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

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ABSTRACT

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.

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BACKGROUND

Pediatric bipolar disorder (PBD) has been estimated to affect close to 1 million children and adolescents in the United States at any given time (Moreno et al 2007). Early onset is associated with heightened familial loading (Faraone et al 2003) and worse course of illness (Geller et al 2000, Post et al, 2010), including a high risk of suicide (Geller at al 2000, 2004, Goldstein et al 2005, Papolos et al 2009), and increased likelihood for substance abuse, lability of mood state, and high psychiatric and medical comorbidity (Faedda et al, 1995).

There is good consensus among researchers that the presentation of BD in childhood is far different than in adults, and is characterized by a chronic course of highly impairing affective symptoms, severely irritable mood, and a mixed or ultra-rapid cycling presentation of depression, mania, and often, psychotic features. Common comorbidities include: conduct and oppositional defiant disorders, anxiety disorders, and attention-deficit hyperactivity disorder (Geller et al, 1996, Papolos and Papolos 1999, Youngstrom et al, 2003).

Importantly, early identification and treatment have been shown to reduce the negative impact of this often chronic condition. Unfortunately, it is estimated that over 80% of PBD cases are refractory to traditional mood-stabilizers and neuroleptics. Therefore, an undeniable public health imperative exists to develop new therapies to address persistent mood symptoms, promote sustained remission and improve quality of life in this condition.

OBJECTIVE

Juvenile bipolar disorder frequently fails to adequately respond to antipsychotics or mood stabilizers. This is often the case in children with a specific subtype, called the fear of harm (FOH) phenotype, characterized by separation anxiety, cold insensitivity, heat intolerance and parasomnias. We reported that ketamine, which is better tolerated by children than adults, has been reported to attenuate symptoms in 12 children with FOH during a 2-week trial (Papolos et al, 2013). Additional clinical practice has developed a titration method that has provided a safe, slow titration of dosing against acute adverse events, while permitting extended treatment effect and duration of response.

METHODS

Subjects who are previously-diagnosed with DSM-5 bipolar I, bipolar II, or bipolar-NOS are then screened using a tool described on the JBRF website (JBRF.org) that asks questions related to rage, FOH, and suicidality.

Parents are asked a series of questions to determine which of the following symptoms are present in their child:

Category	Item
Manic/ Hypomanic Behaviors	*Rapid, abrupt switches of mood – easily shifts between any or all of the following moods: silly, goofy, giddy, angry, irritable, extreme boredom, sadness, depression*
	Racing thoughts and or pressured speech
	Hyperactivity – frequently unable to sit still, in constant movement
	Often feels a sense of urgency – mission mode; will not yield when wants or perceives need for something
	Is easily distracted – goes from one subject to another, cannot stay with one activity very long
Depressive Behaviors	*Withdraws from others, isolates self*
	Frequently complains of being bored and wants to do something, but nothing seems interesting enough
	Energy level is low and/or is easily stressed and frustrated by minimal demands
	Complains that parents, siblings or friends do not love or care about them
	Has suicidal thoughts --says I don't want to live, or I wish I were dead
Sleep Disturbance	Difficulty getting to sleep at night
	Wakes up in the middle of night
	Difficulty getting up in AM
	Restlessness during sleep- always moving around in bed at night
	Day for night reversal --goes through periods where he/she cannot sleep at night and sleeps during the day.
Arousal Disorders of Sleep	Nightmares
	Night terrors
	Teeth-grinding
	Bedwetting
	Sleep-walking
	Restless legs
	Talks in sleep
Temperature Disturbance	Complains of body being warm/hot at bedtime and/or overheats during night
	Complains of overheating during day (hot flashes) in neutral temperatures
	Complains of overheating or sweats profusely on exertion
	Has moderate to extreme tolerance to the cold – e.g. able to go out into the cold without a jacket
	Complains of being cold when the ambient temperature is warm
Fear of Harm	Afraid that others will hurt, be critical, reject or judge them
	Afraid of hurting others
	Afraid will say something that is embarrassing
	Easily misjudges other people's facial expressions or tone of voice or intent as threatening, intimidating, critical
	Is self-conscious and feels easily humiliated in social situations
Aggressive Behaviors Towards Others, Self or Objects	Attempts to control and dominate others (e.g. is bossy and demands to get their way) and /or is aggressive in response to limit setting (e.g. is angered when parents set limits or use the word "no")
	Aggressive behavior towards sibling(s), parents, or other authority figures, and/or curses viciously or threatens others when angry
	Aggressive towards self-bangs head, picks scabs, scratches or cuts self, has made suicide attempts
	Aggressive in response to requests to transition from one context to another
	Often threatens or breaks objects, slams doors, smashes walls
Anxiety	Separation anxiety – afraid to be alone, clings to figures of safety
	Phobias: fear of germs, bugs, spiders, other
	Morbid preoccupation with death and gory themes
	Frequently anxious in social situations
	Afraid to sleep in own bed at night
Psychotic Symptoms	Grandiose ideas about self, about what others may do to them
	Auditory hallucinations --hears voices inside of head
	Visual hallucinations --sees things that are not there
	Embellishes reality, tells tall tales, lies to others about their experience
	Paranoid thought or ideas --believes others may harm them

