 60% showed remission • No serious adverse events reported

Griffiths RR, et al. Psychopharmacol 2016;30:1181-1197.

Psilocybin: Cancer-Related Psychological Distress





Griffiths RR, et al. Psychopharmacol 2016;30:1181-1197.

Psilocybin: Cancer-Related Psychological Distress

Objective	• To evaluate the role of psilocybin in treating cancer-related anxiety and depression
Design	• Randomized, double-blind, crossover trial
Patient Population	• 29 patients with cancer diagnosed with one of several DSM-IV anxiety-related disorders
Intervention	• High-dose psilocybin (0.3 mg/kg, ~21 mg/70 kg) vs. niacin (active control) administered 7 weeks apart, both in conjunction with psychotherapy
Results	• Prior to the crossover, psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life • At 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects, sustained benefits in existential distress and quality of life, and improved attitudes towards death

Ross S, et al. Psychopharmacol 2016;30:1165-1180.

Psilocybin: Treatment Resistant Depression

Objective	• To investigate the feasibility, safety, and efficacy of psilocybin in patients with unipolar treatment-resistant depression
Design	• Open-label feasibility study
Patient Population	• 12 patients with moderate-to-severe, unipolar, treatment-resistant major depression
Intervention	• Two oral doses of psilocybin (10 mg and 25 mg) administered 7 days apart in a supportive setting
Results	• Mean self-rated intensity (on a 0–1 scale) was 0.51 (SD 0.36) for the low-dose session and 0.75 (SD 0.27) for the high-dose session. • Psilocybin was well tolerated by all patients; no serious adverse events occurred. Adverse reactions included transient anxiety during drug onset (all patients), transient confusion or thought disorder (9 patients), mild and transient nausea (4 patients), and transient headache (4 patients). • Relative to baseline, depressive symptoms were markedly reduced 1 week and 3 months after high-dose treatment. • Marked and sustained improvements in anxiety and anhedonia were noted.

Carhart-Harris RL, et al. Lancet Psychiatry 2016;3:619-627.

Psilocybin: Smoking Cessation

Objective	• To determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment
Design	• Open-label pilot study
Patient Population	• 15 psychiatrically-healthy nicotine-dependent smokers
Intervention	• Moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin administered within a structured 15-week smoking cessation treatment protocol
Results	• Biomarkers assessing smoking status, and self-report measures of smoking behavior demonstrated that 12 of 15 participants (80%) showed abstinence at 6-month follow-up. • The observed smoking cessation rate substantially exceeds rates commonly reported for other behavioral and/or pharmacological therapies (typically <35%)

Johnson MW, et al. J Psychopharmacol 2014;28:983-992.

Psilocybin: Other Therapeutic Uses

- **Cluster Headaches**
  - Case series of 53 self-medicating patients suggested that psilocybin, in addition to LSD, may be effective in terminating or preventing the regular occurrence of cluster headaches
  - Efficacy reported with psilocybin/LSD doses that do not result in noticeable psychoactive effects
- **Obsessive Compulsive Disorder**
  - Pilot study in 9 participants examined the effect of 4 different doses of oral psilocybin, administered 1 week apart. All participants showed substantial symptom reduction during at least one session

Sewell RA, et al. Neurology 2006;55:1920-1922.
Moreno FA, et al. J Clin Psychiatry 2006;67:1735-1740.

Psilocybin: Safety

- The four S's are essential
  - **Screening** – Those with cognitive and emotional conditions associated with disorganized or diminished ego strength (e.g., borderline personality disorder or schizophrenic tendencies) are not good candidates
  - **Supervision** – Important for ensuring safety and helping guide patients through their experiences to optimize the drug's potential
  - **Set and Setting** – Controlled settings with elements of soft light, art, and appropriate music or nature and gentle, compassionate people

Byock I. J Palliat Med 2018;21(4):417-421.

