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BRIEF REPORT

Brief Report: Intranasal Ketamine in Adolescents and Young Adults with Autism Spectrum Disorder—Initial Results of a Randomized, Controlled, Crossover, Pilot Study

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Abstract

Dysregulation of glutamate neurotransmission plays a critical role in autism spectrum disorder (ASD) pathophysiology and is a primary target for core deficit research treatment trials. The mechanism of action of ketamine has striking overlap with the theory of ASD as a disorder of synaptic communication and neuronal networks. This two-dose, double-blind, placebo controlled, cross-over pilot trial of intranasal (IN) ketamine targeting core social impairment included individuals with ASD ($N=21$) between 14 and 29 years. Participants were randomized to received two doses of IN ketamine (30 and 50 mg) and two doses of matching placebo. No significant impact was noted on the Aberrant Behavior Checklist Social Withdraw subscale. The IN ketamine was well tolerated, with only transient mild adverse effects.

Keywords Autism · Ketamine · Clinical trial

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder associated with marked impairment in social behavior. The rising prevalence of ASD, currently estimated at 1 in 59 children, is a national health concern with an estimated annual cost to society of $95 billion (Baio 2012; Ethridge et al. 2017; Interagency Autism Coordinating Committee [IACC] 2010). To date, pharmacotherapy research in ASD has been most successful at developing treatments for co-occurring behavioral symptoms such as irritability, hyperactivity, and inattention (McCracken et al. 2002; Owen et al. 2009; Research Units on Pediatric Psychopharmacology Autism Network 2005). However, two decades of pharmacotherapy research has failed to identify a single drug proven to reduce the core social deficits of ASD in controlled trials (Posey et al. 2008b; IACC 2010). Drug development in ASD has been hindered by the heterogeneous clinical presentation of study participants as well as absence of established ASD biomarkers and objective outcome measures.

Dysregulation of glutamate neurotransmission plays a critical role in ASD pathophysiology and has been a primary target for core deficit research treatment trials (Belsito et al. 2001; Minshawi et al. 2015; Posey et al. 2009; Wink et al. 2017). Glutamate is the primary excitatory brain neurotransmitter and influences neuronal development and synaptic plasticity. Studies have identified abnormal peripheral glutamate levels, aberrant glutamate expression in postmortem brain, and genetic abnormalities in glutamate signaling genes in individuals with ASD (Carlson 2012; Choudhury et al. 2012; Erickson et al. 2008). Attenuation of N-methyl-D-aspartate (NMDA) specific glutamate neurotransmission via use-dependent inhibitors of NMDA neurotransmission such as d-cycloserine (DCS), amantadine, and memantine have been subject of several studies in ASD with mixed results (King et al. 2001; Minshawi et al. 2016; Posey et al. 2004, 2008a; Wink et al. 2017). Despite significant interest in the non-competitive NMDA receptor (NMDAR) antagonist ketamine in psychopharmacology research more broadly (Aan Het Rot et al. 2012; Berman et al. 2000; Krystal et al. 2013; Lapidus et al. 2014; Lara et al. 2013; Papolos et al. 2013; Zarate et al. 2012; Zarate et al. 2006), to date

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no controlled trials of ketamine in ASD have been reported (Wink et al. 2014).

Ketamine is a unique NMDAR antagonist which blocks the open NMDA channel to decrease channel open time and employs allosteric modulation to reduce mean channel opening frequency (Orser et al. 1997). Ketamine is hypothesized to exert its antidepressant action via four proposed mechanisms of action: (1) enhanced glutamatergic firing resulting in brain derived neurotrophic factor (BDNF) release, activation of the tropomyosin receptor kinase B (TrkB) receptor, and activation of mechanistic target of rapamycin complex 1 (mTORC1), (2) selective blockade of extra-synaptic NMDARs increasing mTORC1 functioning and inducing protein synthesis, (3) blockade of NMDAR-mediated neurotransmission inhibiting elongation factor 2 kinase (eEF2K) activity and enhancing BDNF activity, and (4) independent action of the hydroxy-norketamine metabolites which promote α-amino-3hydroxy-5methyl-4isoxazole-propionic acid receptor (AMPAR)-mediated synaptic potentiation (Zanos and Gould 2018). These proposed mechanisms of action have striking overlap with the pathophysiology theory of ASD as a disorder of synaptic communication and neuronal networks resulting from abnormalities in the glutamatergic system including impaired function of metabotropic and ionotropic glutamate receptors, disruption of BDNF/TrkB signaling, and abnormal mTOR signaling (Carlson 2012; Correia et al. 2010; Uzunova et al. 2014; Wang and Doering 2013).

