Experiences of Awe Mediate Ketamine’s Antidepressant Effects: A Randomized Controlled Trial in Treatment-Resistant Depression

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BACKGROUND

- Depression is a leading cause of morbidity and mortality worldwide
- NMDA-receptor antagonist Ketamine provides rapid and short-lived anti-depressant effects
- It is important to consider psychological mechanisms that may contribute to its therapeutic efficacy, including mystical or psychedelic experiences
- Understanding ketamine’s psychedelic properties may help to inform development of novel approaches that prolong and/or heighten its effects

METHODS

- 116 participants were randomized in a 2:1 ratio to receive ketamine (0.5mg/kg over 40 minutes, n= 77) while matched controls (n=39) received saline placebo
- All participants completed a validated measure of awe (the AWE-scale) at 40 minutes post-infusion
- Mean AWE-scores (total and sub-domains) were tested as potential mediators of clinical depression outcomes, measured by % improvement in Montgomery-Asberg Depression Rating Scale (MADRS) at five time points post-infusion (24 hours, 5 days, 12 days, 21 days, 30 days)

RESULTS

- Total AWE score (and each sub-component) & total CADSS differed significantly by treatment group (p < 0.0001) at 40 minutes
- In accordance with previous studies, there was a significant improvement in MADRS % change in the treatment group compared to controls at 24 hours (p=0.0001) and 5 days (p=0.0001) post infusion
- Significant relationship between AWE and % improvement in MADRS day 30

CONCLUSIONS

- Ketamine infusion strongly induced heightened feelings of awe
- These experiences significantly mediated depression outcomes until at least 30 days post-infusion while general dissociative side effects did not
- The specific awe-inspiring properties of ketamine may contribute to its antidepressant effects
- Further research is needed to elucidate the role of mindfulness and other practices that support an experience of ‘awe’ in the setting of ketamine infusion

Figure 4: Comparison of AWE and CADSS in % improvement in MADRS day 30 in the Ketamine Group

- At all 5 timepoints the total AWE-scores significantly mediated the relationship between ketamine and MADRS (% mediation effect: p=0.0028, p=0.0154, p=0.0018, p=0.0052, respectively).
- By contrast, CADSS scores did not mediate outcomes at any timepoint

Figure 4: Mediation Pathway

6 Subdomains: Physical, connectedness, vastness, self-loss, accommodation, time distortion

Reference to Primary Paper: