Commentary: Objective aids for the assessment of ADHD – further clarification of what FDA approval for marketing means and why NEBA might help clinicians. A response to Arns et al. (2016)

Mark A. Stein,1,2,* Steven M. Snyder,3,4,* Thomas A. Rugino,5,6 and Mady Hornig7

1Department of Psychiatry and Behavioral Science and Pediatrics, University of Washington, Seattle, WA; 2Department of Psychiatry and Behavioral Medicine, Seattle Children’s Hospital, Seattle, WA; 3Department of Research and Development, NEBA Health, Augusta, GA; 4Department of Psychiatry and Health Behavior, Georgia Regents University, Augusta, GA; 5Children’s Specialized Hospital, Toms River, NJ; 6Robert Wood Johnson School of Medicine, Piscataway, NJ; 7Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

The editorial of Arns et al. on the meaning of FDA approval for marketing of objective aids for the assessment and diagnosis of ADHD helps clarify the distinction between FDA approval and a more general recommendation of a tool as part of best practice. In order to make their point Arns et al. focus on NEBA (Neuropsychiatric EEG-Based ADHD Assessment Aid), an EEG measure based upon the concept that individuals with ADHD have an aberrant theta/beta ratio (TBR), as a case example. We accept this core point and have never claimed that FDA recommend NEBA as a stand-alone diagnostic tool or that the FDA have recommended it as best practice in ADHD assessment. This is important because in the Arns et al. editorial, there is a suggestion that this is a claim we are making. In fact our claim is that NEBA is an integration method that provides additional information to help the clinician address specific questions relating to the ADHD assessment (FDA, 2013a, b, Snyder, Rugino, Hornig, & Stein, 2015). Of note, the title of the validation article is Integration of an EEG biomarker with a clinician’s ADHD evaluation (Snyder et al., 2015).

Why might NEBA or the examination of TBR more generally be a helpful addition to the assessment battery? Consider the case of a second-grade boy referred by his teacher to his doctor for evaluation of ADHD. He is at a private school and not learning to read (presumably due to ADHD). However, he is the youngest in his class, one of the few boys in the class, and new to the school. His father was also a poor reader. Vanderbilt teacher ratings are elevated for inattention and parent ratings are also slightly elevated. The differential diagnosis includes ADHD, Reading Disability, as well as poor fit between child and current classroom. What we have found out is that children with ADHD symptoms who display a relatively low TBR are more likely to have other conditions that could explain the ADHD symptoms such as sensory deficits or head injury (Snyder et al., 2015). In cases in which the clinician has determined that ADHD is a possible diagnosis and TBR is low, NEBA provides a prompt to widen the consideration of differential diagnosis and give further consideration to other conditions. Adding NEBA to the clinician’s regular ADHD evaluation improved positive predictive value from 56% to 92%, while maintaining a fairly steady negative predictive value from 79% to 85% (the reference prevalence to the positive condition was 47%). So a low TBR sends the message to clinicians to be cautious and more closely consider other conditions that may mimic ADHD before proceeding (Pearl, Weiss, & Stein, 2015). Having such an objective measure to pause the diagnostic process in cases that are ambiguous is desirable in an era where there is concern that ADHD may be being too readily diagnosed perhaps especially by primary care physicians (Visser, Zablotsky, Holbrook, Danielson, & Bitsko, 2015). Indeed, this is how NEBA is designed to help, specifically assisting the clinician with criterion E of DSM-IV and -5, which excludes cases when symptoms and impairment are better explained by another disorder. In the regulatory trial, 85 of 93 children who had ADHD symptoms but were less likely to meet criterion E had lower TBR (Snyder et al., 2015). Data presented to FDA and by Snyder et al. (2015) suggests that this is both reliable and clinically useful, although certainly replication and more data on clinical utility is desirable and now possible as clinicians and researchers become familiar with NEBA.