The goal of this randomized, double-blind, placebo-controlled, cross-over pilot study of intranasal (IN) ketamine in adolescents and young adults with ASD was to evaluate the safety and tolerability of IN ketamine and to examine potential signs of impact on core social impairment which could be further examined in a future larger placebo-controlled trial. In this manuscript we present initial results of the trial including the primary and secondary outcome measures, the Aberrant Behavior Checklist Social Withdraw (ABC-SW) subscale (Aman et al. 1985) and the Clinical Global Impressions Improvement (CGI-I) scale (Guy 1976), respectfully, and evaluation of the safety and tolerability of IN ketamine in the target population.

Methods

Participants

This study was a 2-dose, randomized, double-blind, placebo-controlled, cross-over pilot study of IN ketamine in adolescents and young adults with ASD. The study was conducted at Cincinnati Children's Hospital Medical Center (CCHMC) between January 2016 and August 2018. The study was approved by the CCHMC institutional review board and was subject to oversight by the United States Food and Drug Administration (FDA) via an Investigational New Drug (IND) application (ClinicalTrials.gov Identifier: NCT02611921). All adult participants (when able) and guardians of dependent or minor participants provided written informed consent prior to study participation.

Study participants were adolescents and young adults (90.5% male, 76.5% Caucasian) ages 14 to 29 years ($M = 19.48$, $SD = 3.83$) inclusive with a diagnosis of ASD confirmed by Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al. 2012) performed at study screen or within the previous 5 years. Subjects with known genetic syndromes associated with autism were excluded (i.e. fragile X syndrome, tuberous sclerosis). All participants weighed ≥ 50 kg and had general good heath as determined by medical history, physical exam, laboratory work-up, and electrocardiogram (EKG). Patients with history of porphyria, thyroid disorder, thyroid medication use, glaucoma, or positive serum pregnancy test were excluded. Participants were required to have a valid full-scale intellectual quotient (IQ) score of ≥ 50 as confirmed by testing (Leiter-3) at screen or within the previous 5 years (any valid testing acceptable). At screen, all participants were judged to have a Clinical Global Impressions Severity (CGI-S) score ≥ 4 (moderately ill) (Guy 1976) and a score ≥ 10 on the ABC-SW subscale. Participants were also required to have stable dosing of all concomitant psychotropic medications at baseline and throughout the study, no evidence of co-morbid psychotic disorder, no history of alcohol or drug use or dependence, no known allergy to ketamine, and no concurrent use of drugs with NMDA glutamatergic activity (i.e. d-cycloserine, amantadine, memantine, lamotrigine, or riluzole).

Following completion of screening measures, participants were randomized via the CCHMC investigational pharmacy to receive either two ascending doses of IN ketamine (30 mg and 50 mg) given one week apart delivered via a mucosal atomization device followed by two doses of matching placebo (saline spray) given one week apart or vice versa. All study participants, guardians, and investigators were blind to study assignment. Due to sedating effects of ketamine, the clinician rater (RCS) did not interact with study participants acutely following drug dosing and was not involved in assessment for adverse effects. Study drug or placebo was administered at four research visits with each visit occurring seven days apart. There was also a two-week washout out period between phases (mid-point visit) and after (final visit). Subjects remained on site for minimum of three hours post-dose and no drug was sent home with study participants at any point in the study. Ketamine doses chosen for this study, 30 mg and 50 mg, were based on discussions with the FDA regarding ketamine exposure in this population, doses used in a similarly designed study in adults (21–65 years

old) with major depressive disorder (Lapidus et al. 2014), our extensive review of ketamine safety literature (Azari et al. 2012; Carr et al. 2004; Green et al. 1999a, 2011, 2009a, 2009b, 1999b; Green and Krauss 2004; Malinovsky et al. 1996; Mion and Villevieille 2013; Yanagihara et al. 2003), and based on input from the FDA during IND application review.