Psilocybin: Regulatory Considerations

- Schedule I Controlled Substance
- Some states have campaigned to decriminalize psilocybin
  - 2019: Denver became the 1st US city to decriminalize psychedelic mushrooms

Psilocybin

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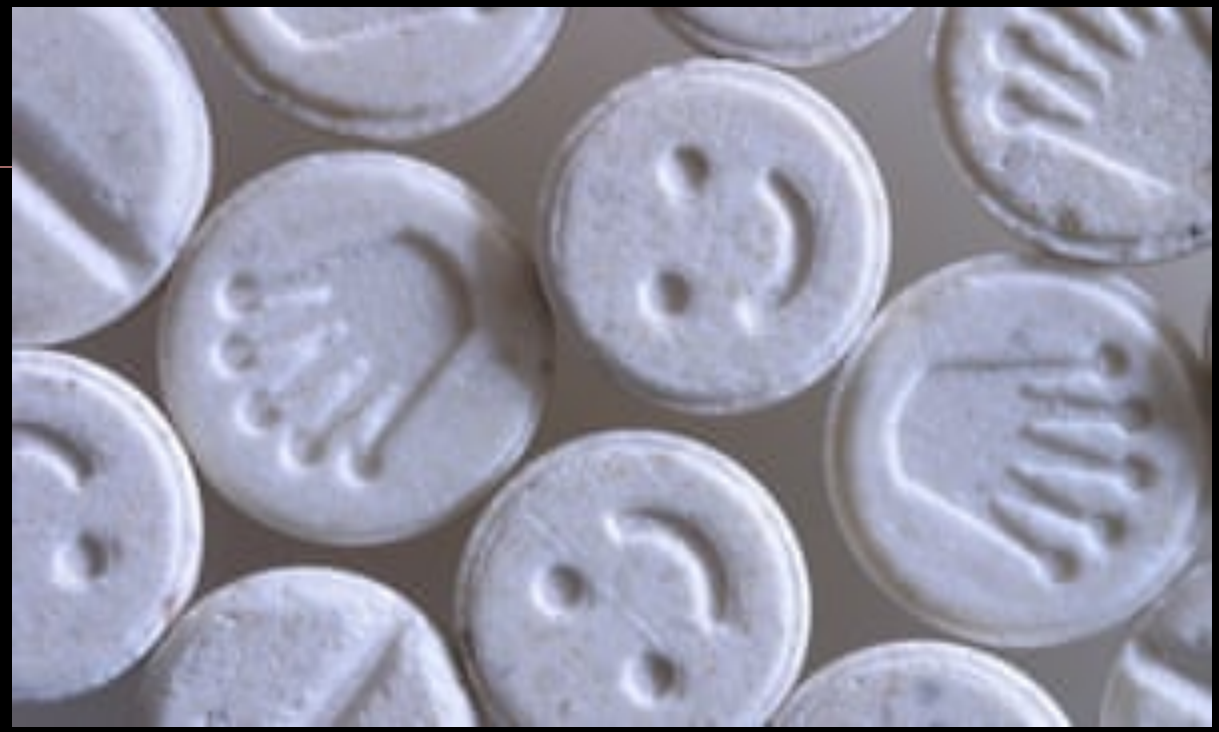
3, 4-methylenedioxymethamphetamine

