Ketamine for the treatment of substance use disorders: a systematic review

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1.Introduction:

- Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with rapid and sustained antidepressant effects[1].
- There is research demonstrating therapeutic benefits of ketamine for mental health disorders, including substance use disorders[2].
- The aim of this review is to systematically collate the evidence on ketamine's therapeutic effects in substance use disorders.

2. Methods:

- Systematic review of Medline, PsychInfo and Clinical Trials.gov

✓ Included randomised controlled trials, non-randomised clinical trials and other observational studies of ketamine on substance use disorders in humans

× Excluded Case studies, letters/replies to editors.

3. Results:

Alcohol (n=4):

Authors, date & design	Patient demographics	Ketamine treatment	Control	Results
Krupitsky et al., 1992, Russia Randomised controlled trial	186 males with alcoholism	Intramuscular ketamine (3mg/kg) & Affective Contra attribution therapy.	Aversive therapy	At 1 year 69.8% of the ketamine group abstinent and 27.9% relapsed.
Krupitsky et al., 1997 Russia Non-randomised clinical study	211 males, alcoholism with alcohol withdrawal syndrome	Intramuscular ketamine (2.5mg/kg) & Ketamine psychotherapy (KTP).	Conventional psychotherapy	65.8% of ketamine group abstinent at 1 year vs 24% of control group.
Dakwar et al., in press. USA Randomised controlled trial	40 participants, (21 females) with alcohol dependence	Ketamine 0.11 mg/kg over 2 min bolus followed by 0.6 mg/kg over 50 minutes.	Active control midazolam 0.025 mg/kg	At 21 days 68.6% of control and 98.6% of ketamine group was abstinent.
Wong et al., 2015, USA Retrospective cohort review	23 participants, (14 females) alcohol withdrawal syndrome	Initial infusion dose mean: 0.21 mg/kg per hour.	N/A	Ketamine resulted in a non-significant decrease in benzodiazepine requirements.

- Increased abstinence at 21 days and 1 year follow-up with ketamine vs control[3-5].
- 33% of the ketamine group remained abstinent at 3 years, however there was no comparison follow-up data for control group[4].
- Ketamine was found to be safe for managing alcohol withdrawal syndrome[6].

Cocaine (n=4):

Dakwar et al.,2014a, USA Randomised controlled cross over trial	8 participants (1 female), dependence on crack cocaine	52 minutes infusions of 0.41 mg/kg and 0.71 mg/kg.	Lorazepam active control	Ketamine increased motivation for changing cocaine use, reduced craving and cocaine use at 4 weeks.
Dakwar et al.,2014b, USA Randomised controlled cross over trial	8 participants (1 female), dependence on crack cocaine	52 minutes infusions 0.41mg/kg first dose 0.71 mg/kg second dose.	Lorazepam active control	Mystical effects mediated the therapeutic effect of ketamine on motivation to quit cocaine but not on craving.
Dakwar et al., 2017, USA Randomised controlled cross over trial	20 participants (9 females), cocaine dependence	Ketamine 0.11mg/kg 2 min bolus followed by 0.60 mg/kg.	Active control 2 minute saline bolus followed by midazolam 0.025 mg/kg	67% reduction in cocaine choices with ketamine compared to baseline. Cocaine use reduction only for several days.
Dakwar et al.,2019, USA Randomised controlled trial	55 participants (14 females), cocaine dependence	Ketamine 0.5 mg/kg, slow drip 40 minutes infusion.	Active control midazolam 0.025 mg/kg	Abstinence in ketamine group 48.2% vs to 10.7% in midazolam group.

- Single dose of ketamine increased motivation to quit cocaine, reduced craving, and reduced cocaine self-administration[7].
- At 2 & 4 weeks: ketamine was associated with increased abstinence[7-8].
- At 6 months: 44% in the ketamine group was abstinent, 0 in the control[9].

Opiates (n=3):

Krupitsky et al., 2002, Russia Randomised controlled trial	70 participants, (15 females), heroin dependence	2.0 mg/kg ketamine infusion vs 0.2 mg/kg Ketamine infusion.	N/A	At 2 years, abstinence in the high dose group> low dose group.
Krupitsky et al., 2007, Russia, Randomised controlled trial	59 participants (10 females), heroin dependence	Intramuscular ketamine at 2mg/kg Single vs 3 doses with KTP.	Addiction counselling	At 12 months, 50% of multiple KPT group and 22.2% of single KPT group abstinent.
Jovaisa et al., 2006, Lithuania Randomised controlled trial	50 participants (7 females), opiate withdrawal syndrome	Single dose of 0.5 mg/kg/hr ketamine infusion.	Saline solution	Ketamine led to less additional clozapine and clonazepam at 48 hours. At 4 months: no difference in opiate use.

