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Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for Major depression: A systematic review and meta-analysis

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Abstract

Objective: Intravenous (IV) racemic ketamine and intranasal (IN) esketamine have demonstrated rapid antidepressant effects in treatment-resistant depression (TRD). This systematic review aims to evaluate the efficacy and safety of ketamine and esketamine at various dosages for depression.

Methods: We included randomized controlled trials (RCTs) with parallel group dose comparison of ketamine and esketamine for depression/TRD. Ovid Medline, Embase, PsycINFO, Scopus and Cochrane databases were searched. Standardized mean differences were calculated using Hedges'-g to complete random effects meta-analysis. The efficacy outcomes were changes in depression outcomes for IV ketamine and IN esketamine respectively. Safety was assessed by reported adverse effects.

Results: A random effects meta-analysis of studies (n = 12) showed efficacy in reducing depression symptoms with IV ketamine (Hedges'g = 1.52 [0.98-2.22], Z = 4.23, p < 0.001) and IN esketamine (Hedges'g = 0.31 [0.18-0.44], Z = 4.53, P < 0.001) compared to control/placebo. Treatment response was observed at IV ketamine doses ≤0.2 mg/kg, >0.2-0.5 mg/kg and > 0.5 mg/kg. Higher IV ketamine doses (>0.5 mg/kg) did not lead to greater treatment response. Esketamine doses of 56-84 mg were superior to 28 mg dose.

Limitations: Overall quality of evidence was low and limited by small number of studies. Publication bias was high.

Conclusions: This meta-analysis suggests that IV ketamine may be efficacious at doses as low as 0.2 mg/kg, with increasing dose response at 0.5 mg/kg, without demonstrable increased benefit at 1 mg/kg, based on a small number of studies. Efficacy for IN esketamine increases with doses above 28 mg with best response being found between 56 and 84 mg for reducing depressive symptoms.

Keywords: Clinical trials; Dose escalation; Intranasal Esketamine; Intravenous ketamine; Major depressive disorder.

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