The most severe symptoms are culled from this list and assessed for reduction as the measure of response

Assessment of Acute AEs (associated with dosing)

Five minutes after completion of the initial dose (where applicable) and 5 min after each administration of any new dose of drug, a series of questions are asked to verify that it is safe and tolerable to continue with nasal administrations.

For the following 5 questions:

If all AEs are absent or mild, another dose may be administered.

Moderate AEs after the 1st Assessment are re-assessed after 10 minutes.

If AEs remain moderate after the 2nd Assessment, STOP

Question #1. Nausea

0- None
1- My stomach is queasy
2- I feel like throwing up
3- Child actually throws up –THIS IS A "hard stop".

Question #2. Dizziness and loss of balance

All responses of mild or moderate are confirmed by asking them to stand up and walk while being observed

0- No, I have no sense of spinning, unbalance. Everything feels and appears solid and grounded. (Observation: gait should be solid, even and straight.)
1- Yes, things feel or look just a little bit floaty or moving. (Observation: Perhaps balance caught off guard but should be able to correct quickly and walk well.)
2- I feel dizzy, e.g. the room feels like it is spinning, I feel like I would be unsteady if I got up. (Observation: be available for assistance, gait is a bit wobbly.)
3- I feel very dizzy, e.g. the room is really spinning; I don't think I could get up and walk now. (Observation: be available for assistance, gait is really veering all over and child is holding on for support.)

Question #3. Sense of Body

0- None, my body feels just like it always does, I feel normal and look normal to myself
1- I have a vague sense that my body isn't the way I expect it to look/feel
2- It seems like my hands, legs and/or body have increased or decreased in size
3- Wow, parts of my body are really large or small.

Question #4. Sense of Place in Space

0- No change, everything feels just like it always does in terms of me relative to objects in my environment.
1- Things feel like they are happening either closer or further away from me than I would expect them to.
2- I don't really feel connected to things that going on around me or to things that are happening to me? It's like I'm not really in reality.
3- I feel totally outside of my body, like I'm are watching things that are happening "over there" or far away and I'm not at all part of what is going on?

Question #5. Sense of Disorientation.

0- When I look around, everything seems normal to me, exactly what I expect to see.
1- When I look around, I'm surprised that things don't seem quite right. I know what everything is but some things are bigger or smaller or faster or slower than I expect them to be.
2- Things are kind of foggy and unclear. I can't quite tell what is going on or why.
3- I feel like I'm in a dream. Things I see and ways I feel are very strange and unexplainable. Everything seems out of my control.

Assessment of Clinical Response

Patients are queried about symptoms culled as most severe from the survey, as well as evidence for changes in thermal dysregulation

At first, assessments are twice-weekly or weekly.

As dose stabilizes, assessments are less frequent, but loss of response is continuously monitored.

RESULTS

Examples of starting MID and doses after 2 months and duration of response (at 2 months) are displayed below. Tolerability is independent of age and weight, as are responses. Nearly all patients demonstrated some initial response, but response at 2 months was variable.