Measures

The ABC-SW subscale was the primary clinical outcome measure in this first in autism study, with the CGI-I serving as a key secondary clinical outcome. The ABC is the gold standard parent/caregiver reported behavioral outcome measure for use in developmental disability clinical trials. The ABC subscales evaluate five behavioral domains including irritability, social withdrawal, stereotypy, hyperactivity, and inappropriate speech (Aman et al. 1985). Items on the ABC are rated on a scale of 0 to 3 ("behavior not a problem" to "behavior is a severe problem") with higher scores indicating more severe problems. The ABC-SW subscale contains 16 items related to socially isolated, withdrawn behavior (e.g., seeks isolation from others, prefers to be alone, prefers solitary activities). Further, the ABC-SW has been broadly considered to describe autism-specific behaviors (Marshburn and Aman 1992) and a valid measure of social communication deficits in acute treatment trials (Scahill et al. 2013; Anagnostou, et al. 2015). Previous factor analysis studies and other clinical trials have reported average ABC-SW scores ranging from 12.1–18.1 for teens and young adults with ASD (Fung et al. 2014; Norris et al. 2019; Scahill et al. 2013). The ABC-SW was completed at all dosing visits (pre-dose), during follow-up phone calls 1-day and 4-days after each dosing visit, and at the mid-point and final visits. The CGI-I is a gold standard measure of clinician-rated change with treatment in placebo-controlled pharmacotherapy trials in ASD (King et al. 2009; McCracken et al. 2002; Wink et al. 2016). The CGI-I is a 7-point Likert scale measuring change from baseline from 1 to 7 (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). In this trial the CGI-I was focused on the target domain of social impairment and was completed at all dosing visits (pre-dose) and at the mid-point and final visits. The CGI-I was not administered immediately post dose as a goal of the present study was to examine the benefits of ketamine beyond the clinic visit as demonstrated in a previous case study using IN ketamine in an adult with ASD (Wink et al. 2014). Additional subject and/or caregiver reported secondary outcome measures include the remaining ABC subscales, the Social Responsiveness Scale (SRS) (Constantino et al. 2003), the Anxiety Depression and Mood Scale (ADAMS) (Esbensen et al. 2003), and the Clinical Global Impression – Severity Scale (CGI-S) (Guy 1976). All secondary outcome measures were completed at baseline and each visit prior to dosing (schedule of measures Table 1).

Safety monitoring provisions included comprehensive metabolic panel (CMP), complete blood count with differential (CBC with differential), serum pregnancy test in female participants of childbearing age, physical exam, medical history, and EKG at screen and final visit. Urine pregnancy tests were performed at each dosing visit prior to drug administration for female participants of childbearing age. Concomitant medication review, adverse effect review, and vital signs were collected at every in-person visit. Adverse effects were also screened for during the post-dose phone calls. The Clinician-Administered Dissociative States Scale (CADSS) was administered prior to dosing and at 30 min, 60 min, 120, and 180 min post-dose to assess for psychotomimetic symptoms following ketamine exposure (Bremner et al. 1998). The CADSS is a 27-item validated measure of dissociative states that can be administered repeatedly to measure changes in dissociative symptoms overtime as experienced by the patient and observed by the rater (Lapidus et al. 2014; Luckenbaugh et al. 2014). The Repeatable Battery for the Assessment of Neuropsychological States (RBANS) was completed prior to dosing (visit 1 of each phase), at the mid-point visit, and at the final visit to assess for change in global neurologic and cognitive functioning due to ketamine exposure (Randolph et al. 1998). The RBANS is comprised of ten subtests that are combined to form five index scores (attention, language, visuospatial

