Relationship between pharmacodynamic measures and efficacy in a clinical trial of a novel serotonergic agonist for Generalized Anxiety Disorder

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What is the Methodological Issue Being Addressed? The pharmacodynamic effects of psychedelic agents are measured using subjective assessments that capture different constructs of the psychedelic experience. The relationship of these pharmacodynamic measures to clinical outcome measures, especially for GAD, has not been well-characterized

Introduction Psychedelic agents induce an acute alteration of consciousness that is characterized by hallucinatory, emotional, and other behaviors. Preliminary evidence suggests that psychedelic agents may have potential efficacy for the treatment of a variety of neurological and psychiatric disorders. It is hypothesized that the efficacy of these agents is dependent upon eliciting a pharmacodynamic effect of sufficient intensity (either directly or indirectly). These measures are subjective in nature and have been developed to assess different constructs of the psychedelic effects. These include ego dissolution, emotional breakthrough, mystical experiences, and other measures of varying constructs. While these measures are commonly included in trials of psychedelic agents, the relationship(s) of these measures and correlations with clinical outcome have not been well characterized. Some data have demonstrated relationships between, for example, the magnitude of the score on the mystical experiences questionnaire (MEQ30) and clinical efficacy in depression and also relationships between the emotional breakthrough inventory (EBI) and well-being.

Methods Data were obtained in a double-blind study of a novel serotonergic agonist (HLP004) for the treatment of generalized anxiety disorder. The study has a 12-week double-blind period and a 40-week observation period. The data presented here are from an analysis of the 12-week, double-blind portion of the study. 36 patients with GAD were randomized (2:1) to be administered either 20 mg or 2 mg of HLP004 on Days 1 and 22 of the study. Patients enrolled in the study had moderate to severe anxiety as measured by the GAD-7, were receiving ongoing treatment with either antidepressant (AD) and/or anxiolytic, and continued treatment with their AD/anxiolytic throughout the study. The primary endpoint of the study was the change from baseline in HAM-A at Week 6. The subjective effects of HLP004 were reported on days of administration of HLP004. Measures of pharmacodynamic effect included the MEQ30, EBI, Bowdle visual analog scale (B-VAS), and an assessment of overall intensity that was completed by both the participant and the person monitoring the participant (ie, Session Monitor) during and after the administration of HLP004 (IRVAS). Post-hoc analyses included correlation analysis of these pharmacodynamic measures reported on Day 1 and clinical outcome such as changes in HAM-A score through Week 12.

Results In both treatment groups, the LS mean change from baseline (CfB) in HAM-A score were similar (-10.42 points in the 20 mg group and -9.88 points in the 2 mg group). Logistic regression modeling identified a statistically significant relationship ($p < 0.05$) between the EBI score therapeutic response (HAM-A). Other relationships between pharmacodynamic measures and treatment response were also explored. For example, while the relationships between the EBI and the HAM-A scores were significant, no relationship was found between the MEQ and HAM-A.

Conclusion These data suggest that the intensity of pharmacodynamic effects, particularly the emotional breakthrough inventory, may correlate with therapeutic response in this study. Further work to characterize these relationships between pharmacodynamic measures and clinical outcome in GAD are needed.

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Keywords

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