



Brief report

Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype



Demitri F. Papolos^{a,b,*}, Martin H. Teicher^c, Gianni L. Faedda^{d,e}, Patricia Murphy^f, Steven Mattis^{g,h}

^a Juvenile Bipolar Research Foundation, Maplewood, NJ, USA

^b Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA

^c Harvard Medical School, Clinical Chronobiology Laboratory, McLean Hospital, MA, USA

^d Lucio Bini Mood Disorders Center, New York, NY 10022, USA

^e New York University Child Study Center, Langone Medical Center, NY, USA

^f Eisai, Inc., Clinical Research Scientist, Woodcliff Lake, NJ, USA

^g Department of Neurology, Weill Cornell Medical Center, New York, NY, USA

^h Mattis & Luck Center for Neuropsychological Services, New York, NY, USA

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ABSTRACT

Objectives: Intravenous ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to exert a rapid antidepressant effect in adults with treatment resistant depression. Children with bipolar disorder (BD) often respond poorly to pharmacotherapy, including polypharmacy. A pediatric-onset Fear of Harm (FOH) phenotype has been described, and is characterized by severe clinical features and resistance to accepted treatments for BD. The potential efficacy and safety of intranasal ketamine in children with BD with FOH-phenotype were assessed by a systematic retrospective chart review of a case series from the private practice of one of the authors, including cases with clear refractoriness to mood stabilizers, antipsychotics and benzodiazepines.

Methods: A comparison was made between routinely collected symptom measures 1–2 weeks prior to and after the administration of ketamine, in 12 treatment-refractory youth, 10 males 2 females ages 6–19 years.

Results: Ketamine administration was associated with a substantial reduction in measures of mania, fear of harm and aggression. Significant improvement was observed in mood, anxiety and behavioral symptoms, attention/executive functions, insomnia, parasomnias and sleep inertia. Treatment was generally well-tolerated.

Conclusions: Intranasal ketamine administration in treatment-resistant youth with BD-FOH produced marked improvement in all symptomatic dimensions. A rapid, substantial therapeutic response, with only minimal side effects was observed. Formal clinical trials to assess safety and efficacy are warranted.

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1. Introduction

Bipolar disorder (BD) is a severe and relatively common, recurrent, psychiatric disorder of depression, mania, hypomania, and mixed episodes. Pediatric bipolar disorder (PBD) is characterized by rapid cycling states, is frequently treatment resistant and associated with multiple comorbidities that confound early diagnosis and complicate treatment (Berry et al., 2011; Chang, 2010; Faedda et al., 1995; Geller and Luby, 1997; Papolos and Papolos, 1999; Papolos, 2003). The Fear-of-harm phenotype of BD (BD-FOH), first described in 2009, includes features not listed among the DSM-IV BD criteria. Symptoms of

co-morbid conditions, that are primary features of BD-FOH, include: aggression, separation anxiety, sleep/arousal disorders (parasomnias and REM sleep-disorders, fearfulness of intruders, vivid recurrent nightmares, carbohydrate cravings, food hoarding, and germ contamination fears (Papolos et al., 2009). Some behavioral and affective symptoms of BD-FOH phenotype are consistent with increased fear sensitization with fear of aggression, and reactive aggression in response to perceived threats (see Table 1). Additionally, BD-FOH cases often overheat in the evening and/or feel cold in the morning, and experience thermo-disregulation: they feel hot/sweating in neutral temperatures and/or feel comfortable in extremely cold temperatures (Papolos et al., 2009).

Young children with BD-FOH experience frequently initial insomnia with bedtime refusal and/or difficulty settling at night, older youth report insomnia with racing thoughts and psychomotor agitation, and both, children and parents often complain of morning

* Corresponding author at: Director of Research, The Juvenile Bipolar Research Foundation, 22 Crescent Rd. Westport, CT, USA.

Tel.: +1 203 246 1939; fax: +1 203 842 2180.

E-mail addresses: demitri@optonline.net, dpapolos@jbrf.org (D.F. Papolos).

