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Research paper

Clinical experience using intranasal ketamine in the longitudinal treatment of juvenile bipolar disorder with fear of harm phenotype

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ABSTRACT

Objectives: Fear of Harm (FOH) is a pediatric onset phenotype of bipolar disorder (BD) characterized by BD plus treatment resistance, separation anxiety, aggressive obsessions, parasomnias, and thermal dysregulation. Intranasal ketamine (InK) in 12 youths with BD-FOH produced marked improvement during a two-week trial. Here we report on the open effectiveness and safety of InK in maintenance treatment of BD-FOH from the private practice of one author.

Methods: As part of a chart review, patients 18 years or older and parents of younger children responded to a clinical effectiveness and safety survey. Effectiveness was assessed from analysis of responses to 49 questions on symptomatology plus qualitative content analyses of written reports and chart review. Adverse events (AEs) were analyzed by frequency, duration and severity. Peak InK doses ranged from 20 to 360 mg per administration.

Results: Surveys were completed on 45 patients treated with InK for 3 months to 6.5 years. Almost all patients were "much" to "very much" improved clinically and in ratings of social function and academic performance. Significant reductions were reported in all symptom categories. There were 13 reports of persistent AEs, none of which resulted in discontinuation. Acute emergence reactions were sporadically observed in up to 75%, but were mild and of brief duration.

Limitations: Retrospective review from a single practice without placebo control with potential for response and recall bias.

Conclusions: InK every 3–4 days at sub-anesthetic doses appeared to be a beneficial and well-tolerated treatment. Use of InK may be considered as a tertiary alternative in treatment refractory cases. Randomized control trials are warranted.

1. Introduction

The FOH phenotype of BD (BD-FOH) is a clinically distinct behavioral phenotype with early age of onset, severe manic and depressive symptoms, early and frequent psychiatric hospitalizations, significant social impairment and school problems (Papolos et al., 2009). Characteristics of this phenotype, and its high rate of heritability, were established in a sample of youths with clinician-assigned diagnoses of BD (N = 1601) (Papolos et al., 2005) and further verified in a large (N = 5335) community sample of children with bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BD (Papolos et al., 2009).

Clinically, it appears that a specific developmental sequence of fear-based (or sensitized) behaviors arises in these individuals and includes night sweats, recurrent night-terrors and vivid nightmares, obsessive bedtime rituals, fear of the dark, separation anxiety, hypervigilance, misperception of neutral stimuli as threatening, reactive aggression in response to limit setting or perceived threat or loss (Papolos et al., 2009). Individuals with FOH also tend to be remarkably cold tolerant and heat intolerant. We have proposed that this phenomenon may be a

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putative biological marker, indicative of a thermoregulatory disturbance in a thermosensory pathway that mediates heat-defense responses (Murphy et al., 2014).

The ability of ketamine to decrease fear sensitization and (dose-dependently) reduce body temperature in animals (Fahim et al., 1973; Pietersen et al., 2006) was the rationale for off-label use of intranasal ketamine (InK) in BD-FOH children. An open-label trial (Papolos et al., 2013) found a substantial, rapid reduction in measures of mania, fear of harm and aggression and significant improvement in mood, anxiety, attention/executive functions in 12 treatment-refractory youth, 10 males 2 females aged 6–19 years. InK every third day during a two-month period also led to remission of symptoms associated with the core features of the FOH phenotype and normalization in thermoregulation. Two questions remained unanswered; could this response be sustained, and was InK tolerable and safe with regular exposure over an extended period of months to years? Herein, we report results from the maintenance use of InK in 45 cases with BD-FOH, mean age 15.6 ± 6.7 years in one clinical practice. To our knowledge, this is the first report to describe sustained effectiveness, tolerability and safety of InK in the treatment of treatment-resistant mood-disorder patients over an extended period.

2. Methods

2.1. Participants

60 patients who met DSM-IV criteria for bipolar disorder as well as the FOH phenotype and demonstrated treatment resistance to traditional mood-stabilizing agents and atypical neuroleptics, were ascertained through the private practice of one of the authors (DFP). Written consent of patients was obtained after informed consent was provided about the risks of short-term and long-term ketamine. As part of a thorough clinical appraisal, information on side-effects and effectiveness was obtained from patients (if aged 18 or older) or parents through regular clinical contact and a retrospective survey. All patients were treated with InK and closely followed for 3 months to 6.5 years.

