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Research paper

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

Demitri Papolos[a,f,*], Mark Frei[b], Daniel Rossignol[c], Steven Mattis[d], Laura C. Hernandez-Garcia[e], Martin H. Teicher[e]

[a] Juvenile Bipolar Research Foundation, 277 Martine Avenue, Suite 226 White Plains, NY 10601, United States
[b] Advanced Signal Analysis and Processing, 2360 Sterling Creek Pkwy, Oviedo, FL 32766, United States
[c] Juvenile Bipolar Research Foundation, 277 Martine Avenue, White Plains, NY 10601, United States
[d] Department of Psychiatry Cornell-Weil Medical College of Medicine, United States
[e] Developmental Biopsychiatry Research Program, McLean Hospital, Department of Psychiatry, Harvard Medical School, United States
[f] Department of Psychiatry, Albert Einstein College of Medicine, New York, United States

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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

* Corresponding author at: Juvenile Bipolar Research Foundation, 277 Martine Avenue, Suite 226 White Plains, NY 10601, United States.
E-mail address: demitri@optonline.net (D. Papolos).

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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

models (R package *'nlme'*) were used to evaluate the tolerance time course for the most frequent acute-time limited reactions, which were the most suitable for modeling. Independent *t*-test was used to compare subjects continuing InK treatment from subjects who discontinued use in age of onset, peak dosage and duration of treatment.

3. Results

3.1. Sample

Of the sixty cases invited to respond to the survey, fifty-one (85%) responded to the invitation. Of these, 45 patients (75% of sample, 25% female) completed the survey. 40 patients (89%) continued to receive InK treatment at the time of survey ("continuers") while 5 patients (11%) had discontinued InK treatment ("non-continuers"). The mean age of the sample was 15 ± 6.7 years. The youngest was 6 years of age the eldest was 37.

3.2. Dosing

The survey respondents initiated treatment with InK at 15.9 ± 6.7 years of age (mean and SD) and, on average, received treatment for 1.71 ± 1.36 years. Mean ketamine dosage (current or at time of discontinuation) was 165 ± 75 mg, (range 20–360 mg) administered once every 2–5 (mean 3.0 ± 0.6) days. Five of the 45 patients discontinued treatment with InK; 3 considered the treatment ineffective, 1 discontinued due to family circumstances, including disagreement over treatment/finances, and 1 found treatment was inconvenient in his new college setting. Comparisons between subjects continuing versus discontinuing ketamine on age of initiation (15.6 ± 6.7 vs 18.5 ± 5.8 years), average dosage (173 ± 40 vs 165 ± 78 mg) and duration of treatment (1.81 ± 1.39 vs 0.88 ± 0.62 years) were not significantly different within this limited sample.

3.3. Effectiveness

3.3.1. Chart review

Concordance in CGI scores between the two raters was high ($r = 0.897$, $p < 10^{-15}$) for the 39 complete charts available for review. Prior to initiation of InK the patients were seen as severely ill (CGIs = 5.7 ± 0.7), with 10 of the patients rated as "amongst the most severely ill" by at least one of the two raters. At endpoint, following addition of InK into their treatment regimen, and months of adjustment and optimization, patients were typically rated as mildly ill (CGIs = 3.2 ± 1.1) with a 2.55-point drop in scores ($t_{38} = -14.21$, $p < 10^{-15}$). Mean improvement on the CGIi was 1.9 ± 0.9. Eight patients were seen as very much improved by both raters, 26 were much improved and only 5 patients were mildly improved or unchanged. None were consistently viewed as worsened. A typical pattern was for the subject to have such severe psychopathology prior to initiation of ketamine that they were unable to attend school and were home schooled to the extent possible. They were also physically aggressive towards parents or siblings, had no friends to speak of and were on several different psychiatric medications. After initiation and titration of InK they were often attending regular school, had ceased fighting with parents, were making friends and were on a simpler drug regimen. Breakthrough symptoms were sometimes seen however on the day prior to the next dose or when the ambient temperature was excessively high. There were no age-related differences in effectiveness ($p > 0.4$),

3.3.2. Survey results – symptom scores

Principal component analysis (PCA) with oblimin rotation was used to reduce the Likert-like symptom items into rotated orthogonal components (Table 1). Four components were selected as recommended by the Velicer Minimum Average Partial (MAP) test criterion (Velicer, 1976; Zwick and Velicer, 1986). These four components accounted for

Table 1
Data reduction using principal component analysis with oblimin rotation to reduce 49 symptom scores into four oblique components.

