

## **Q&A on the significance of the longitudinal study of intranasal ketamine in novel phenotype of bipolar disorder**

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

Papolos D1, Frei M2, Rossignol D3, Mattis S4, Hernandez-Garcia LC5, Teicher MH5. J Affect Disord. 2017 Aug 30.

### **1. Were you surprised by your findings, why, why not?**

I was surprised by the magnitude of the effect when we actually did the statistical analysis. Even though this study was not blinded or placebo controlled, it brought home to me the significance of the efficacy of ketamine treatment for this population (estimated to be > than 1/3rd of youth with bipolar disorder) that typically does not respond to traditional somatic therapies. In addition, the response we saw was durable, and required only small adjustments to dose once a therapeutic dose was found. Since this work began over 10 years ago when we first identified this novel phenotype (bipolar disorder – Fear of Harm phenotype [FOH]), we have used intranasal ketamine in over 110 cases. The effects have been, (and I don't use this word lightly) transformational for a large majority of cases. Jon Hamilton did an excellent piece on FOH for NPR's Morning Edition three years ago which may provide some context:

<http://www.npr.org/sections/health-shots/2013/03/25/174928768/how-an-unlikely-drug-helps-some-children-consumed-by-fear>

Because this behavioral phenotype was originally defined in heritability studies that were part of a clinical ramp up to a future GWAS study that was to be funded by the Juvenile Bipolar Foundation, we sought to first identify homogeneous clinical phenotypes. This work was not fully elaborated before DSM-5 field trials were undertaken, therefore, it is not part of our current diagnostic nomenclature. I include below more information that will provide you the context to understand the evolution of the work to date, and further delineate a phenotype with a clear

biological marker (a deficit in thermoregulation) that is rarely assessed as part of a psychiatric evaluation that we feel needs to be widely disseminated to clinicians who regularly diagnose these children with an alphabet soup of DSM diagnoses and treat them with drugs that actually are destabilizing and worsen prognosis (See below).

## **2. Why was it important to do this study?**

It was important to undertake this review as current expert opinion, based on the reported side-effects of IV ketamine administration at higher doses than we typically needed to use, have concluded that ketamine is not ready for prime time because of the side-effect profile which includes dissociative symptoms, and of course because there were no long term studies (e.g greater than 4 weeks) that demonstrate safety. This study codifies our clinical experience, which goes beyond the current research base, to provide preliminary evidence for both efficacy and safety of 2-3 treatments per week over an extended period. Moreover, we report that tolerance to the side-effects of ketamine diminishes over time while efficacy persists.

It is very important to inform the field that racemic ketamine, a generic drug, that is affordable and readily available appears safe and highly efficacious, at least in this specific population. Further, we provide data from clinical experience on the ease and utility of intranasal administration. Hence, we provide clinical insights that stand in contrast to some expert opinions that essentially warn clinicians not to use this inexpensive and effective form of ketamine, and to wait for “safer versions” that will be patented and much more expensive. Our experience also offers an alternative to the dozens of ketamine advocacy centers that have recently sprung up where desperate patients can receive IV ketamine infusions for several hundreds of dollars per dose. Finally, we bring attention to the field, and to parents, that there is a well-defined subtype of bipolar disorder, that typically emerges in childhood that generally responds poorly to available treatments, but may respond dramatically to ketamine.

### **3. What unanswered questions do you have about these study results?**

While the FDA recognizes the severity and lack of effective treatments for BPD-FOH, the absence of extended repeat-dose studies in relevant animal models has made it difficult for them to approve execution of a double-blind placebo-controlled clinical trial of over one month duration (8 doses) of intranasal ketamine. Clearly such a study would help to prove efficacy and safety of this drug in a BPD-FOH. I would like to see such a study performed to confirm our findings. Unfortunately, pharmaceutical companies, who have the resources to do this, have no incentive because racemic ketamine is generic – leaving little possibility that they can recoup their costs.

### **4. What should practicing clinicians know about your findings?**

Clinically significant benefits to ketamine in BP-FOH were often apparent after the first treatment. These benefits persisted with only minor subsequent dose adjustments in most cases. Though titration to a therapeutic dose (defined as three days of > 80% abolishment of target symptoms) took a period of dose titration upward that could last weeks or months). The most common initial breakthrough symptom was difficulty in thermoregulation, typically manifested by overheating at night prior to sleep resulting in arousal disorders of sleep. The return of this symptom ushered in a return of behavioral symptoms. 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.

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 study 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.

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