Table 1

Key factors of the fear of harm phenotype.

Aggression (territorial) ^a	Self-esteem
Has irritable mood states	Complains of being bored
Is intolerant of delays	Experiences periods of self-doubt and poor self-esteem
Relentlessly pursues own needs and is demanding of others	Feels easily criticized and/or rejected
Is willful and refuses to be subordinated by others	Feels easily humiliated or shamed
Argues with adults	
Is bossy towards others	Psychosis/parasomnias/sweet cravings/obsessions (PPSO)
Defies or refuses to comply with rules	Has acknowledged experiencing auditory and/or visual hallucinations
Blames others for his/her mistakes	Has night terrors and/or nightmares
Is easily angered in response to limit setting	Wets bed
Lies to avoid consequences of his/her actions	Craves sweet-tasting foods
Has protracted, explosive temper tantrums	Hoards or avidly seeks to collect objects or food
Has difficulty maintaining friendships	Has concern with dirt, germs, or contamination
Displays aggressive behavior towards others	
	Sleep/arousal
Harm to self and others	Has difficulty arising in the AM
Has destroyed property intentionally	Has difficulty settling at night
Curses viciously, uses foul language in anger	Has difficulty getting to sleep
Makes moderate threats to others or self	Sleeps fitfully and/or awakens in the middle of the night
Makes clear threats of violence to others or self	
Has made clear threats of suicide	
Is fascinated with gore, blood, or violent imagery	
Anxiety	
Displays excessive distress when separated from family	
Exhibits excessive anxiety or worry	

^a The term territorial is used to describe the nature of aggressive symptoms associated with this factor, typically defensive in reaction to limit setting, deprivation or perceived threat that distinguishes them from other forms of aggressive behaviors.

lethargy sleep-inertia (14). These sleep- and temperature-related symptoms may stem from a circadian phase delay and/or impaired ability to dissipate heat, particularly near the evening circadian temperature peak (Papolos et al., 2009).

Zarate et al., reported that i.v. ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, produced a rapid, robust, and relatively sustained antidepressant effect in adults with treatment-resistant unipolar and bipolar depression (Zarate et al., 2006, 2012). Ketamine, an approved anesthetic agent, is routinely used as a premedication for pediatric anesthesia, and appears to be better tolerated by children than adults. Ketamine has a wide margin of safety, does not depress respiratory and cardiovascular functions and rarely causes emergence reactions (transient psychotomimetic symptoms during anesthesia induction, almost never distressing, Green and Johnson, 1990; Howes, 2004). We decided (DFP) to administer ketamine, to one severely ill treatment refractory child (off label, with the parents' consent and the child's assent). Her dramatic positive response, along with literature indicating ketamine's ability to decrease fear sensitization and (dose-dependently) reduce body temperature in animals (Pietersen et al., 2006; Fahim et al., 1973), led to the off-label use of ketamine in a group of children (> 40) over a 4-year period. All individuals had received most conventional mood stabilizers, antipsychotics and anxiolytics, but remained highly symptomatic and impaired.

We report here on 12 cases where complete ratings of symptoms and side-effects were recorded. All individuals studied have continued maintenance treatment with ketamine, one for over 4 years.

2. Methods

2.1. Retrospective chart review

A systematic chart review of the 40 subjects with BD-FOH treated with off-label ketamine was conducted, and patients were selected based on: (1) availability of at least one pre-treatment

symptom rating assessment (completed 1–2 weeks prior to ketamine treatment); (2) two or more post-treatment symptom rating extending over > 2-month period. All subjects were diagnosed with BD according to DSM-IV criteria, and were treatment refractory (GAF < 55). The Child Bipolar Questionnaire (CBQ), Overt Aggression Scale (OAS) and Yale Brown Obsessive-compulsive Scale (YBOCS) were used to identify BD-FOH cases, and periodically to assess symptom severity and treatment response (Papolos et al., 2006; Yudofsky et al., 1986; Storch et al., 2006).