Clinical Symptoms	TC1	TC3	TC4	TC2	Category
Fearful new challenges, situations	**0.86**	–	−0.10	–	FOH
Devalues self or others	**0.86**	–	–	−0.12	BPD
Easily shamed or humiliated	**0.85**	−0.18	–	–	FOH
Fearful of separation	**0.74**	0.16	–	–	FOH
Abrupt mood swings	**0.71**	0.17	0.20	–	Both not core
Low energy, lack of motivation	**0.71**	–	–	0.10	BPD
Suicidal ideation or planning	**0.66**	–	0.18	−0.26	BPD
Difficulty sleep initiation or maintenance	**0.66**	0.10	0.14	–	Both not core
Difficulty initiating actions	**0.63**	0.26	−0.18	–	Both not core
Fearful of injury / accident	**0.62**	–	0.22	0.14	FOH
Hypersexuality	**0.61**	−0.40	0.23	0.10	BPD
Misperceives limit setting as threat	**0.60**	0.34	–	0.13	FOH
Avoidance of tasks	**0.59**	0.36	–	–	Both not core
Social withdrawal	**0.56**	0.26	−0.21	0.14	BPD
Misperceives neutral situations as threat	**0.55**	–	0.30	–	FOH
Sensitive to heat	**0.55**	0.28	0.11	–	FOH
Sensitive to cold	**0.51**	−0.49	–	–	FOH
Irrational fears (ghosts, monsters)	**0.49**	0.20	0.14	0.28	FOH
Highly vigilant, easily startled	**0.49**	0.15	0.27	–	FOH
Unrealistic expectations	**0.49**	0.36	–	–	BPD
Irritability	**0.48**	0.44	0.11	–	BPD
Perfectionistic worries	**0.48**	–	0.31	–	FOH
Nightmares	**0.47**	–	0.37	0.26	FOH
Aggressive thoughts	**0.43**	0.20	0.42	–	Both not core
Excitability, pressured speech, racing thoughts	**0.41**	0.20	0.34	–	BPD
Physical aggression to parents severity	–	**0.85**	0.11	–	Both not core
Physical aggression to parents frequency	–	**0.77**	0.19	–	Both not core
Physical aggression to sibs frequency	−0.12	**0.72**	–	0.19	Both not core
Oppositionality	0.34	**0.67**	−0.11	–	Both not core
Strong unyielding drive	0.23	**0.63**	–	0.12	FOH
Physical aggression property severity	–	**0.62**	0.35	–	Both not core
Verbal aggression	0.29	**0.61**	0.16	−0.13	Both not core
Physical aggression property frequency	–	**0.60**	0.44	–	Both not core
Physical aggression to sibs severity	0.12	**0.59**	−0.10	0.14	Both not core
Deflection of blame	0.39	**0.55**	–	0.10	Both not core
Inflexibility	0.46	**0.54**	–	–	Both not core
Impulsivity	0.41	**0.50**	–	0.15	BPD
Difficulty concentrating / distractability	0.32	**0.41**	–	0.20	BPD
Sensory sensitivity	0.35	**0.37**	−0.10	0.21	FOH
Physical aggression non-family frequency	−0.10	–	**0.67**	0.40	Both not core
Physical aggression self frequency	0.16	0.13	**0.62**	–	Both not core
Physical aggression self severity	0.18	0.16	**0.61**	−0.14	Both not core
Physical aggression non-family severity	–	0.16	**0.56**	0.24	Both not core
Suicide attempts	–	0.14	**0.53**	−0.24	BPD
Hallucinations / psychosis	0.26	–	**0.38**	0.21	Both not core
Physical aggression animals severity	0.10	–	–	**0.87**	Both not core
Physical aggression animals frequency	–	–	0.14	**0.84**	Both not core
Psychomotor retardation	–	0.10	−0.40	**0.70**	BPD
Other sleep disturbance	–	0.18	0.27	**0.54**	FOH

62.2% of the variance in the individual item ratings. Items with high loadings on the first component involved fear, low self-esteem, suicidal ideation, mood swings and low energy. Items with high loading on the second component reflected aggression towards parents, siblings and property, oppositionality and irritability. Items with strong loading on the third component involved aggression towards self, non-family members and suicide attempts. Items loading onto the fourth component included aggression towards animals, psychomotor retardation and sleep disturbances.

