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| **Study**  **(Ref.  #)** | **Population** | **Study Design** | **Intervention** | **Outcomes and Endpoints (primary and secondary)** | **Results** |
| **Krupitsky et al. 2002** | * Adults with OUD (DSM-IV or ICD-10 criteria of opioid dependence for at least one year) aged 18-30 and abstinent from all “substances of abuse” for 2+ weeks      * *n* = 70 * Age, mean 22.3 * 78.57% male) * Race not reported | * Randomized control trial  (parallel group, double-blind, placebo-controlled)      * Single-center: * St. Petersburg Regional Center of Addictions and Psychopharmacology, Russia | * High-dose group received 2.0 mg/kg ketamine intramuscularly      * Low-dose (active placebo) group received 0.20 mg/kg ketamine intramuscularly      * All participants received a single ketamine session from a specially trained practitioner. * All participants received ten hours of psychotherapy before and five hours of psychotherapy after the ketamine session. | * Primary: * Abstinence until 24 months or relapse      * Secondary: craving scale, depression scale, and anxiety scale | * High-dose group significantly more likely to be abstinent for up to two years post-treatment. * Both groups showed significant craving reduction for up to 2 years (1.7 vs. 29.2, p<0.01). * Both groups experienced reduced anhedonia, anxiety, and depression with no significant differences between groups.   *Conclusion*: Ketamine-assisted psychotherapy of people with heroin addiction is more effective at prolonging abstinence when a high, psychedelic dose is administered compared to when a low, non-psychedelic dose is administered. |
| **Krupitsky et al. 2007** | * Adults inpatients at an addiction treatment hospital with OUD (DSM-IV or ICD-10 criteria of opioid dependence for at least one year) aged 18-35 and abstinent from all “substances of abuse” for 2+ weeks      * n = 59 * Age, mean 22.6 years * 83.1% male * Race not reported | * Randomized clinical trial   .   * Single center: * St. Petersburg Regional Center of Addictions and Psychopharmacology, Russia | - Participants received either one or three ketamine-assisted psychotherapy sessions, all receiving 2.0 mg/kg intramuscularly each session. All received five hours of psychotherapy and five hours of psychotherapy after the first ketamine session.  All participants received the initial ketamine session post-detox and pre-discharge, followed by two addiction counseling sessions at 1 and 2 months  Those in the multiple-session arm received two more ketamine sessions, preceded by addiction counseling. | - Primary: Abstinence up to 12 months  - Secondary: craving scale, Purpose-in-Life Test (PLT), a depression scale, and an anxiety scale | * At 1-year, 50.0% of participants in the three-session group were abstinent compared to 22.2% of the participants in the single-session group. * No significant differences in depression, state and trait anxiety, and craving scores between groups   *Conclusion:* The three-session program was more effective in promoting abstinence than the single-session program, despite also receiving similar standard addiction counseling. |