Table 1 Schedule of measures administered

Visit type	ABC-SW	CGI-I	CGI-S	ABC	SRS	ADAMS	RBANS	Labs, EKG, Physical Exam	AE Review
Screen/baseline	X		X	X	X	X	X	X	X
Pre-dose	X	X	X	X	X	X	X		X
Post-dose									X
1-day post-dose	X								X
4-days post-dose	X								X
Mid-point/final	X	X	X	X	X	X	X	X	X

abilities, immediate memory, and delayed memory) and a total scale score Higher scores on the RBANS suggests greater cognitive functioning ($M = 100$; $SD = 15$).

To ensure safety following ketamine exposure, vital signs (heart rate, blood pressure, respiratory rate, and pulse oximetry) were collected prior to each dose of study drug, monitored continuously for 30 min post-dose, and repeated every 30 min thereafter for total of 3 h of monitoring post-dose. Furthermore, study staff were instructed to call the study physician with a 20% change from baseline in blood pressure or heart rate that persisted for 20 min and the rapid response code team in the rare case of a clinically dangerous change in vital status. Additional study safety oversight was provided by the medical monitor for this study within the Division of Child and Adolescent Psychiatry at CCHMC and by a member of the Anesthesia Faculty at CCHMC.

Statistical Analysis

Baseline demographic data including age, sex, race, full scale IQ, concomitant medications, and clinical ratings (CGI-S, ABC, ADAMS, SRS) were compiled and means and percentages were calculated to describe the study participants groups (Table 2). Baseline demographic differences between groups (ketamine-placebo versus placebo-ketamine) were tested using chi-square tests (categorical data) and independent sample t-test (continuous data) using a two-tailed p-value of 0.05 for the alpha.

Repeated measures linear models for crossover designs were conducted for the ABC (all subscales), SRS, CGI-I, CGI-S, and ADAMS outcome measures. Since baseline values were available for each treatment period, the models as described by Jones and Kenward (2015) were used). The independent variable was the treatment (ketamine or placebo) at each period. The covariates were period, visit, day post treatment (for ABC-SW only), and a variable to indicate whether the response was measured at baseline (for each period) or not. Of note, CGI-I was dichotomized to categories 2 and 3 versus 4 and 5 to define the groups who demonstrated improvement (a score of 2 or 3) or no improvement (a score of 4 or 5) due to none of the participants obtaining a 1, 6, or 7. The resulting model of the dichotomous groups for CGI-I was a logistic regression. Adverse event data was compiled to describe the impact of ketamine versus placebo. The frequency of AEs was analyzed using student's t-test.

Table 2 Participant demographic data at baseline ($N = 21$)

Variable	Mean (SD)
Age (years)	19.48 (3.83)
Full-Scale IQ	102.14 (23.62)
CGI-S	4.10 (0.30)
ABC irritability	10.05 (5.86)
ABC social withdrawal	17.90 (7.46)
ABC stereotypy	4.67 (5.30)
ABC hyperactivity	11.29 (7.50)
ABC inappropriate speech	3.38 (3.01)
SRS total T score	74.43 (12.64)
ADAMS depressed mood	7.62 (5.54)
ADAMS manic/hyperactive	7.90 (3.40)
ADAMS social avoidance	11.19 (5.08)
ADAMS general anxiety	8.10 (4.88)
ADAMS obsessive compulsive	2.95 (2.31)
RBANS total score	83.48 (16.62)

Results

Twenty-two subjects were screened for the study and 21 participants were randomized. One subject failed screening due to history of thyroid disease. Seventeen participants completed both study phases. Four subjects withdrew from the study, one due to emesis following first dose of study drug (ketamine), one due to seizure during the two-week washout period (seven days post-ketamine; determined unrelated to study drug), and two due to scheduling issues after Phase 1 (one ketamine, one placebo). Participants were mostly young adults with average IQ and significant social impairment at baseline (Table 2). Most participants were taking at least one psychotropic medication ($M = 2.3$, range 0–8; antidepressants $n = 14$, stimulants $n = 10$, atypical antipsychotics $n = 7$, alpha-2 agonists $n = 5$, sleep aides $n = 6$, and benzodiazepines $n = 1$). At baseline, no statistically significant differences between the two groups (ketamine-placebo versus placebo-ketamine) were identified in sex, race, age, IQ, number of concomitant medications, CGI-S, ABC, SRS, or ADAMS scores (all $ps > 0.17$).