Overall, there were highly significant within subject differences in pretreatment versus post-treatment ratings. Reduction in scores on component 1 following ketamine titration was associated with a very large effect size (Cohen's d = 2.92, 95% CI 2.27–3.57, t_{39} = 14.9, $p < 10^{-16}$). Similarly, there were also a large pre-post ketamine differences in component 2 (d = 1.71, 95% CI 1.19–2.24, t_{39} = 10.70, $p < 10^{-12}$) and component 3 (d = 1.10, 95% CI 0.616–1.58, t_{39} = 5.82, $p < 10^{-6}$). There was a moderate pre-post ketamine difference on component 4 (d = 0.626, 95% CI 0.164–1.09, t_{39} = 3.63, p = 0.0008). Based on 95% confidence intervals Component 1 showed a greater pre-post difference than any of the other components. Component 2 also showed a greater pre-post difference than Component 4. Twelve of the 15 symptoms unique to the FOH phenotype loaded onto Component 1.

Other useful information gleaned from the survey was that 21 of the 40 continuers (52.5%) had one or more psychiatric hospitalizations prior to initiation of ketamine. None of the continuers had a psychiatric hospitalization after ketamine was initiated. Those with prior hospitalizations had no subsequent hospitalizations during a 2.1 ± 0.6 year post initiation of ketamine follow up period. Table 2 summarizes data on changes in medication treatment after initiation of ketamine. There were 41 instances in which antipsychotics were reduced or eliminated. Mood stabilizers, antidepressants and anxiolytics were reduced or eliminated in 25, 11 and 7 subjects, respectively. Following initiation of ketamine 3 subjects were prescribed oxcarbazepine, 2 clonidine, 1 trazodone and 1 mixed amphetamine salts. Concomitant psychotropic medications were discontinued in 43% of continuous users. The remainder received from 1 to 3 additional medications (mean 1.6 ± 0.7), typically a low dose of an antipsychotic, mood stabilizer or clonidine.

Table 2
Number of subjects in whom specific medications were decreased, eliminated or added after initiation of ketamine.

	Decreased	Eliminated	Added
Antipsychotics			
aripiprazole	4	9	
asenapine		1	
clozapine	1		
fluphenazine	1		
olanzapine		1	
quetiapine	3	4	
risperidone	5	10	
ziprasidone	2	2	
Mood Stabilizers			
lamotrigine		7	
lithium	3	5	
oxcarbazepine	2	1	3
topiramate		1	
valproate	2	4	
Antidepressants			
duloxetine		1	
escitalopram		2	
fluoxetine		1	
fluvoxamine		1	
nortryptiline		1	
sertraline		3	
trazodone		1	1
venlafaxine		1	
Anxiolytics			
clonazepam	1	5	
lorazepam		1	
Others			
modafinil	1		
benztropine		2	
clonidine	1	1	2
guanfacine		1	
propranolol		1	
psychostimulants	1	2	1

3.3.3. Content analysis

Thirty-nine open ended written reports on how INK affected the life of the patients were provided by parents or older patients, and codified using content analysis. Clinical global impressions derived from these reports identified 3 patients as minimally improved, 11 as much improved and 25 as very much improved for an average CGI improvement score of 1.44 (95% CI 1.23–1.64). Information on academics or work performance was provided for 21 cases. One family reported no change, 7 were much improved and 13 very much improved in their ability to attend or perform. It was noted in 24/24 reports that the patient was easier to get along with and in 24/24 cases that family life had improved. Patients were noted to be less confrontational in 22/23 reports, less angry in 21/22, less fearful in 24/26, less depressed in 25/27, engaging in more activities in 24/26 and sleeping better in 6/6. In 12/13 reports an improvement was noted in ability to make friends, and in 14/14 there was an improvement in ability to socialize.