**Table 1. Summary of Studies on Ketamine and Opioid Use Disorder**

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| **Study**  **(Ref.  #)** | **Population** | **Study Design** | **Intervention** | **Outcomes and Endpoints (primary and secondary)** | **Results** |
| **Jovaisa et al. 2006** | - Adult patients 18-35 with opioid dependence, otherwise healthy,  as defined by DSM IV, duration of substance use more than one year  n=58  Age, mean 22.7 (ketamine group), 23.4 (control group) - ages provided only by group  - Race not reported | - Randomized, placebo-controlled, double-blind study  - Single-center at Vilnius University Emergency Hospital, Lithuania. | - Intervention: Subanesthetic infusion of ketamine (0.5 mg/kg) administered after induction of anesthesia, 5 minutes before RAI  - Control: Normal saline infusion  - All patients underwent rapid opiate antagonist induction (RAI) under anesthesia. Patients underwent 48-hr postanesthesia phase treatment, then discharged to aftercare program (abstinence-based, naltrexone-supported outpatient counseling or residential rehabilitation programs) | -Primary:  Withdrawal severity was measured according to Objective Opiate Withdrawal Scales  (OOWS-A).  -Secondary:  - Mean arterial pressure (MAP) and heart rate (HR)  - Cortisol levels  - Medication requirements for symptom relief (i.e., clonazepam, carbamezepine)  - Addiction Severity Index questionnaire at 4-months | * Opiate withdrawal scores were significantly lower in Ketamine group for 1st and 2nd hour post-RAI. * Ketamine significantly reduced MAP, HR, and post-RAI morning cortisol levels * The ketamine group required significantly less clonazepam and carbamazepine in the 48-hr postanesthesia phase. * There were no significant differences in opioid abstinence rates between groups, and no significant outcomes from the 4-month follow-up were observed.   *Conclusion*: Ketamine infusion suppressed the expression of precipitated opiate withdrawal and prevented significant rise in cardiovascular, respiratory, and neuroendocrine response especially during the first two hours of opiate antagonist induction. No significant differences across groups for relapse. |
| **Freye et al. 2006** | Adults enrolled in methadone maintenance programs or were regularly using heroin who had 5-10 unsuccessful inpatient detoxifications  n=31  Age, mean = 31.7  74% male  Race not reported. | Prospective cohort study  Heinrich-Heine University, Dusseldorf, Germany | All patients pre-medicated with propofol, clonidine and somatostatin infusion, as well as naltrexone 50 mg administered 2x one hour apart.  IV ketamine was administered at 1.5 mg/kg | Primary: Intensity of central excitatory effects (EEG-power spectra in the β, α, Θ, and ẟ-band) after ketamine administration | Administration of S(+)-ketamine led to a reversal of acute abstinence-related changes in EEG power: compared to anesthesia with naltrexone, EEG power increased by 65% in the delta band and decreased by 723% in the beta band.  *Conclusion:* While sympathetically induced hemodynamic alterations in anesthesia-assisted opioid detoxification can be attenuated by clonidine and sedation, central nervous sensory activation can be attenuated by the administration of S(+)- ketamine (1.5 mg/kg). |
| **Grande et al. 2024** | Adult patients transitioning to buprenorphine from fentanyl or methadone  n=37  Age range 19-62 years (mean /median not provided). 54% female -Race not reported | Pilot case series  Washington State, US | - Sublingual ketamine (16 mg) per administration, taken 2-3 times daily as needed for withdrawal symptoms for a total of 8 doses.  - All patients were initiated on buprenorphine or buprenorphine/ naloxone with doses ≥8 mg within 24 hours for successful initiation.  Clonidine, gabapentin, and other supportive medications were prescribed as needed to manage withdrawal symptoms or anxiety. No further counseling provided. | Primary: Successful buprenorphine initiation, defined as tolerating ≥8 mg of buprenorphine within 24 hours without worsening withdrawal symptoms, as measured by COWS. | * In patients who received ketamine, 67% (16/24) successfully completed buprenorphine initiation. * 92% of patients who completed initiation (11/12) achieved 30-day retention. * No serious adverse effects were noted.   Conclusion: Ketamine prescribed at a sub-dissociative dose allowed for successful initiation of buprenorphine with reduced/elimination of opioid withdrawal symptoms. |
| **Christian et al. 2023** | 38-year-old male patient with severe OUD presenting with suicidal ideation and withdrawal 24 hours after last fentanyl use | Case report (Yale  New Haven Hospital, Connecticut, USA) | Patient was initially treated with sublingual buprenorphine-naloxone (BNX) 16–4 mg, exacerbating withdrawal symptoms, raising his Clinical Opiate Withdrawal Scale (COWS) score to over 36, then  received two (24 and 36h) ketamine infusions at 0.3 mg/kg over 15 minutes, followed by a third ketamine infusion 0.3 mg/kg over one hour, along with additional BNX 8–2 mg. | COWS score | * After the first ketamine infusion, the patient's COWS score improved from over 36 to 18, though some symptoms remained. * A second ketamine infusion at the same dosage, along with additional BNX, completely resolved the patient's POW symptoms within 8 hours, and he was stabilized for discharge. * No severe side effects were noted.   Conclusion: Ketamine shows potential to mitigate precipitated opioid withdrawal (POW) symptoms through μ-opioid receptor potentiation, making it a viable adjunctive treatment in hospitalized settings. |
| **Hailozian et al. 2022** | 32-year-old male patient with opioid use disorder who developed severe buprenorphine precipitated opioid withdrawal (BPOW) from a failed outpatient microdose treatment plan. | Case report  - Highland Hospital, Oakland, CA | Patient was treated with ketamine (0.6 mg/kg intravenous over 1 hour) and high-dose buprenorphine (16 mg sublingual single dose) followed by administration of month-long dose of extended-release subcutaneous buprenorphine which was repeated monthly for three months. | Primary outcomes: COWS,  treatment adherence, and abstinence from opioid use disroder. | * One-hour post-ketamine administration, COWS decreased from 18 to 2. * At 120 days, patient remained in treatment and reported continuous abstinence from fentanyl use. * No severe side effects were noted.   Conclusion:  Ketamine is effective for reducing symptoms of precipitated opioid withdrawal and may have a role in continued abstinence as an adjunctive treatment to buprenorphine. |
| **Lalanne et al. 2016** | - 36 yo woman with severe opioid use disorder in context of lumbo-sciatic pain, presenting with a regimen of oxycontin extended-release 120 mg daily, oxycodone 60 mg daily, and acetaminophen/codeine 300 mg/25 mg 6 times per day). | Case report  - University Hospital of Strasbourg, Strasbourg, France | Patient received ketamine oral solution 1 mg/kg, then opioid regimen was downtitrated by 10% every 48 hours  Patient also receivd consultation with psychiatrist, addictologist, and pain specialist | Primary outcomes:  Withdrawal symptoms | * No report of withdrawal symptoms (COWS Score of 0 out of 11), pain, or cravings while her opioid treatment was being reduced over 2 weeks. * No side effects of ketamine other than “unusual weakness.” * Pain regimen reduced to 50 mg codeine three times a day for pain.   Conclusion: Withdrawal from ketamine was achieved without withdrawal symptoms. |

**Table 2 Summary of Studies on Ketamine and Opioid Withdrawal**