No crossover effects were noted on any analysis. There was no statistically significant improvement with ketamine on the repeated measures linear model employed for analysis of the ABC-SW ($p = 0.48$) (Table 3). No statistically significant improvement on the CGI-I evaluated as a continuous Likert scale was noted with ketamine versus placebo ($p = 0.30$). The odds of dichotomous treatment response (CGI-I = 2 or 3, no CGI-I = 1 reported) was higher with ketamine but this was not statistically significant ($OR = 0.51$). The frequency of reported improvement (CGI-I = 2) with ketamine 30 mg was higher than with ketamine 50 mg or placebo (Table 4). No statistically significant results for the repeated measures models for the other ABC subscales, SRS, or ADAMS were identified.

Study drug was well tolerated with only mild transient adverse effects (AEs) reported ($M = 3.3$, $SD = 2.05$). Significantly more AEs were reported with ketamine than placebo ($p < 0.001$), with bad taste, dizziness, fatigue, headache,

Table 3 ABC-SW results across treatment for ketamine and placebo

Visit type	*n*	ABC-SW mean (SD) Ketamine	*n*	ABC SW mean (SD) Placebo
Baseline (pre-30 mg dose)	20	16.3 (10.0)	18	18.6 (10.6)
1-day post-dose	20	11.1 (7.8)	18	13.5 (8.7)
4-days post-dose	20	12.2 (8.5)	18	15.8 (11.8)
Baseline (pre-50 mg dose)	19	14.6 (10.1)	18	14.7 (11.4)
1-day post-dose	19	11.8 (8.5)	18	12.3 (6.7)
4-days post-dose	19	11.7 (9.4)	18	11.9 (7.5)

Table 4 Frequency of CGI-I scores after low (30 mg) and high (50 mg) dose ketamine

Dose/drug	CGI-I = 2	CGI-I = 3	CGI-I = 4	CGI-I = 5	Total
Low dose (30 mg)					
Placebo	0	6	10	2	18
Ketamine	4	6	8	1	19
High dose (50 mg)					
Placebo	3	6	7	1	18
Ketamine	4	4	10	1	19

nausea, and throat irritation being most common. Two subjects experienced transient tachycardia and one experienced transient bradycardia post-ketamine. Two participants experienced transient hypertension (one ketamine, one placebo). There were other brief changes in vital signs noted post-ketamine dosing, including changes in heart rate, blood pressure, respiratory rate, and oxygen saturation; however, these changes were not clinically significant and all participants returned to baseline prior to departing the research clinic. No subject lost consciousness, and there were no episodes of vital sign instability that were medically concerning or that necessitated involvement of the rapid response team. No medically meaningful changes were noted on safety labs from screen to final visit (CBC, CMP). Participant CADSS scores were low throughout the study, with minimal transient changes in sensory perception reported. Maximum total CADSS score on the observer-rated items was four recorded at 30 min post-dose (one participant), and three recorded at 30 min post-dose (two participants). All CADSS scores returned to 0 or 1 by the time the participant was discharged from clinic. On the RBANS, three participants (14%) had a small decline in score from baseline to final visit (2–5-point drop in total score), and fifteen participants (71%) scored higher on the RBANS at the final visit.

Discussion

Identifying a single drug proven to reduce the core social deficits of ASD has yet to be discovered across decades of pharmacotherapy research and clinical trials (Posey et al. 2008b; IACC 2010). Several studies examining use-dependent inhibitors of NMDA have provided mixed results of effectiveness in ASD (King et al. 2001; Minshawi et al. 2016; Posey et al. 2004, 2008a; Wink et al. 2017). The mechanisms of action of the NMDAR antagonist, ketamine, have significant overlap with the pathophysiology theory of ASD suggesting disrupted synaptic connections and neuronal networks. However, despite the broad interest in ketamine across psychopharmacology research, ketamine has yet to be explored through clinical trials in ASD. This is the first report on ketamine use in a randomized, placebo-controlled design in autism.