MDMA, Ecstasy, Molly



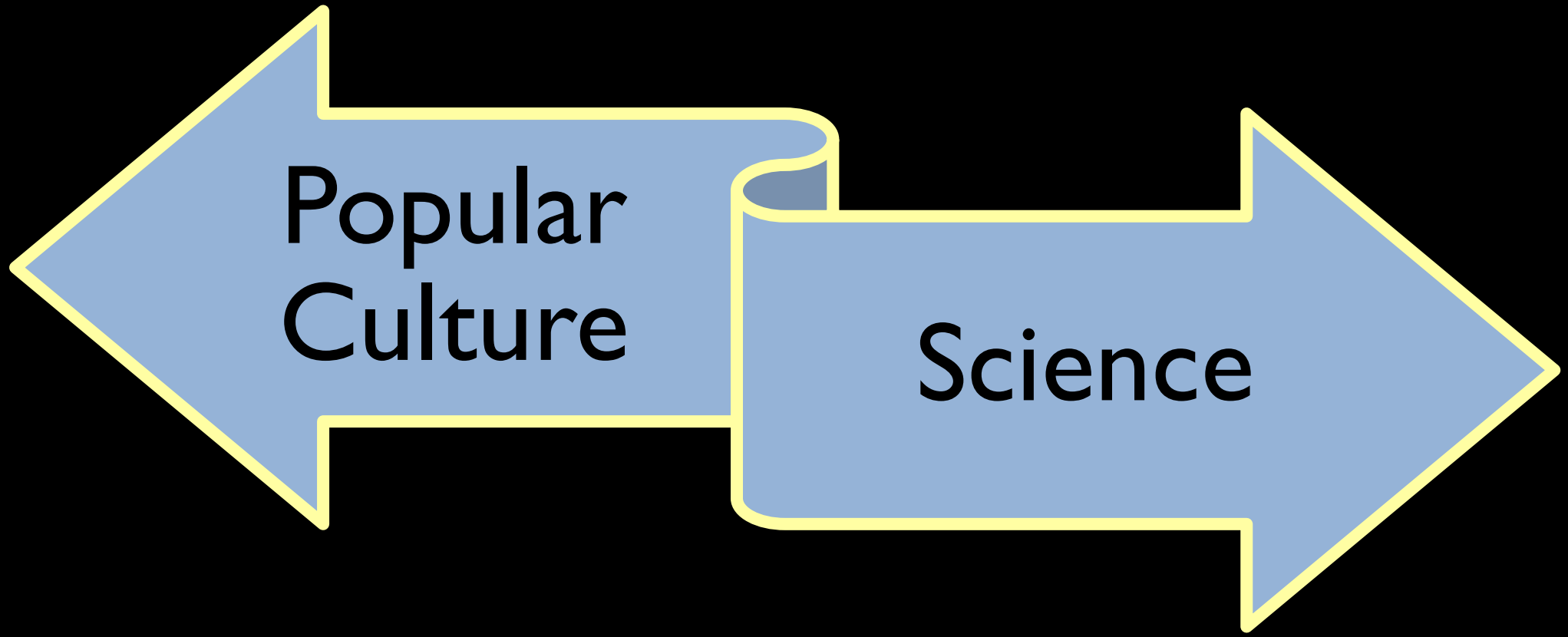
Empathy, love, tolerance….

A kinder, gentler LSD

MDMA

- Not a “classic” psychedelic drug
- Known as an “entactogen”
- MDMA products a more gentle and easily tolerated state compared to LSD
- It is shorter-acting, which makes it more clinically manageable, it enhances feelings of empathy and bonding, and allows users to access and process memories of emotional trauma

Who owns the psychedelics?



4 Conditions MDMA May Help

Total Pain – Trauma – PTSD Sufferers

- There is no single drug that gets to the root cause of trauma
  - Antidepressants, hypnotics, mood stabilizers, antipsychotics
- Multiple psychotherapies are only partially effective
  - Cognitive behavioral therapy, dialectical behavioral therapy, eye-movement and desensitization reprocessing

How does MDMA psychotherapy work??

Receptors or Brain Region Involved	MDMA Effects
Serotonin	• Reduces depression and anxiety • Stimulated alterations in the perceptions of meaning
Dopamine and norepinephrine	• Raises levels of arousal
Alpha-2- adrenoreceptors	• Increases relaxation
Hormonal effects	• Improves fear extinction learning • Increases emotional attachment and feelings of trust and empathy • More likely to use words relating to friendship, and intimacy • Reduced social exclusion phenomena
Regional brain changes	• Improved detection of happy faces and reduced detection of negative faces • Reduced subjective fear responses on recall of negative memories

Clinical Trials

- Uncontrolled case studies described beneficial use
  - Before banned in the mid-1980's
  - Between 1988 and 1993 by the *Swiss Medical Society of Psycholytic Therapy*
- Multidisciplinary Association for Psychedelic Studies (MAPS)
  - Amassed positive data from Phase 2 studies in the US, Switzerland, Israel and Canada for treatment-resistant PTSD
  - Planning Phase 3 studies in US and Europe

Studies with MDMA

- 2010 – 22 patients with treatment-resistant PTSD
  - Inactive placebo or two or three session of MDMA
    - 125 mg followed by 62.5 mg booster two hours later
  - At 2- and 12-month follow-up, 83% of experimental group no longer met criteria for PTSD vs. 25% of placebo grouop
  - No serious drug-related adverse effects
  - No adverse neurocognitive effects
  - Remission maintained from PTSD for up to 6 years with no further doses of MDMA

Mithoefer et al. J Psychopharmacol 2010;25:439-452.