3.4. Safety

3.4.1. Acute-time limited reactions

Fourteen potential acute-time limited reactions (ATLRs) were observed (see Table 3). The most commonly reported ATLR was “a sense of relaxation calm and bodily warmth” reported in over half of the patients as lasting for 40 min or longer. A large majority (88%) of this group reported that experience to be enjoyable. The most frequently reported negative short-term side-effects were dizziness (84.4%), wobbly gait (73.3%), and stinging sensation in the nose (71.1%). Of these, most were reported to be of relatively brief duration (< 20 min). Once therapeutic doses were achieved, the experience of dizziness, wobbly gait and stinging in nose were reported as present but reduced in intensity. Significant alterations in severity, frequency and duration for the most common ATLRs at therapeutic dose (affecting $\geq$ 10 subjects) are indicated on Table 3. There were no age-related differences in severity of common side effects (e.g., burning nose, elation, sleepiness, heaviness in limbs) in those reporting these side effects, except for diziness, which was less severe in older individuals ($r = -0.65$, $p < 0.02$)

The ATLRs that showed the most significant reduction with continued treatment, and which affected the greatest number of subjects, were dizziness and wobbly gait. Non-linear mixed effects analyses fitting to a 4-parameter logistic time course equation were used to estimate time to half-maximal reduction in severity for these two ATLRs. For dizziness there was a relatively rapid decline in severity (time to half-maximal was 0.20 years, 95% CI 0.05–0.35 years, $F_{1,19}$ = 7.43, $p < 0.02$). In contrast wobbly gait / loss of coordination took substantially longer to diminish (time to half-maximal was 1.17 years, 95% CI 1.01–1.33 years, $F_{1,20}$ = 15.04, $p < 10^{-16}$). The decrement in severity occurred despite the fact that later doses were almost universally greater than doses administered at the initiation of treatment.

3.4.2. Persistent adverse events

Two patients reported persistent sensory changes. One subject reported loss of temperature sensation in all areas of his body except for the tongue. Neurological exam found gamma neuron loss at the level of the spinal cord, determined not to be progressive. The second patient experienced numbness in their upper extremities (fingers to mid-arms) when ambient temperature increased above 80 °F and when exposed to a warm shower. Neurological exam concluded that this was not a progressive deficit. In both cases, family and patient elected to continue

Table 3
Acute-time limited reactions immediately following intranasal ketamine administration.

Symptoms	Subjects experiencing it with some regularity initially or at therapeutic dose	Subjects experiencing it with some regularity at therapeutic dose	Ratings of severity, frequency, duration and nature in subjects experiencing symptoms at therapeutic dose				
			Period	Severity[a]	Frequency[b]	Duration[c]	Nature[d]
Sense of Calm or Relaxation[e]	39 (86.7%)	34 (75.6%)	Initial	2.2 ± 0.9	2.8 ± 0.9	51 ± 28	0, 4, 30
			Current	2.1 ± 0.7	2.9 ± 0.9	49 ± 31	
Dizziness[e]	38 (84.4%)	24 (53.3%)	Initial	2.3 ± 0.9	3.3 ± 0.9	26 ± 19	6, 16, 2
			Current	1.5 ± 0.7[§]	2.7 ± 1.1[¥]	17 ± 16[†]	
Wobbly Gait/Loss of Coordination[e]	33 (73.3%)	25 (55.6%)	Initial	2.0 ± 0.8	2.8 ± 1.1	30 ± 24	2, 21, 2
			Current	1.5 ± 0.3[¥]	2.0 ± 1.1[**]	17 ± 16[¥]	
Nasal Burning or Stinging[e]	32 (71.1%)	17 (37.8%)	Initial	2.4 ± 0.8	3.1 ± 0.8	12 ± 18	11, 6, 0
			Current	1.8 ± 0.9[**]	2.4 ± 1.2[**]	8 ± 7	
Sensory Distortions[e]	24 (53.3%)	16 (35.6%)	Initial	2.1 ± 0.9	2.6 ± 0.9	23 ± 17	4, 6, 6
			Current	1.6 ± 0.6[*]	1.6 ± 0.8[**]	16 ± 19[**]	
Elated, Silly or Giddy Feeling[e]	24 (53.3%)	10 (22.2%)	Initial	2.2 ± 1.0	2.6 ± 1.1	31 ± 19	2, 1, 7
			Current	1.5 ± 0.5	2.1 ± 1.1	23 ± 23[*]	
Sleepy, Tired or Fatigued[e]	23 (51.1%)	13 (28.9%)	Initial	2.3 ± 0.9	2.7 ± 1.0	46 ± 27	4, 8, 2
			Current	1.7 ± 0.6[*]	2.1 ± 1.0[*]	38 ± 29	
Head or Limbs Heavy or Light	22 (48.9%)	7 (15.6%)	Initial	2.0 ± 0.8	2.4 ± 1.0	15 ± 11	1, 6, 0
			Current	1.1 ± 0.4	1.4 ± 0.5	9 ± 5	
Warmth or Cold Sensations	18 (40.0%)	9 (20.0%)	Initial	2.0 ± 0.9	2.3 ± 1.1	31 ± 29	0, 6, 3
			Current	2.0 ± 0.7	2.4 ± 1.2	29 ± 30	
Distorted Sense of Time	16 (35.6%)	7 (15.6%)	Initial	2.4 ± 1.0	3.0 ± 1.0	36 ± 31	2, 4, 1
			Current	1.3 ± 0.5	1.9 ± 0.9	24 ± 26	
Nausea	12 (26.7%)	4 (8.9%)	Initial	2.3 ± 1.5	2.0 ± 0.8	45 ± 41	4, 0, 0
			Current	3.0 ± 0.8	2.3 ± 0.5	48 ± 38	
Numbness	10 (22.2%)	7 (15.6%)	Initial	1.9 ± 1.1	2.4 ± 1.3	28 ± 21	2, 4, 1
			Current	1.3 ± 0.5	2.0 ± 1.4	28 ± 16	
Outside of Body	10 (22.2%)	6 (13.3%)	Initial	2.3 ± 1.0	2.7 ± 1.2	42 ± 30	1, 2, 3
			Current	1.8 ± 0.8	2.2 ± 1.0	38 ± 34	
Sweating on the Hands or Feet	7 (15.6%)	5 (11.1%)	Initial	1.6 ± 0.9	2.0 ± 1.0	22 ± 33	1, 4, 0
			Current	1.6 ± 0.9	1.8 ± 1.1	22 ± 33	

