Title:
Safe Extended Titration of q3d Intranasal Ketamine for Treatment of Juvenile Bipolar Disorder with Fear of Harm (JBD/FOH).

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Methodological question being addressed: IN ketamine has been shown to provide clinical response in JBD/FOH, but continuous symptom relief requires extended repeated dosing that cannot be performed with IV administration. Therefore, a titration method using intranasal (IN) delivery and development of tolerance to side effects has been established that accounts for individual differences in nasal architecture and absorption in delivering effective doses.

Introduction. The FOH phenotype is a specific subtype of JBD that frequently fails to adequately respond to antipsychotics or mood stabilizers. Symptoms of JBD/FOH that have not generally been associated with bipolar disorder include separation anxiety, sleep/arousal disorders, parasomnias (night-terrors, enuresis) and REM sleep-related problems as well as thermal discomfort (e.g., feeling hot, excessive sweating) in neutral ambient temperatures, and no discomfort during exposure to cold.

Methods: Patients aged 6 and older are extensively screened as having DSM-IV criteria for JBD with FOH phenotype, and parents and children are informed and consented/assented prior to treatment.
Dosing is performed with a metered nasal pump spray bottle that delivers 0.1mL sprays of a 100 mg/mL solution. After each spray, the subject is queried for common symptoms associated with ketamine administration and tested for equilibrium. After a 5 minute pause, if no dose-limiting adverse events emerge, the entire process is repeated until a dose-limiting AE is experienced and defines the minimum intolerable dose (MID). Three days later, the MID is administered and if symptom relief has not been observed over the past 48 hours, further dose increases may be explored as tolerability improves.

Results: MID found at initial doses generally range from 20-30 mg, but symptom relief lasts <24 h at these low doses. Titration of dosing that provides continuous symptom relief often requires 30-60 days of titration. Most initial adverse events (bad taste, nasal burning, dizziness, impaired coordination, visual distortions, and time "warps"), prevalent and dose-limiting at early treatment, are of short-duration and diminish in severity with repeated dosing.
Practice-based treatment has found no serious adverse events or treatment discontinuations due to adverse events, and stable doses of 2-3 mg/kg can be safely administered for up to 10 years. Extended treatment is not associated with any evidence of cognitive dysfunction or addiction and no symptoms of withdrawal have been observed.

Conclusions: Persistently-effective dosages require an extended period of dose titrations of IN ketamine administered every 3-4 days that enable development of tolerance to acute effects. This dosing regimen appears to be safe and tolerable and results in a dramatic and enduring response in a population that is typically unresponsive to traditional psychotropic drugs and poses a considerable social, economic and familial burden. Improved quality of life is experienced through significant relief of symptoms associated with JBD with FOH.
Reduction of symptoms of thermal dysregulation precedes re-emergence and accompanies resolution, of psychiatric symptoms, making thermal dysregulation a possible biomarker for the FOH subtype of JBD.

Disclosures:
The authors report no conflicts of interest for this work.