Studies with MDMA

- 2013 – MDMA psychotherapy for treatment-resistant PTSD
  - Results showed statistically significant improvement
- Phase 2 trials
  - 2018 – Colorado – dose-response model
    - 100 and 125 mg vs. 40 mg; showed significance at 12 months
    - No serious adverse effects
  - Several other Phase 2 trials completed
- FDA and EMA has authorized Phase 3 trials (ongoing)

Sessa et al. Frontiers in Psychiatry 2019;10, article 138.

Studies with MDMA

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Adverse Effects with MDMA

- Clinical trials vs. recreational use
- Recreational ecstasy frequently involves:
  - Impure samples
  - Taking multiple other drugs
  - Paying little attention to the physiological aspects of the drug experience
- Acutely – transient neurocognitive effects (verbal and spatial memory deficits, slow processing speeds and executive functioning impairments)

Adverse Effects with MDMA

- Approximately 750,000 people use MDMA every weekend in the UK!
- After removing confounding factors (concomitant drugs) – only 3 deaths/year attributed to MDMA
- No neurotoxicity when used in isolation
- No lasting neurocognitive impairment

Use of MDMA-Assisted Psychotherapy

- Typically delivered by a male-female co-therapist dyadic pair
  - Some research has combined with cognitive behavioral therapy for couples in which one person had PTSD, used some co-therapy teams with two female therapists
- Drug-assisted sessions are non-directive; encouraging the patient to go with the experience

Use of MDMA-Assisted Psychotherapy

- MDMA catalyzes the patient's innate healing ability
- The therapists create a sense of safety and communicate trust in their patient's ability to explore their issues
- Eyeshades may be used
- Music may be played through headphones
- BP and temperature measure common throughout session
- Non-drug therapeutic sessions before and after MDMA psychotherapy are essential

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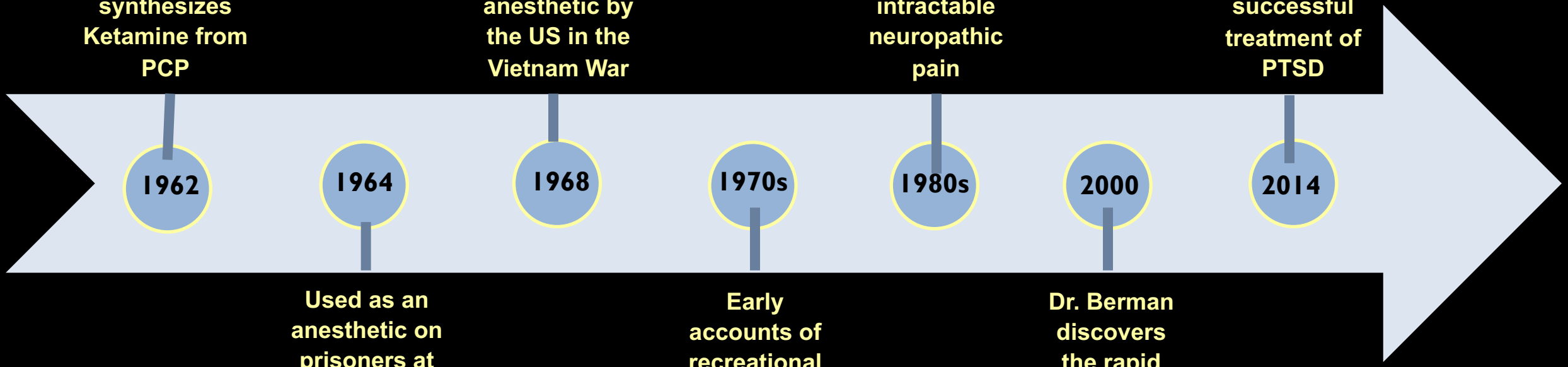
Ketamine

Goals

- Describe the pharmacokinetics and pharmacodynamics of ketamine.
- Assess a patient's pain history and previous treatments to determine appropriateness for ketamine initiation.
- Identify and treat ketamine related side effects.