2.2. Rating instruments

Four rating instruments were used periodically in the course of clinical practice. Three were used to monitor symptom severity, and one was used to monitor the dissociative side effects of ketamine.

2.3. The child bipolar questionnaire (CBQ)

The CBQ is a 65-item parent-report scale, originally designed to identify cases with possible BD-FOH for further structured diagnostic assessment, and sub-grouping (based on symptom dimensions) for genotyping. It uses a scoring algorithm to identify DSM-IV BD, and attention-deficit/hyperactivity disorder (ADHD, 13). The CBQ assesses 10 domains, and provides a Total score, a Core Index score (core features of BD-FOH) and a FOH Subscale score (sum-score of 6 FOH factors). The Cronbach's alpha coefficient, to assess the internal consistency of the CBQ, in clinician-assigned diagnosis of BD, was 0.929 ($n=2427$; Papolos et al., 2006).

2.4. Overt aggression scale (OAS)

The OAS is a 15-item clinician rating of four categories of aggression: Verbal (VA), Physical Against Objects (PAO), Physical Against Self (PAS), and Physical Against Other People (PAP) (Yudofsky et al., 1986).

2.5. Yale Brown obsessive-compulsive scale (YBOCS)

The YBOCS is a clinician rated scale of obsessive-compulsive symptoms in six dimensions which contains three subscales with symptoms relevant to the BD-FOH: Contamination-Fear Obsessions (CO), Aggressive Obsessions (AO), Hoarding/Saving Obsessions (HSO) (Storch et al., 2006).

2.6. The clinician administered dissociative states scale (CADSS)

The CADSS (16) was used to assess dissociative side effects of pre- and post-ketamine treatment. This 27-item scale has two components: a subjective, 19 item scale of clinician-read, subject-endorsed ratings (0=not at all, 1=slightly, 2=moderately, 3=considerably, 4=extremely). The observer component rates eight behavioral items consistent with a dissociative state (Bremner et al., 1998; Coons, 1998; Spiegel and Cardena 1991). The CADSS was completed by the clinician 10' before and 1 h following ketamine administration.

2.7. Ketamine administration

Subjects were given a racemic mixture of intranasal ketamine compounded in a 100 mg/ml solution and delivered intranasally in metered doses of 10 mg/administrations to 12 treatment-refractory youth, 10 males 2 females ages 6–19 years. Drug was delivered by an FDA approved metered nasal pump spray bottle made of white polyethylene plastic (Gallipot pharmaceuticals). It consists of a 1 ounce container that delivers 0.1 cc spray per pump. Dose adjustments were based on CADSS' side-effects profile and clinical response, and occurred at 3–6 day intervals until remission (of primary symptoms) was obtained. Doses ranged from 30 to 120 mg every 3–7 days, as clinically indicated and tolerated by individual patients.

2.8. Statistical analyses

The Pretreatment (PRE) ratings were obtained by parent interview ~1 to 2 weeks prior to initiation of intranasal ketamine. The post-treatment (POST) ratings were obtained from the same parent after multiple ketamine doses (an average of 6 administrations spanning 20 weeks). These ratings were averaged to provide a single POST measure for each instrument/subscale. PRE and POST comparisons were made using repeated-measure multivariate analysis of variance (MANOVA). Data were analyzed using R (R Development Core Team, 2010).

Our hypothesis, that side-effect probability or severity was dose dependent, was tested using non-linear least squares regression in which a two parameter logistic regression model was compared to a null-hypothesis model positing equal probability or severity across the four ketamine doses. Calculations were made using NL2SOL, an adaptive iterative non-linear algorithm implemented in R (*nls*) (Dennis et al., 1981). The null and dose-dependent models were evaluated by ANOVA to ascertain if the reduction in degrees of freedom by the more complex dose-dependent model was accompanied by a significant reduction in residual error.