2.2. Administration and dosing

Patients were administered InK, as 0.1 ml sprays of 50–200 mg/ml ketamine in 0.01% benzalkonium chloride to alternating nostrils. Patients were instructed to administer sprays until a minimum intolerable dose (MID) was found and to repeat this administration every 3–4 days. If a satisfactory clinical response was not sustained for at least 3 days (as determined by twice weekly clinical evaluation), doses were raised incrementally by increasing the number of intranasal sprays until a new MID was achieved, or there was an 80% or greater reduction in symptom severity.

2.3. Chart review

A retrospective chart review was conducted by two independent raters (MHT, LCHG). Raters reviewed clinician notes, redacted to remove identifying information. The Clinical Global Impression Severity scale (CGIs) (National Institute of Mental Health, 1985) was used to rate the patient's overall clinical status prior to initiation of treatment as well as their most recent status on ketamine. The CGI – Improvement (CGIi) scale was used to record their overall degree of improvement based on all treatment notes.

2.4. Survey

All patients treated for ≥ 3 months and parents (if patient < 18 years of age) were invited to complete a survey of their retrospective observations of treatment response and side-effects. Measures were obtained through Likert scale responses that provided a measure of severity of symptoms both before and after ketamine for each category. The survey contained 49 items rated according to indices of severity or frequency and converted to 1–4 numerical scores.

Patients/parents were also asked to provide a narrative of the long-term use of ketamine, which was subjected to qualitative content analysis (Mayring, 2000). Briefly, this is a multistep process, guided by the key research question as to what were the primary positive and negative spontaneously reported features or outcomes of InK ketamine. The narratives were read and re-read many times to formulate tentative categories, which were discussed and within a feedback loop were revised and eventually reduced to main categories and checked regarding their reliability. We then determined, for each category, the percent of narratives in which the category was reported and the percentage of those reports that were endorsed in a positive manner. For two broad categories (overall degree of improvement and degree of improvement in work or school performance) results were coded using CGI-improvement scale.

For some analyses, patients were divided into two groups; those who had discontinued ketamine use (non-continuers), and those who continued to use ketamine at the time the questionnaire was completed (continuers). The questions for non-continuers comprised three sections: 1) reasons for discontinuation, 2) health issues and 3) side effects experienced during treatment. Questions for continuers included questions on age, weight, current dose, treatment summary, acute and enduring side-effects, health issues, life measures, and questions on behaviors and symptoms pre and post treatment. Each question was answered using a Likert scale that ranked severity and, in some cases, frequency.

2.5. Adverse events categories

Side effects to ketamine were classified as acute-time limited or prolonged. Acute-time limited reactions, such as dizziness or burning sensation in the nose, occurred during IN administration and generally abated over a 15–120 min period. Potential long-term side effects from ketamine use included: (i) torso acne, (ii) problems with urination, (iii) sustained loss in sensory perception, or (iv) other medical concerns the patient thought might be associated with ketamine.

2.6. Statistical analyses

2.6.1. Data reduction

Principal component analysis (PCA) with oblimin rotation was used as a data reduction tool that combined the 49 Likert-rated survey items into four composite oblique symptom clusters. Oblimin was selected over more conventional rotational strategies (e.g., varimax) as it does not force the components to be uncorrelated, as this is an unreasonable assumption with symptom scores. Symptoms were also categorized as either unique to FOH phenotype (e.g., thermal insensitivity), diagnostic for BPD (e.g., high energy - pressured speech - racing thoughts) or strongly associated with FOH as well as other subtypes of BPD (e.g., physical aggression) based on consensus ratings from two psychiatrists (DFP, MHT).

2.6.2. Within subject response

Paired *t*-tests were used to assess within subject differences in pre-treatment versus post-treatment symptom ratings on the four composite ratings. Within subject effect size measures and 95% confidence intervals were computed using procedure developed by Gibbons et al. (1993), (implemented in the R package '*effsize*'), which provides numerically equivalent results to Dunlap et al. (1996).

2.6.3. Tolerance

Paired *t*-tests were also used to test for development of tolerance to side-effects of InK by comparing side-effect ratings at the time InK was initiated to current side-effect ratings. Further, non-linear mixed effects