[a] Severity: 1 = mild, 2 = moderate, 3 = strong, 4 = severe.
[b] Frequency: 1 = infrequent, 2 = frequent, 3 = almost always, 4 = always.
[c] Duration: minutes.
[d] Nature: distressing/unpleasant, neutral, enjoyable/pleasant.
[e] Initial versus current ratings with n > 10 on therapeutic dose.
* $p < 0.05$.
** $p < 0.01$.
¥ $p < 0.001$.
† $p < 0.0001$.
§ $p < 10^{-5}$.

ketamine because of the significant benefits that had accrued from treatment. Additional persistent AEs included urination problems in 5 patients (11.1%) and torso acne in 4 patients (8.9%).

3.4.3. Substance abuse

One potential concern with ketamine is that it might serve as a gateway drug and lead patients to use other psychoactive substances. Hence, degree of alcohol and drug use prior to initiation with ketamine was compared to degree of use during ketamine treatment. As seen in Table 4, there was no increase in use. Rather, there were trend level decreases in frequency of alcohol and marijuana use while receiving IN ketamine.

4. Discussion

This retrospective chart review and survey of the off-label longitudinal use of InK in 45 youth with refractory BD-FOH provides preliminary support for the potential effectiveness and tolerability of this treatment in clinical practice. The data presented are preliminary, neither blind nor placebo-controlled, and must be interpreted with caution. Nevertheless, the results of this case series are consistent with earlier reports of the efficacy and safety of ketamine administered by intranasal instillation to 12 BD-FOH youth over a 2-month period.

Patients were treated for 3 mos. – 6.5 years. Peak InK doses ranged from 20 to 360 mg per administration, and attenuated symptoms of BD/FOH for variable periods of time, typically 2–5 days. Clinically significant benefits were often apparent after the first treatment. Analysis of patient charts and written impressions revealed a substantial improvement in CGI severity scores with most patients who continued on ketamine rated as much to very much improved. Principal component analysis was used to reduce individual symptom scores into 4 components. All components were significantly reduced by ketamine, with components 1 and 2 showing the largest therapeutic effect sizes. Twelve of the 15 unique FOH symptoms loaded onto component 1. Component 2 consisted primarily of aggressive and oppositional symptoms common to both FOH as well as other subtypes of bipolar disorder. As all the subjects had the FOH subtype of bipolar disorder it is unclear how beneficial ketamine might be in bipolar patients who do not have the FOH subtype.

