Icahn School of Medicine at Mount Sinai

The Mount Sinai Health System
Mount Sinai Hospital
Icahn School of Medicine
Department of Psychiatry
alexander.kolevzon@mssm.edu

Alexander Kolevzon, MD
Professor of Psychiatry and Pediatrics
One Gustave L. Levy Place, **Box 1230**
New York, NY 10029-6574
212-659-9134

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Re: Low-Dose Ketamine in ADNP Syndrome

I am writing to share exciting preliminary results from the recently completed study of low-dose ketamine in ADNP syndrome. Studies in animal models suggest that low-dose ketamine can induce expression of the ADNP gene, and that neuroprotective effects of low-dose ketamine are in part mediated by ADNP. These preclinical data served as the basis for our study of low-dose ketamine in children with ADNP syndrome.

Study Design
Ten children aged 6-12 with ADNP syndrome were enrolled. All participants received intravenous (IV) racemic ketamine at a dose of 0.5 mg per kg over 40 minutes. Dosing was based on data from previous clinical studies in children and adults and according to participants' weight. Ketamine is commercially available and approved by the Food and Drug Administration (FDA) as an anesthetic for children in the proposed age range; we received investigational new drug (IND) approval from the FDA (IND #147201). All preparation and packaging was performed in the Mount Sinai Research Pharmacy.

The study was comprised of: (1) Screening period; (2) Baseline visit on Day 0 for baseline assessments and administration of study drug; (3) Clinic visits for safety and efficacy assessments at Day 1, and Weeks 1, 2, and 4. Results are intended to inform ketamine clinical development and the design of future and larger studies in ADNP syndrome.

Safety was monitored throughout the study period and efficacy was assessed using a variety of instruments to measure core symptoms of ADNP-related deficits. Further, we sought to explore the feasibility of objective biological markers in ADNP syndrome using electrophysiological measurement of auditory and visual evoked potentials, computerized eye tracking, RNA sequencing to measure ADNP expression, and DNA methylation profiles.

Data Analysis
Adverse event and other safety data are summarized as frequencies and percentages and described in terms of severity. To examine treatment effects, the Wilcoxon signed-rank test was calculated for the differences in change over time from Baseline to Week 1, Week 2, and Week 4. Herein we report our primary analysis which was to test differences between Baseline and Week 1. All tests of statistical hypotheses were done on the two-sided 5% level of significance. Since this is an initial proof-of-concept study that is exploratory in nature, no multiplicity-related adjustments are made in the reported p-values

Results
Ketamine was generally well tolerated and adverse events (AEs) were mild to moderate. The most common AEs were fatigue (50%), increased aggression (50%), decreased appetite (30%), elated/silly behavior (30%), and worsening anxiety (20%). There were no serious adverse events.

Using parent-report instruments to assess treatment effects, ketamine was associated with nominally statistically significant improvement in a wide array of domains, including social behavior, attention deficit and hyperactivity, restricted and repetitive behaviors, and sensory sensitivities.

Importantly, results derived from clinician-rated assessments aligned with findings from the parent reports. Overall, improvement was evident based on the Clinical Global Impressions - Improvement scale, in addition to clinician-based scales reflecting key domains of social communication, attention deficit and hyperactivity, restricted and repetitive behaviors, speech, thinking and learning, activities of daily living, and sensory sensitivities. No significant improvement was seen in sleep in either parent-report or clinician-rated measures.

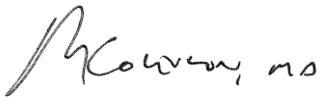
Preliminary data on ADNP expression analyzed using quantitative polymerase chain reaction (qPCR) methods suggest that we are seeing approximately two-fold level increases in ADNP. However, the significance of this increase remains difficult to interpret and RNA sequencing studies are underway.

We are extremely encouraged by the early results but have more analyses to do to better understand the time course of change across the four-week study period – these data will be critical in designing future studies. Further, we are waiting for results from the electrophysiological, eye tracking, and blood-based biomarker studies.

These results must be interpreted with caution given the small number of participants, absence of a placebo-control group, lack of correction for multiple testing (which may increase the risk for false positives), and use of clinical outcome measures that have not been validated in ADNP syndrome. However, our findings from this initial small pilot study clearly provide robust support for continuing the ketamine clinical development program in ADNP syndrome, and identify useful endpoints for such a program.

We are extremely grateful to the families who participated and to the ADNP Kids Foundation for its support. We look forward to providing updates on our progress and to continued collaboration with the community.

Sincerely,



Alex Kolevzon, MD
Clinical Director, Seaver Autism Center for Research and Treatment
Icahn School of Medicine at Mount Sinai