Repurposing an Over-the-Counter Formulation of Dextromethorphan (DXM) as the first Oral, Ketamine-like Psychedelic Antidepressant: Preliminary Results and Implications

Mike Wang MHS[1]; Paul Kim MD/Ph.D[1]; Adam Kaplin MD/Ph.D[1]; Anupama Kumar MBBS[1]
Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD 21287

Background: Ketamine and its enantiomers are rapid acting antidepressants of the NMDA receptor (NMDAR) antagonist class known for inducing a rapid antidepressant response among patients with severe and/or treatment resistant depression. The highly regulated nature of the drug and specialized programs necessary for ketamine treatment for TRD have greatly limited its widespread use. Thus, exploring other readily accessible NMDA receptor antagonists is warranted for curtailing the mounting rates of depression and suicide. DXM, the active ingredient in over-the-counter antitussives, demonstrates high similarity to ketamine in pharmacology and subjective effects. In our ongoing open-label unblinded feasibility and safety study, subjects with an incomplete response to their current antidepressant were randomized to one of three DXM adjunct treatment regimens for 28 days, during which depressive symptoms and adverse events were intensively tracked. **Methods:** Subjects (n=4, mean age=27.4yrs, 2M/2F) with an incomplete response to their current stable antidepressant regimen (as determined by a Montgomery Asberg Depression Rating Scale [MADRS] score of >20 after >6 weeks stable dose of current antidepressant) were randomized to one of two regimens (300mg every 2 weeks, 300mg once + 60mg daily) for 28 days with a washout and follow-up period up to 90 days. The primary outcome measure was time-to-all-cause-discontinuation. Adverse events were tabulated for 90 days. Kruskal-Wallis tests, including a variable Time (t0, t4h, t24, t7d, t14d, t21d, t28d) were used to assess the treatment effects on MADRS scores. Symptoms of dissociation were tracked using the Clinician Administered Dissociative States Scale (CADSS). **Results:** All subjects completed the treatment and follow up phases with no premature trial discontinuation. Baseline MADRS was 30.5 +/- 4.1 and t24h MADRS was 8.3 +/- 3.9 In this preliminary report, all subjects met criteria for response (>50% reduction from baseline) at 24 hours. Treatment effects were not significantly different between the two treatment arms ($p = 0.56$). No severe adverse events were reported in the dosing or washout period. Most common acute side effects included dissociation (n=4), dizziness (n=3), and nausea (n=2). The most common side effect during follow-up was change in appetite (n=2 increased, n=2 decreased) with no accompanied weight loss or gain (defined as > +/- 5% baseline body weight). Transient hypertension reported in ketamine administration was not observed during DXM dosing. Despite recommendations that DXM be contraindicated for those utilizing monoamine-elevating drugs, no symptoms of serotonin toxicity were observed among all subjects. No subjects were prematurely discontinued due to significant adverse events. **Conclusions:** Preliminary results indicate that oral high-dose DXM is well tolerated while exhibiting rapid antidepressant effects and dissociative sensoria comparable to ketamine. Up to 15 subjects will be ultimately recruited by DEC 2022, after which significance of treatment effects and interaction variables will be reported. We felt compelled to present these preliminary data to discuss the medical, social, and policy implications associated with the observation that DXM, an unregulated molecule found at drugs stores worldwide, might be a ketamine-like antidepressant.