CGI analyses of surveys and patient records following ketamine were supported by observations regarding risk for psychiatric hospitalization. More than half of the subjects who continued to receive

Table 4
Average days per month of alcohol, marijuana and other psychoactive substance use prior to and following initiation of ketamine treatment.

	Before mean {95%CI}	After mean {95% CI}	*t*-test	df	p value
Alcohol	1.85 {0.07–3.62}	0.36 {−0.08–0.80}	1.91	38	< 0.07
Marijuana	2.05 {0.11–3.99}	0.30 {−0.12–0.72}	1.76	39	< 0.09
Other drugs	1.69 {−1.62–5.00}	1.54 {−1.79–4.86}	0.07	12	> 0.9

ketamine had at least one psychiatric hospitalization in the year preceding initiation of ketamine. Indeed, this may have been a precipitant to seeking out or agreeing to try a course of IN ketamine. None of these individuals were hospitalized during the ca 2-year period following initiation of ketamine. If this preliminary finding is confirmed in treatment trials it would suggest that InK ketamine may be a very cost effective treatment.

Most acute-time limited reactions occurred specifically during administration and persisted for 15–120 min. The intensity, frequency and duration of these reactions tended to gradually decrease with repeated administrations without loss in efficacy. Interestingly, tolerance did not appear to develop to the most pleasurable ATLR, which was a sense of relaxation, calm or warmth. At the onset of treatment drug and alcohol abuse was not a significant factor and did not increase even as the patients matured during the study.

Long term AEs were limited and relatively rare, but, in a few cases were of a severe nature, (loss of temperature sensation over most or part of the body) but not progressive. Earlier reports indicated that the most common AE associated with ketamine abuse was ulcerative cystitis, which was reported to occur in 15–20% of chronic users (Jalil and Gupta, 2012), In the present sample a self-limiting (non-ulcerative) cystitis was reported to occur in 5 individuals. Complaints were of pain on urination. These side-effects were non-persistent or intermittent. All urinalyses in these patients were WNL. One patient experienced numbness of hands and forearms when exposed to high ambient temperature (above 80 °F, or when exposed to a warm shower). This condition was found to not be progressive, and could not be conclusively attributed to ketamine treatment.

Ketamine was generally titrated over a number of weeks until an effective dose was reached that resulted in marked attenuation or remission of symptoms. Clinically significant benefits were often apparent after the first treatment. These benefits persisted with only minor subsequent dose adjustments in most cases. The most common initial breakthrough symptom was difficulty thermoregulating, typically, overheating at night prior to sleep resulting in arousal disorders of sleep. Other than the acute-time limited reactions during the administration period most subjects experienced no side effects during the typically 2–5 day period between doses. Following titration it was usually possible to eliminate or reduce many of the other medications patients were receiving. This was particularly true for antipsychotic medications and mood stabilizers. Most patients however received 1–3 concomitant medications.

Finally, a deficit in thermoregulation appears to be tightly linked to symptoms of BP-FOH, and thermoregulatory deficits are known to disrupt sleep-onset, sleep offset and are associated with arousal disorders of sleep. Thus, it was interesting that one apparent conclusion from the chart review was that heat sensitivity and cold tolerance were two key target symptoms useful for dose titration and for determining an appropriate time period between ketamine treatment cycles.

Neuropharmacologically, the diverse array of symptoms seen in youths with BD-FOH including fear of harm, territorial aggression, arousal disorders of sleep, deficient thermoregulation and more classic symptoms of mania may result from dysregulation of the oxerigenic system. Orexins are neuropeptide transmitters whose cell bodies reside in the lateral, dorsomedial and perifornical hypothalamus (Nambu et al., 1999; Richardson and Aston-Jones, 2012), densely innervate all portions of the hypothalamus (e.g., ventrolateral preoptic area, suprachiasmatic nucleus) and have primary projections to cell bodies for the noradrenergic, serotonergic, dopaminergic, histaminergic and cholinergic systems in the locus coeruleus, raphe nuclei, ventral tegmental area, tuberomamillary nucleus and laterodorsal and pedunculopontine nuclei, respectively (Alexandre et al., 2013; Emeson and Morabito, 2005; Nambu et al., 1999; Richardson and Aston-Jones, 2012). The orexin system also has widespread projection to amygdala, hippocampus, septal area and neocortex. Overall, this system appears to play a critical role in wakefulness, arousal, sleep and circadian rhythms (Alexandre et al., 2013), thermoregulation and energy balance (Nattie and Li, 2012), stress response (Nattie and Li, 2012), panic and anxiety (Johnson et al., 2012), reward processing (Richardson and Aston-Jones, 2012), fear conditioning (Wang et al., 2017), feeding behavior (Nambu et al., 1999) and defensive flight or flight reactions (Kayaba et al., 2003). Loss or hypofunction of orexin neurons is associated with narcolepsy (Alexandre et al., 2013) Conversely, we propose that overactivation or dysregulation of portions of the orexin system may be responsible for FOH.

