

Improvement to Quality of Life and Depression Show Independent Pathways in Psilocybin Response

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Abstract Introduction

Psychedelics continue to show efficacy as a potential treatment for depressive disorders. It is still unclear what mechanism could be responsible for changes in functioning after a psychedelic intervention. Two small open-label studies by Aaronson ST, et al. demonstrate the efficacy of psilocybin in improvement of depression and quality of life (QoL) in patients with difficult-to-treat depressive disorders. To explain this finding, we examined whether improvements in depression mediate sustained improvement in QoL or if improvements in QoL mediate sustained improvement in depression.

Methods

N = 20 adults (n = 7 P-TRD, n = 13, BP-II) received a single 25mg dose of COMP360 with therapeutic support. The Montgomery Asberg Depression Rating Scale (MADRS) was used to measure depression symptomology. The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) was used as a proxy for satisfaction with QoL. The scales were administered pre-dose at Baseline and post-dose at Week 3, and Week 12.

Results

Two regressions established the stability, or sustained improvement, within subjects through MADRS and Q-LES-Q scores at two timepoints (Week 3 to Week 12 $\beta = 0.553$ $p = .001$, $\beta = 0.679$ $p < .001$, respectively). Two distinct mediation analyses were performed. Mediation 1 tested whether early improvement in QoL scores (Baseline to Week 3) mediates sustained improvement in depression. In Mediation 1, there was no evidence that QoL improvement had an indirect effect on increasing the stability of depression improvement from Week 3 to Week 12 ($\beta = 0.076$, $p = .419$). Mediation 2 tested whether early improvement in depression scores (Baseline to Week 3) mediates sustained improvement in QoL. In Mediation 2, there was no evidence that depression improvement had an indirect effect on increasing the stability of QoL improvement from Week 3 to Week 12 ($\beta = -0.007$, $p = 0.905$).

Conclusions

Lack of a bidirectional relationship between QoL and depression suggests one or more independent extraneous mediators are aiding symptom improvement. A significant limitation of this conclusion is a low sample size which contributed to underpowered analyses. Additionally, the Q-LES-Q-SF may

not capture the entire spectrum of QoL symptom change and individual perceptions. It is crucial to continue exploring possible mediators of psilocybin response to develop effective interventions for these underserved populations.

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