Arns et al. make three specific points that we would like to query. First, they argue that findings relating ADHD to aberrant TBR are ‘widely disparate’ and conclude that there is ‘no reliable association’ anymore. They highlight the decline in effect sizes, which were large in early studies while more recent studies had a low to medium effect size on the relationship between theta beta ratio (TBR) and ADHD. However, this does not represent a nonreplication. Notably, during the time period during which these were published, the prevalence of ADHD in the United States has increased dramatically by an average of 5% a year from 2003–2011, with a current estimate of
greater than 10% of US children having an ADHD diagnosis (Visser et al., 2014, 2015). One possibility is that as diagnostic practices and ADHD subject demographics have changed, this group contains a significant number of false positives (reflecting over-diagnosis). Snyder et al. (2015) showed that the reduction in effect size of the association between ADHD and TBR reported by Arns et al. is strongly linked to rapid increase in the rate of ADHD diagnosis ($R^2$, 0.89). Further, the effect is strong using the NEBA approach to TBR and when a multidisciplinary team is the reference standard for ADHD (Cohen’s $d$, 1.53). (See Fig. S1). In contrast, the effect is weaker when the common field approach to TBR is used and when an individual clinician is the reference standard for ADHD. This evidence is consistent with the idea that diagnostic practices have changed and the increasing prevalence is related to an increase in the rates of false positives and therefore a reduction in the association between ADHD and aberrant TBR readings. It is therefore possible that historical and cohort effects could help explain the waning of the TBR and ADHD association.

Second, Arns et al. speculated as to whether FDA expertise was sufficient in all necessary areas. Clinical reviewers had backgrounds in psychology, psychiatry, neurology, and pediatrics. In fact, FDA created a new device classification as part of NEBA regulation, namely the neuropsychiatric interpretative electroencephalograph assessment aid (FDA, 2013b), differentiating NEBA from other EEG applications and assessment aids. Regulation of NEBA essentially spanned the time frame of 2004–2013, and involved over 30 meetings, submissions, and reviews. The reviewers not only addressed clinical validation but also, and very importantly, clinical integration. NEBA’s de novo classification involved validation according to FDA’s Class III regulatory pathway, which requires the highest level of evidence with substantive bias-control (FDA, 2013a, Snyder et al., 2015).

Finally, when discussing reliability, Arns et al. missed that NEBA reliability has been backed up by replication at 13 independent sites representing three disciplines (psychiatry, psychology, pediatrics). And, unlike ADHD prevalence that differs markedly between regions (Visser et al., 2014), NEBA performance was consistent across different US geographic regions (Snyder et al., 2015).

**Conclusions**

We agree that FDA marketing approval is not the same as a recommendation of best practices. We endorse the need for further study of the discriminant and predictive validity of NEBA, especially when used in combination with other measures. However, we would like to highlight the potential value of NEBA as a prompt for clinicians to further explore differential diagnoses. Our hope is that clinicians and research-ers will utilize NEBA, when used along with other objective, reliable, and biologically relevant measures to refine the diagnostic process, and this may lead to improved understanding of the disorder and ultimately improved outcomes.

**Supporting information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** The effect size for theta/beta ratio dramatically increases, when the biomarker approach and ADHD reference standard sufficiently address criterion E.

**Acknowledgements**

This commentary was invited by JCPP editors and has been subject to internal review. M.A.S. receives research support from Pfizer, Ironshore Pharmaceuticals, and Shire, and is an advisor to Alcobra and Ironshore Pharmaceuticals. S.M.S. is head of research at, owns stock shares with, and is board member at NEBA Health. T.A.R. has been a consultant to and/or speaker for Shire, Bristol-Myers Squibb, and NEBA Health. M.H. reports no conflicts of interest in relation to this article.

**Correspondence**

Steven M. Snyder, 753 Broad Street, Suite 701, Augusta, GA 30901, USA; Email: ssnyder@nebahealth.net

**References**


Accepted for publication: 13 January 2016