The Difference a Diagnosis Makes:
How Understanding Fear of Harm Syndrome May Help Save Your Child

Alice* is artistic, intelligent and on her third school placement. Her parents remember that she was always very hot as a baby. Growing up she would constantly kick off the bed covers, often waking up in a pool of sweat with terrifying nightmares that no one could explain. She was often afraid to go to sleep. She would worry about everything, howled when she was separated from her parents and often demanded to sleep in their bed.

Alice could never seem to wake up in the morning. She would get angry about getting up, and always had dark circles under her eyes. Criticism crushed her. She complained constantly of being bored, and couldn't handle delays. It was hard for her to keep friends because of her bossiness and tendency to be argumentative. She'd erupt in a rage when her parents tried to set limits. And recently, she'd taken a dark turn, brooding, cursing, getting lost in gory graphic novels.

She's seen several doctors and counselors. They diagnosed ADHD, depression and an alphabet soup of other labels (ODD, OCD, DMDD) that almost but didn't quite fit. She's been given a host of stimulants like Ritalin and Adderal, as well as antidepressents, but nothing seemed to do much good. And according to Dr. Demitri Papolos, Director of Research for the Juvenile Bipolar Research Foundation (JBRF), those drugs probably won't help, and may even cause more irritability, agitation and mood cycling.

That's because Alice, and thousands more children, likely suffers from a specific sub-type of juvenile bipolar disorder. The clues from her history indicate Alice may have Fear of Harm (FOH) syndrome, which occurs in a subgroup of children with bipolar disorder. It's a relatively new diagnosis, but it's a critical one, because research sponsored by JBRF has not only discovered this syndrome, it's determined there is an effective treatment for it, too.

"Juvenile bipolar disorder and FOH are major social as well as medical issues," says Dr. Papolos. A study that examined the clinical profiles of over 5000 youth diagnosed with bipolar disorder suggests that fully one-third have FOH. It's estimated that hundreds of thousands of children may suffer from FOH, and that it may be rampant in juvenile justice cases. "These children are usually misdiagnosed, and the typical drug treatments used can make them more aggressive," explains Dr. Papolos.

Breakthrough Biomarker

JBRF has been working to change the way juvenile bipolar disorder is diagnosed and treated since 1999. Through the use of big-data analytics, over the course of eight years researchers identified a sub-set within the population of patients diagnosed with juvenile bipolar disorder. This sub-set is defined by symptoms that include extreme anxiety and fear of harm to self or others, or what is termed "Fear of Harm" (FOH) syndrome.

What is unique about FOH is that it includes, for the first time, a physical symptom, or biomarker, for a mental illness. Among other symptoms, these children feel hot much of the time, a sign that their bodies are not able to self-regulate their internal temperature. This thermoregulatory disturbance plays a significant role in the development of symptoms of their illness.

"The thermoregulation problem impacts many functions in the body, including sleep," explains Dr. Papolos. "Kids with FOH have problems with the dissipation of heat, so they have challenges getting to sleep and arising. The smooth transitions from REM to non-REM sleep are also affected, and they often have frequent vivid nightmares very early on in their development, even at pre-verbal stages. They have a fluidity between waking and dream states and may see frightening and morbid images – REM intrusions – as soon as they close their eyes. Their brains

may experience this imagery as if it's real, so fear sensitivity develops very early and they may develop symptoms akin to PTSD where even neutral experiences can trigger a fight or flight response. This state of threat can lead to other behavioral issues."

A Breath of Hope

Once Dr. Papolos and the JBRF sponsored researchers discovered the FOH syndrome, they set about looking for treatments that could be used to mitigate it. One drug, ketamine, was known to affect both fear sensitivity and thermoregulation. Originally developed as an anesthetic, ketamine is used by dentists for children, and has recently shown promise in treating people who come into emergency rooms with suicidal thoughts. Could ketamine help FOH kids?

The team determined that ketamine can indeed be used via intranasal administration to mitigate FOH symptoms and manage bipolar disorder. Ketamine is known to influence the regulation of body temperature and to reduce the intensity of conditioned fear. They embarked on research to evaluate if intranasal ketamine could be effective and safe for long term use. Their findings offer hope for thousands.

For FOH patients, the administration of intranasal ketamine combined with therapeutic levels of lithium salts or another mood stabilizer results in a substantial reduction in measures of mania, fear of harm and aggression. A rapid, substantial therapeutic response showed significant improvement in patients' mood, anxiety and behavioral symptoms. And in what proved to be the clearest marker of a response to intranasal ketamine treatment, the patients' thermoregulation improved significantly.

JBRF sponsored researchers published their initial findings in the *Journal of Affective Disorders* in 2012. They also published a follow up study in the same journal in 2017, which documented treatment results over a span of six years. The bottom line? For patients who fit the FOH diagnosis, intranasal ketamine treatments can change their lives.

The challenge now is to raise awareness of the FOH diagnosis in the broader world, and to have the use of intranasal ketamine adopted as a standard clinical practice for treatment of this condition. JBRF is taking steps to make that happen, offering information on their website for families and medical professionals, and launching a series of informal presentations aimed at increasing awareness of FOH and ketamine treatment. Training for mental health professionals and inclusion of the FOH diagnosis in the DSM are future goals.

"For children and adolescents with FOH, accurate diagnosis of FOH and treatment with a mood stabilizer and intranasal ketamine can be transformational," says Dr. Papolos. "I believe there are many, many more children out there who can benefit."

For more on FOH and juvenile bipolar disorder, the JBRF website has helpful information.

For in depth information on FOH:
https://www.jbrf.org/what-is-fear-of-harm/

For an online diagnostic questionnaire:
https://www.jbrf.org/the-child-bipolar-questionnaire-for-families-use/

For a list of research and useful tools:
https://www.jbrf.org/

**This patient profile is drawn from real examples, but is a fictional conflation to protect privacy.*

Juvenile Bipolar Research Foundation