Ketamine History

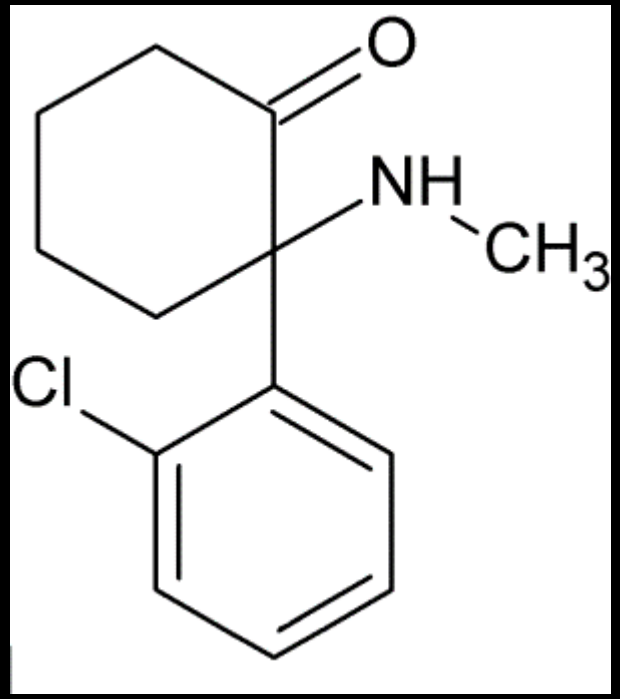


Mechanism of Action

- Ketamine is an NMDA Antagonist
  - Blocks NMDA receptors on neurons
  - Result:
    - Ketamine at high doses: state of dissociative anesthesia
    - Ketamine at low doses: sensory loss, analgesia, amnesia
  - Weak mu-opioid receptor agonist=potentiates the effect of opioids
  - Potentiates the effects of GABA

Pharmacology

- Plasma half-life
  - –Ketamine = 1-3 hours
  - –Norketamine (metabolite) = 12 hours
- Time to C_{max}
  - –PO 30-60 minutes
  - –SC 15-30 minutes
  - –IV < 15 minutes



Pharmacokinetics

- Bioavailability
  - ~25% SL
  - ~20% PO
  - 93% IM
  - 100% IV
  - 100% SQ
- Excretion
  - Urine

- Metabolism
  - 80% first pass
  - Cytochrome P450 mediated N-demethylation to norketamine by CYP3A & CYP2B6
- Metabolite
  - Norketamine
    - 1/3 more potent as an anesthetic
    - Equipotent for analgesia
    - Long half-life (12 hours)

Pharmacology

- Metabolism
  - –Converted to norketamine (NK) via hepatic metabolism
    - Provides equipotent analgesic effects
    - Peak analgesic effect of ketamine is associated with NK
- Water and lipid soluble
  - –Can be given via multiple routes

Pharmacology

- Wide therapeutic range
  - –Makes overdose difficult
  - –LD50 in animals is ~ 100 times the average IV dose for humans
    - Average IV dose humans: 5-50mg

Case #1

- 26 year old s/p trauma involving a pane of glass. Crushed pelvis and bilateral femurs.
- Fentanyl PCA using approximately 200mcg/hr for pain control, extremely sedated and potentially developing neurotoxicity. Does not want to be intubated.
- The primary team is supremely uncomfortable with the opioid requirements

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When should I think of it?