3. Results

Twelve subjects (10 males) met criteria for the chart review, ranging in age from 6 to 19 years, all had psychotic symptoms and were diagnosed by DSM-IV nomenclature as BP-I, and all were significantly impaired, with GAS scores of less than 50, indicating a moderate to major degree of interference in functioning in most

Table 2

Pre-versus post-ketamine ratings on the child bipolar questionnaire, overt aggression scale and Yale-Brown obsessive-compulsive scale.

CBQ dimension	Pre		Post		p-value*
	Mean	SD	Mean	SD	
Territorial aggression ^a	43	9	22	6	< 0.0001
Attention/executive function	35	7	23	5	< 0.0001
Mania	36	7	21	6	< 0.0001
Harm to self/others ^a	15	4	9	3	< 0.0001
Self esteem ^a	20	2	11	3	< .0001
Sleep ^a	13	2	7	2	< 0.0001
Sensory sensitivity	8	3	5	2	< 0.01
Hypersexuality	6	3	4	1	< 0.05
PPSO ^a	14	4	9	2	< 0.01
Anxiety ^a	7	2	3	1	< 0.0001
CBQ total	196	27	111	22	< 0.0001
Core index	65	9	34	6	< 0.0001
FOH score	111	16	58	13	< 0.0001

^a FOH factor.

social areas or severe impairment of functioning in one area (i.e., suicidal ideation). School refusal, comorbid anxiety, obsessive rituals and poor social skills contributed to their impairment. These subjects were all treatment refractory having failed trials of mood-stabilizers (lithium and anticonvulsants), antipsychotics, and/or benzodiazepines, usually in combination (mean number of medication=4.3). Intranasal ketamine doses of 30–120 mg, administered at intervals of 3–7 days, produced a rapid therapeutic response, usually within 1-hr of the administration (within 24-h in all cases). Therapeutic benefits typically lasted 72–96 h, and were followed by a dramatic return of FOH symptoms.

As seen in Table 2, there were marked PRE and POST differences in CBQ ratings across the 10 symptom dimensions. The composite MANOVA revealed a robust PRE POST treatment difference (Pillai's Trace=0.95, $F=227.01$, $df=1,11$, $p < 10^{-7}$). While there were significant differences between different CBQ factors (Pillai Trace=0.99, $F=56.29$, $df=9,3$, $p < 0.004$), the within-subject interaction between PRE POST treatment ratings and CBQ items was not significant (Pillai Trace=0.95, $F=6.62$, $df=9,3$, $p < 0.1$), thus suggesting that PRE-POST treatment effects were reasonably consistent across different dimensions. Overall, there was a 48% reduction in Core Index scores ($F=247.78$, $df=1,11$, $p < 10^{-8}$) and a 48% reduction in FOH scores ($F=140.33$, $df=1,11$, $p < 10^{-6}$).

OAS' ratings of aggression were also substantially reduced by ketamine treatment (Pillai's Trace=0.78, $F=40.00$, $df=1,11$, $p < 0.0001$) (Table 2). Differences between the subscale measures and a significant PRE POST treatment by measure interaction (Pillai's Trace=0.80, $F=11.67$, $df=3,9$, $p < 0.002$) were found. Using multivariate effect size, within-subject reduction was the greatest on ratings of verbal aggression (Pillai's Trace=0.87), and smallest on ratings of aggression towards self (Pillai's Trace=0.48).

Table 2 shows mean scores for the three relevant YBOCS subscales from Pre to Post ketamine. The composite MANOVA showed a PRE POST treatment effect (Pillai's Trace=0.65, $F=20.83$, $df=1,11$, $p < 0.001$) and a significant PRE POST treatment by subscale interaction (Pillai's Trace=0.66, $F=9.8$, $df=2, 10$, $p < 0.005$). The individual MANOVA tests showed that among the obsessive dimensions, only aggressive obsessions were significantly reduced by ketamine treatment.