Age at start	Initial weight (kg)	Initial dose (mg)	Dose at 2 months	Dose (mg/kg)	Duration of relief (h)
9	32.3	30	120	3.72	48
11	109.68	30	140	1.28	72
11	50.5	30	150	2.97	48
12	41.8	30	100	2.39	24+
16	70	30	70	1.00	48
16	108.2	30	140	1.29	48
17	118	30	90	0.76	*
9	42.27	40	170	4.02	36**
12	70.45	50	180	2.56	<24
15	49.5	50	80	1.62	60

*originally had strong response but relapsed

** living in a residential facility never achieved full therapeutic response

RESULTS

Safety:

- No serious AEs have been reported in over 100 subjects treated for up to 10 years (manuscript in preparation)
- No AEs have lead to discontinuation of treatment- although lack of convenience has proven burdensome and lead to discontinuation in some cases
- No reported loses in cognition or reports of cognitive changes other than improvements in focus and attention

Clinical Response:

The most immediate responses seen are:

- Sense of Calm
  Reductions in racing thoughts and improvement in ability to focus
- Increase in expression of feelings and perceptions
- Experience of Cooling
  Parents have claimed that they feel a warming of their child's hands
  Descriptions of being cold in bed for the first time
- Reduction in intensity and/or duration of tantrums
  prior to treatments, patients can have multiple "complete meltdowns" in a single day
- Improvements in sleep
  subjects describe cooling and better quality of sleep/ sleeping on their own rooms on multiple nights- sometimes for the first times in their lives

These responses usually last for ½ to one full day after the first dose

Slower onset (months to years):

- Relief of fear and social anxieties
- Development of ability to learn
  Subjects gain an ability to learn coping skills, develop relationships, return to school
  Long term need for therapy with development of coping skills now possible

Abuse and addiction/dependence

Parents are required to store drug under lock and key.

Once full clinical response is established, doses can remain stable levels for extended periods of time (months), even as emergence events become less pronounced and more tolerable.

Incidence of abuse (as indicated by requests to fill drug prescription early) is estimated to be approximately 2% and of single events.

Response dictates that there is a psychological dependence for symptom relief, but there have been cases of discontinuation without any withdrawal effects.

There is no evidence of physical addiction.

CONCLUSIONS

- Dose titration for tolerability and clinical response requires extended periods of individualized treatment and development of tolerance.
- Effective doses are variable and likely depend on ability to absorb drug (nasal architecture), as well as metabolism.
- Once stable doses are established, drug is well-tolerated.

References:

Faedda GL, Baldessarini RJ, Suppes T, Tondo L, Becker I and Lipschitz DS; Harv Rev Psychiatry 3: 171-195, 1995
Faraone SV, Glatt SJ and Tsuang MT,. Biol Psychiatry 53: 970-977, 2003
Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP and Gundersen K; J Am Acad Child Adolesc Psychiatry 39: 1543-1548, 2000
Geller B, Tillman R, Craney JL and Bolhofner K; Arch Gen Psychiatry 61: 459-467, 2004
Geller B, Todd RD, Luby J and Botteron KN; Psychiatr Clin North Am 19: 253-267, 1996
Goldstein TR, Birmaher B, Axelson D, Ryan ND, Strober MA, Gill MK, Valeri S, Chiappetta L, Leonard H, Hunt J, Bridge JA, Brent DA and Keller M; Bipolar Disord 7: 525-535, 2005
Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB and Olfson M; Arch Gen Psychiatry 64: 1032-1039, 2007
Papolos D, Mattis S, Golshan S and Molay F;. J Affect Disord 118: 28-38, 2009
Papolos D and Papolos J (1999). The Bipolar Child: The Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder. New York, Broadway Books.
Papolos DF, Teicher MH, Faedda GL, Murphy P and Mattis S; J Affect Disord 147: 431-436, 2013
Post, M. R, Leverich, S. G, Kupka, W. R, Keck, E. P, McElroy, L. S, Altshuler, L. L, Frye, A. M, Luckenbaugh, A. D, Rowe, Michael, Grunze, Heinz, Suppes, Trisha, Nolen and A. W (2010). Early-Onset Bipolar Disorder and Treatment Delay Are Risk Factors for Poor Outcome in Adulthood. Memphis, TN, ETATS-UNIS, Physicians Postgraduate Press.
Youngstrom EA, Findling RL and Calabrese JR; J Abnorm Child Psychol 31: 231-245, 2003