There are several ways in which ketamine may act to either modulate the orexin system or overcome effects of excessive stimulation. First, ketamine, as an NMDA receptor antagonist, should be able to directly attenuate the effects of orexin (Peever et al., 2003; Tose et al., 2009). Second, orexin-mediated fear conditioning may be reversed through normalization of BDNF gene methylation that can be brought about via long-term ketamine use (Ju et al., 2017). In animal studies, ketamine has been found to increase BDNF gene expression that results in an increase in resilience to stress (Duman and Agajanian, 2014). BDNF also plays a critical role in thermoregulation. A recently described facet in the orchestration of the homeostatic response to heat are warm sensitive neurons within the preoptic area that have been molecularly defined by the co-expression of the neuropeptides BDNF and pituitary cyclase activating peptide (PCAP) (Tan et al., 2016). Taken together, we believe these findings support the idea that ketamine's actions on BDNF gene induction through orexigenic transmission has multiple salutory effects in the FOH phenotype; to improve thermoregulatory responses to the environment and to stressors, as well as in the reduction of fear sensitization.

5. Limitations

The limitations of this study include a small sample size that was drawn from a single private practice, as well as those of any retrospective study that employs survey data and recall of severity of symptoms. In particular, contemporaneous data on the patient's clinical state prior to initiation of ketamine was available in the chart review. The survey, in contrast, asked subjects or parents to recall how the subject was prior to initiation of ketamine, so impressions may be filtered or amplified by the contrast. Response to survey was incomplete (45 of 60 responded), possibly leading to bias towards survey response from patients who responded positively to treatment.

Another concern is that some of the patients were referred to DFP for treatment with ketamine and may have benefited from DFP's particular expertise in treating youths with BD-FOH. However, most of the patients had been treated with traditional agents by DFP prior to ketamine without significant improvement. Carefully designed trials will need to be conducted. Further research should focus on the spectrum of type of patients that will benefit from ketamine use, as well as the long-term sequelae of ketamine treatment.

Disclosures

Dr. Teicher receives consulting fees and royalties from BioBehavioral Diagnostic Company/Pearson as inventor of the Quotient ADHD System through a licensing agreement with McLean Hospital. Dr. Teicher holds nine patients related to the diagnosis of psychiatric disorders and six patents related to the treatment of ADHD or depression. None of these involve ketamine. Dr. Teicher has recently commenced a consulting relationship with Abide Therapeutics.