Table 3 describes the incidence, dose-dependent changes in incidence, and severity of CADSS items reported as experienced by the 12 patients. The side effects are listed in order of overall incidence (percent of patients reporting this item at any dose), from highest to lowest. The table also provides data on the number of subjects experiencing side-effects on each dose, and the number of subjects experiencing mild-1, moderate 2–3, or

were rarely observed beyond the first 60 min post administration. The development of tolerance to side effects was observed in over 90% of the sample. Side effects that were observed early, diminished over time or remained minimal following 4–5 administrations of the final effective dose. Dissociative side effects, when they did occur on initial dosing, also diminished subsequently, and were rarely reported or observed once tolerance to side-effects developed.

Several findings require further discussion. Ketamine produced rapid improvement of (hypo)manic hyperactivity, mood lability, hyperarousal, aggressive behaviors and obsessions. Improvement was also seen in ratings of anxiety, sleep, inattention, racing thoughts and carbohydrate craving. In most cases we observed a complete abolishment of manic/hypomanic and depressive symptoms. Ketamine administration also led to remission of symptoms associated with the core features of the FOH phenotype, including fear of harm, sleep-onset and sleep-offset disturbances, parasomnias, and the thermoregulatory symptoms associated with this syndrome.

Ketamine produced a dramatic reduction in the thermoregulatory symptom ratings. Of note, improvement of the behavioral symptoms appears to be temporally associated with the resolution of the thermoregulatory deficits. For example, the improvement of night-time overheating, and extreme cold tolerance have been noted to immediately precede symptomatic improvement. Furthermore, we also noted that once the patients' therapeutic window (typically 36–60 h) was exceeded, there was re-emergence of previously improved symptomatology.

Once remission of symptoms was achieved (marked reduction of symptoms rated as severe prior to treatment), ketamine administration maintained remission of symptoms with virtually no side effects for variable periods of time, typically 3–7 days. Ketamine successfully maintained full remission of symptoms even when previous concurrent treatments were tapered and withdrawn. In all cases, previously prescribed psychotropic medications were continued until a clear and consistent benefit of ketamine treatment could be observed. Over the course of several months of treatment other psychotropic agents were discontinued or tapered without loss of stability. This seems to indicate the specific efficacy of ketamine in resolving symptoms without causing any apparent development of pharmacological tolerance or development of unwanted side effects.

Conversely, as the effect of ketamine wore off, symptoms recurred in a fairly rapid progression, including a rapid return of the thermoregulatory deficits, which were followed within hours by the reappearance of clinical and behavioral symptoms and return to pre-treatment, full phenotypic manifestations until ketamine was administered.

The broad spectrum of ketamine treatment effects, and concurrent recurrence of cognitive, behavioral, affective, sleep and thermoregulatory manifestations as the ketamine effect wears off, lends support to the co-occurrence and interconnectedness of several psychopathological and pathophysiological dimensions observed in the FOH phenotype.

More importantly, this study suggests the effectiveness of ketamine in early-onset treatment-refractory BD, both in monotherapy and for maintenance treatment of BD-FOH. This case series raises the possibility that the benefits of ketamine treatment extend beyond its acute antidepressant effect in adults with treatment refractory depression, pointing to additional areas of psychopathology and impairment that might respond to this experimental treatment. Ketamine was highly effective in resolving both classic bipolar symptoms and symptoms that are integral part of the FOH phenotype. Although these are preliminary findings and require independent replication, they open the possibility for the clarification of a subtype of bipolar disorder characterized by pediatric onset, high rates of psychosis, treatment

resistance, temperature dysregulation and the "Fear of Harm" phenotype. It remains to be seen whether this treatment may benefit other subtypes of pediatric bipolar disorder regardless of age of onset, polarity or comorbidity.

Our experience with the use of intranasal ketamine as an off-label option in severely ill children with PBD who have failed to benefit from conventional treatments provides only the most preliminary support. Carefully designed trials will need to be conducted. To this end we have obtained FDA Investigational New Drug and IRB approval to conduct a randomized double-blind placebo-controlled trial in this population.

Conflict of interest

No conflict declared.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2012.08.040>.

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