Nonmalignant Pain

Malignant Pain

Neuropathic Pain

Mucositis

Ketamine

Ischemic Pain

Dressing Changes

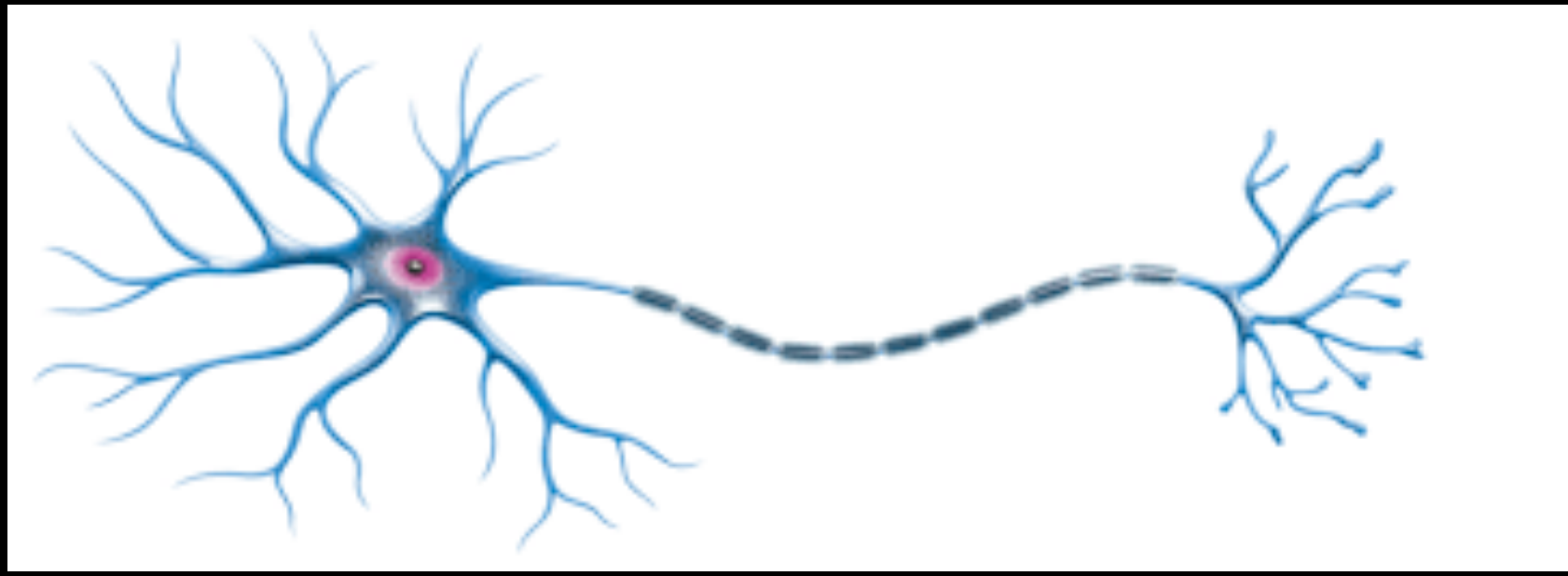
Post-Herpetic Neuralgia

Depression

Opioid Induced Neurotoxicity

Symptoms of Neurotoxicity

- Allodynia
- Delirium
- Hallucinations
- Hyperalgesia
- Myoclonus
- Seizure



Hyperalgesia

Chronic use of opioids = chronic hyper-stimulation

Pain signaling pathways altered

Ketamine

- Delays desensitization
- Improves the re-sensitization of the mu receptor
- Prevents opioid tolerance and hyperalgesia

Neuropathic Pain

World Health Organization (WHO)

- " Agents, which block the activity of NMDA receptors, are helpful to treat poorly responsive pain syndromes, especially, neuropathic pain "
- "The addition of ketamine to opioid treatment has been shown to be beneficial in chronic pain"