Aligning with the first goal of this randomized, double-blind, placebo-controlled, cross-over pilot study, IN ketamine was found to be generally well tolerated and safe to use in adolescents and young adults with ASD with only transient overall minimal AEs associated with ketamine use. As the first study to examine IN ketamine in a group of adolescents and young adults with ASD, this project demonstrates that ketamine as administered in this project exhibits tolerability that would allow for future larger-scale study.

In contrast to our hypotheses, no IN ketamine-associated statistically significant improvement was noted on the patient report and clinician rated measures employed in this study. Specifically, scores on the ABC-SW declined slightly across both doses of ketamine; however, similar results were found during the placebo trials. Additionally, reported improvement using the CGI-I was greater with a lower dose of ketamine (30 mg), though this did not meet statistical significance. The lack of findings could be due to the measures that were used to assess change in treatment specific to the core social deficits observed in ASD. A recent panel of ASD experts determined only a few measures are appropriate for use in ASD intervention studies, which included the ABC-SW subscale utilized in the present study (Anagnostou et al. 2015). Although this project was designed as a target engagement and safety Phase Ib study, it was likely

inadequately powered to detect clinical treatment change in the context of placebo effects inherent in clinician and parent report. Although the ABC-SW has been identified as a valid measure for clinical trials, additional work is needed with larger samples to confirm the validity of the ABC-SW and other clinical measures to detect treatment change given the increased need and interest for identifying valid and reliable measures that accurately quantify the core phenotypic symptoms of ASD. Further, the small sample size limited the ability to identify treatment-responsive subgroups with the clinician- and parent-reported measures utilized. With ASD being a heterogenous disorder, not every individual is going to respond the same to different treatment approaches. The utility of identifying treatment responders is necessary for future clinical trials in order to identify which ASD specific phenotype will respond to the different treatments.

Although IN ketamine was well tolerated and deemed safe, there are several limitations to consider when interpreting the studies findings. Specifically, the lack of significant clinical response in this report should be interpreted in the context of the small sample size in a heterogeneous disorder given the primary outcome measure has been determined to be valid for clinical trials in ASD (Anagnostou et al. 2015). Further, unlike other clinical trials, the present pilot study categorized a CGI-I score of 3 as improvement due to the limited range of CGI-I scores obtained. Like several other small placebo-controlled pilot studies in ASD, the heterogenous sample, use of clinician- and caregiver-reported outcome measures, and small sample size likely contributed to the lack of improvement observed in core social functioning in ASD and limited identification of potential treatment-responsive sub-groups.

In conclusion, the initial results of this pilot study of IN ketamine in adolescents and young adults with ASD demonstrated that IN ketamine was relatively well tolerated with only mild and expected adverse effects noted. Future analyses should incorporate quantitative outcomes of ketamine response and target engagement including, but not limited to, eye tracking, computer based testing, and observational measures such as the Brief Observation of Social Communication Change (BOSCC) (Grzadzinski et al. 2016). Further, larger-scale trials should consider incorporating a pharmacokinetic and pharmacodynamic (PKPD) model-informed trial design to extended findings beyond clinician and parent informed measures (Vermeulen et al. 2017). This could include the use of measures assessing central nervous system (CNS) engagement to examine drug effects on brain physiology as well as potential changes within the body based on ketamine exposure and response.

Authors Contributions LW conceptualized experiments and wrote the primary draft of the manuscript. DR participated in data analysis, results interpretation, and in the writing of the manuscript. PH is the primary biostatistician on this project. RS, LS, KR, KO, and EP all participated in data collection and contributed to data analysis, results interpretation, and edited and reviewed the manuscript. CE participated in conceptualizing the experiments and contributed to the writing of the manuscript.

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