- Higher abstinence with repeated KPT than single KTP and with high dose ketamine (2mg/kg) vs low dose ketamine (0.2mg/kg) at 1 and 2 years[10-11].
- Ketamine was an effective adjunct treatment for opiate withdrawal[12].

4. Conclusions:

- Some evidence to support ketamine's therapeutic effects in substance use disorders from a small number of studies[3-13].
- Limitations of included studies: Lack of clarity over randomisation and allocation concealment, lack of placebo control, small sample sizes, ineffective blinding, missing data, lack of pre-registration and pre-specified statistical analysis plan.
- Need for higher quality, randomised, active placebo controlled, appropriately blinded and larger studies with pre-registration.
- Ongoing studies include a trial of ketamine for the treatment of alcohol use disorders taking place at the University of Exeter and University College London[14].
- Another ongoing trial is examining the effects of ketamine and psychological therapy for cannabis use disorders at the New York[15].

5. References:

1. Serafini, G., Howland, R.H., Rovedi, F., Girardi, P., Amore, M. (2014). The role of ketamine in treatment-resistant depression: a systematic review. *Current Neuropharmacology, 12*(5), 444-61. doi: 10.2174/1570159X12666140619204251. **2.** Ivan Ezquerra-Romano, I., Lawn, W., Krupitsky, E., Morgan, C. J. A. (2018). Ketamine for the treatment of addiction: Evidence and potential mechanisms. *Neuropharmacology*, *142,* 72-82. doi: 10.1016/j.neuropharm.2018.01.017 **3**. Dakwar, E. Glutamatergic Modulation of Disordered Alcohol Use, *ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02539511?id=NCT02539511&draw=2&rank=1* **4**. Krupitsky, E.M., Grinenko, A.Y. (1997). Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *Journal of Psychoactive Drugs, 29*(2), 165-83.**5**. Krupitsky, E.M., Grinenko, A.Y., Berkaliev, T.N., Paley, A. I., Tetrov, U. N., Mushkov, K. A. & Borodikin, Yu S. (1992). The Combination of Psychedelic and Aversive Approaches in Alcoholism Treatment. *Alcoholism Treatment Quarterly, 9*(1), 99-105, doi: 10.1300/j020v09n01_09 **6.** Wong, A., Benedict, N.J., Armahizer, M.J., Kane-Gill, S.L., (2015). Evaluation of adjunctive ketamine to benzodiazepines for management of alcohol withdrawal syndrome. *Ann Pharmacother, 49*(1), 14-9. doi: 10.1177/1060028014555859. **7**. Dakwar, E., et al. (2014). The effects of subanesthetic ketamine infusions on motivation to quit and cue-induced craving in cocaine-dependent research volunteers. *Biological Psychiatry*, *76*(1): 40-46. **8**. Dakwar, E., et al. (2017). Cocaine self-administration disrupted by the N-methyl-D-aspartate receptor antagonist ketamine: a randomized, crossover trial. *Molecular psychiatry 22*(1): 76-81. **9**. Dakwar et al. (2019). A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial. *Am J Psychiatry*, Jun 24:appiajp201918101123, [Epub ahead of print].**10**. Krupitsky, E., et al. (2002). Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *Journal of Substance Abuse Treatment, 23*(4), 273-283. **11**. Krupitsky, E. M., et al. (2007). Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *Journal of Psychoactive drugs, 39*(1), 13-19.**12**. Jovaisa, T., et al. (2006). Effects of ketamine on precipitated opiate withdrawal. *Medicina, 42*(8), 625-634. **13**. Dakwar, E., et al. (2014). Therapeutic infusions of ketamine: do the psychoactive effects matter? *Drug and Alcohol Dependence, 136*, 153-157. **14**. McAndrew, A., Lawn, W., Stevens, T. et al. (2017). A proof-of-concept investigation into ketamine as a pharmacological treatment for alcohol dependence: study protocol for a randomised controlled trial. *Trials 18*, 159. doi:10.1186/s13063-017-1895-6. **15**. Dakwar, E., Facilitating the Behavioral Treatment of Cannabis Use Disorder, *Clinical trials.gov*. https://clinicaltrials.gov/ct2/show/NCT02946489?term=ketamine&cond=Cannabis+Use&draw=2&rank=1

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