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References

Alexandre, C., Andermann, M.L., Scammell, T.E., 2013. Control of arousal by the orexin neurons. Curr. Opin. Neurobiol. 23, 752–759.
Duman, R.S., Aghajanian, G.K., 2014. Neurobiology of rapid acting antidepressants: role of BDNF and GSK-3[beta]. Neuropsychopharmacology 39, 233.
Dunlap, W.P., Cortina, J.M., Vaslow, J.B., Burke, M.J., 1996. Meta-analysis of experiments with matched groups or repeated measures designs. Psychol. Methods 1, 170–177.
Emeson, R.B., Morabito, M.V., 2005. Food fight: the NPY-serotonin lInK between aggression and feeding behavior. Sci. STKE 2005, pe12.
Fahim, I., Ismail, M., Osman, O.H., 1973. Role of 5-hydroxytryptamine in ketamine-induced hypothermia in the rat. Br. J. Pharmacol. 48, 570–576.
Gibbons, R.D., Hedeker, D.R., Davis, J.M., 1993. Estimation of effect size From a series of experiments involving paired comparisons. J. Educ. Stat. 18, 271–279.
Jalil, R., Gupta, S., 2012. Illicit ketamine and its bladder consequences: is it irreversible? BMJ Case Rep. 2012.
Johnson, P.L., Molosh, A., Fitz, S.D., Truitt, W.A., Shekhar, A., 2012. Orexin, stress, and anxiety/panic states. Prog. Brain Res. 198, 133–161.
Ju, L.S., Yang, J.J., Lei, L., Xia, J.Y., Luo, D., Ji, M.H., Martynyuk, A.E., 2017. The combination of long-term ketamine and extinction training contributes to fear erasure by Bdnf methylation. Front. Cell Neurosci. 11, 100.
Kayaba, Y., Nakamura, A., Kasuya, Y., Ohuchi, T., Yanagisawa, M., Komuro, I., Fukuda, Y., Kuwaki, T., 2003. Attenuated defense response and low basal blood pressure in orexin knockout mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285, R581–R593.
Mayring, P., 2000. Qualitative content analysis. Forum: Qual. Soc. Res. 1 (Art. 20). ⟨http://nbnresolving.de/urn:nbn:de:0114fqs0002204⟩.
Murphy, P.J., Frei, M.G., Papolos, D., 2014. Alterations in skin temperature and sleep in the fear of harm phenotype of pediatric bipolar disorder. J. Clin. Med. 3, 959–971.
Nambu, T., Sakurai, T., Mizukami, K., Hosoya, Y., Yanagisawa, M., Goto, K., 1999. Distribution of orexin neurons in the adult rat brain. Brain Res. 827, 243–260.
National Institute of Mental Health, N., 1985. CGI (Clinical Global Impression) scale–NIMH. Psychopharmacol. Bull. 12, 839–844.
Nattie, E., Li, A., 2012. Respiration and autonomic regulation and orexin. Prog. Brain Res. 198, 25–46.
Papolos, D., Hennen, J., Cockerham, M., 2005. Obsessive fears about harm to self or others and overt aggressive behaviors in youth diagnosed with juvenile-onset bipolar disorder. J. Affect. Disord. 89, 99–105.
Papolos, D., Mattis, S., Golshan, S., Molay, F., 2009. Fear of harm, a possible phenotype of pediatric bipolar disorder: a dimensional approach to diagnosis for genotyping psychiatric syndromes. J. Affect. Disord. 118, 28–38.
Papolos, D.F., Teicher, M.H., Faedda, G.L., Murphy, P., Mattis, S., 2013. Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype. J. Affect. Disord. 147, 431–436.
Peever, J.H., Lai, Y.Y., Siegel, J.M., 2003. Excitatory effects of hypocretin-1 (orexin-A) in the trigeminal motor nucleus are reversed by NMDA antagonism. J. Neurophysiol. 89, 2591–2600.
Pietersen, C.Y., Bosker, F.J., Postema, F., Fokkema, D.S., Korf, J., den Boer, J.A., 2006. Ketamine administration disturbs behavioural and distributed neural correlates of fear conditioning in the rat. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 1209–1218.
Richardson, K.A., Aston-Jones, G., 2012. Lateral hypothalamic orexin/hypocretin neurons that project to ventral tegmental area are differentially activated with morphine preference. J. Neurosci. 32, 3809–3817.
Tan, C.L.1, Cooke, E.K.1, Leib, D.E.2, Lin, Y.C.1, Daly, G.E.1, Zimmerman, C.A.2, Knight, Z.A.3, 2016. Warm-sensitive neurons that control body temperature. Cell 167 (1), 47–59. http://dx.doi.org/10.1016/j.cell.2016.08.028. (Epub 2016 Sep 8).
Tose, R., KushInKata, T., Yoshida, H., Kudo, M., Furukawa, K., Ueno, S., Hirota, K., 2009. Interaction between orexinergic neurons and NMDA receptors in the control of locus coeruleus-cerebrocortical noradrenergic activity of the rat. Brain Res. 1250, 81–87.
Velicer, W., 1976. Determining the number of components from the matrix of partial correlations. PsychometrInKa 41, 321–327.
Wang, H., Li, S., Kirouac, G.J., 2017. Role of the orexin (hypocretin) system in contextual fear conditioning in rats. Behav. Brain Res. 316, 47–53.
Zwick, W.R., Velicer, W.F., 1986. Comparison of five rules for determining the number of components to retain. Psychol. Bull. 99, 432–442.