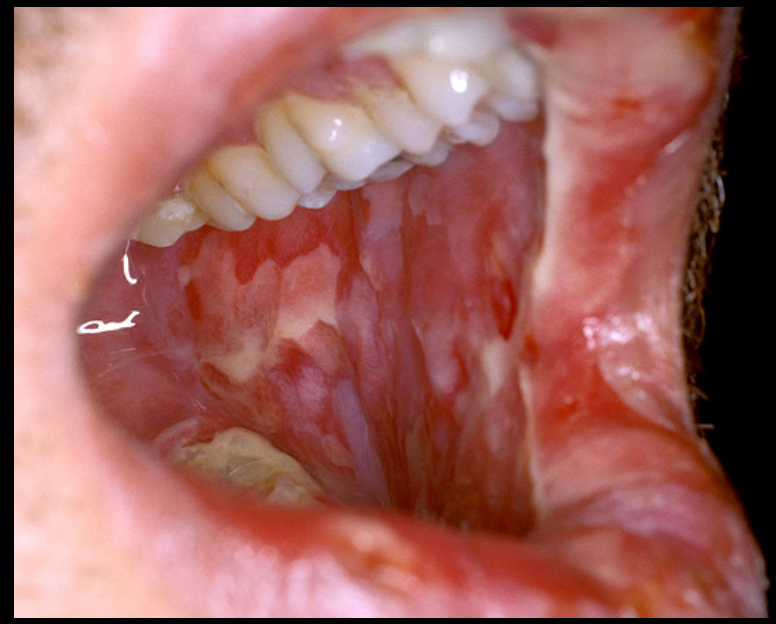
Cancer-related Pain

Ketamine can be used

- As an adjuvant with opioids
- Potentiation of current pain regimen when added
- Opioid sparing effect
- Anti-inflammatory effects (TNF-alpha, IL-1)

Topical

- Mucositis/oral tumors
- Swish and swallow
  - Ketamine 4mg/ml in artificial saliva



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How do I use it?

Patient Selection

- Relative contraindications
  - –Severe cardiovascular disease
  - –Previous psychotic illness (schizophrenia, PTSD)
  - –Both due to side effect profile
- Patient assessment is important

Side Effects

- Increased BP, intra-ocular pressure
- Psychomimetic
- Delirium
- Vivid dreams
- Hallucinations
- Dizziness

Dosing Examples

Route	Initial Dose	Max Initial Dose	Titration
PO/SL	2.5-5 mg Q6-8h	10-25 mg Q6-8h	50-100% of initial dose Q24h
SQ	2.5-5 mg Q6-8h	10-25 mg Q6-8h	Assess pain 30-45 min after dose completion. If no significant decrease in pain, increase dose by 25-35%
IV	2.5-10mg Q6-8h	15-30mg Q6h	Assess pain 15 min after dose completion. If no significant decrease in pain, increase dose by 25-35%
SQCI	0.3-0.6 mg/hr	1.25-4 mg/hr	Increase by 50-100 mg/day
IVCI	0.3-1.5 mg/hr	100 mg/24hr	Increase by 50-100 mg/day

Dosing

Pain relief at doses < 200 mg/day

Max recommended daily dose = 500-700mg/day

Treatment Duration

- Withdraw ketamine after:
  - Analgesia has been obtained
  - Opioid dose have been weaned to an acceptable level

- The benefit from a short course can last several days to weeks
  - Treatment can be repeated if necessary

Withdrawal

- Ketamine withdrawal is not expected in short-term use
  - If use >10 days, taper the dose over minimum 24-48 hours
  - Maximum de-escalation with chronic use:
    - 15-20 mg (5 mg per dose) every 3 days
  - Whole body hyperalgesia and allodynia have occurred with abrupt discontinuation of courses ≥ 3 weeks
- Development of tolerance is possible

What does the literature say?

Efficacy

- Courade and colleagues
  - French multi-center study of 38 pts
  - 2-14 yo
  - Evaluated pain scores for 48 hours after ketamine administration as an adjuvant to their current regimen

- Results
  - Decrease in mean pain scores from 6.7 on day 1 to 4.3 on day 3

Efficacy

- Marchetti and Colleagues
  - 5 yr retrospective study
  - 51 patients
  - Pain scores evaluated before treatment and immediately after ketamine administration
- Results
  - 40 +/- 33% decrease in pain and provided opioid sparing effect

Summary

- Effective for pain management at lower doses than required for anesthesia
- Can use lower doses via oral route
- Mix with cranberry juice, lemonade or soda to mask taste
- Helpful in cases of suspected neurotoxicity
- Potential to decrease opioid utilization
- Effective for topical pain relief

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