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Editorial Perspective: How should child psychologists and psychiatrists interpret FDA device approval? Caveat emptor

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Introduction

In recent years, new tools to aid in the diagnosis of attention deficit hyperactivity disorder (ADHD) have been promoted, and some have received Federal Drug Administration (FDA) marketing approval, such as the Neuropsychiatric electroencephalogram (EEG)-Based ADHD Assessment Aid (NEBA) Health test in 2013, the Quotient ADHD test marketed by Pearson since 2008 (previously called OPTAx) and the QbTest. All of these tests have in common a claim to improve the objectivity of ADHD assessment compared to traditional behavioral rating scales and diagnostic interviews currently widely used by mental health professionals to determine an ADHD diagnosis. However, these new assessment tools are neither included in the latest DSM-5 revision nor in the best practice guidelines of the American Psychological Association (APA) or American Academy of Pediatrics, because as concluded by F. Xavier Castellanos, when specifically discussing the QbTest and Quotient: '...the evidence base is simply too weak...' (for further overview see: Dolgin, 2014). As indicated by the FDA labeling, none of these tests are considered 'stand-alone' diagnostic tests, but merely *aids* in the diagnosis of ADHD. Therefore, caution is warranted in any over-reliance on such technologies for diagnostic assessments, given their current lack of empirical support for diagnostic validity and specificity (Arns & Gordon, 2014).

The FDA medical device approval process

The FDA Center for Devices and Radiological Health (CDRH) is the organ that regulates the approvals of an extremely diverse set of medical devices, ranging from shunts and stents, to neurocognitive assessments. Originally, the Medical Device Amendments of 1976, which established medical device regulation in the United States, established that any device currently being legally marketed at that time could continue to be marketed. In addition, any device that could be shown to be substantially equivalent in safety and efficacy to a legally marketed device could be 'cleared' for marketing. Any device that was not substantially equivalent to a legally marketed device would be defaulted to the highest risk classification, Class III, and would require premarket approval. The FDA Modernization Act of 1997 introduced the new de novo process by which developers of novel, low-to-moderate risk devices that were found to be not substantially equivalent to a legally marketed device could petition for a Class I or II designation; this was presumably done to prevent automatic Class III designation of low-risk devices simply because they were novel. In 2012, the de novo process was substantially shortened through an amendment that allowed companies to apply directly for de novo designation in the absence of a legally marketed predicate device. The de novo application is then reviewed for 'reasonable assurance of safety and effectiveness' of the device's intended use.

The theta/beta ratio and ADHD diagnosis

The earlier mentioned NEBA test relies upon an EEG-based measure, called the theta to beta ratio (TBR). The TBR is a ratio of spectral power in the theta frequency band (4–7 Hz) relative to power in the faster, beta frequency band (13–21 Hz), which is sometimes measured at a single electrode site (Cz) during rest. This measure has often been investigated in ADHD samples, with widely disparate findings depending on the publication date of the study (see Arns, Conners, & Kraemer, 2013; Lenartowicz & Loo, 2014, for review). In brief, studies at the end of the 1990s through 2009 have reported a higher TBR among children and adolescents with ADHD

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compared to non-ADHD groups, with overall large effect sizes (ES) of 1 Standard Deviation or greater. Since 2009, however, several independent research groups have reported findings that have contradicted these earlier TBR-ADHD results (Lenartowicz & Loo, 2014). Effect sizes have diminished significantly over the past 6 years, with a highly significant correlation between effect size and year of publication (Pearson $r = -.97$) emerging in a meta-analysis by Arns et al. (2013). Furthermore, despite being studied for 40 or more years, the exact functional significance of the TBR is still unknown, suggesting that more research is needed to understand the meaning of elevated TBR and whether it is related to the pathophysiology of ADHD. Overall, these studies suggest that, at present, the TBR is not reliable in discriminating between individuals with and without ADHD for diagnostic purposes [see Figure S1, which is modified and updated from the Arns et al. (2013) meta-analysis].

Surprisingly, this failure to replicate a significant association between TBR and ADHD applies even to the subsequent work of the authors of the original positive reports. In 2008, Snyder and colleagues published the results of a large, blinded multicenter study where the TBR was found to differentiate between children and adolescents with and without ADHD with 87% sensitivity and 94% specificity and a large effect size (see Figure S1, ES = 1.1). Furthermore, the clinical value of the TBR was reportedly not affected by comorbid conditions (Snyder et al., 2008). The details behind the clinical study that resulted in the NEBA FDA approval were recently published (Snyder, Rugino, Hornig, and Stein (2015), in which Snyder and colleagues were unable to replicate the large effect size of their earlier results (see Figure S1, ES < 0.4). So what did the Snyder et al. (2015) study find that resulted in the NEBA FDA de novo device approval? Their main conclusion was that TBR might help improve the accuracy of ADHD diagnosis by supporting greater DSM Criterion E[1] certainty – or in other words, when a subject presents with a low TBR, the likelihood that ADHD symptoms can be explained by another disorder is higher, thus requiring further evaluation. This could be an interesting finding, had they indeed used the exact Criterion E uncertainty definition from the DSM; however, their definition of uncertainty rested in part on nonresponse to and/or adverse effects of ADHD-medication (as if some one who does not respond to methylphenidate implies they do not have ADHD?), among other criteria. Another limitation in the 2015 study is that clinical endpoints, particularly for the 'gold-standard', multidisciplinary team review are grouped together (e.g., ADHD + need further testing for ADHD) such that the actual data for each endpoint is obscured. This precludes full assessment of the data and whether specific endpoints drive the NEBA findings.

These methodological weaknesses of the empirical study make it difficult to determine what clinical value the NEBA device adds. However, it remains clear that the association between standard ADHD diagnoses and TBR are contradicted within their own studies, and the new claim for Criterion E certainty never previously reported, requires replication before implementation in clinical practice.

Parsing the meaning of FDA device approval

Is FDA device approval for marketing equivalent to 'best clinical practices'? The answer here is no and, in all fairness, the FDA does not claim that device (or drug) approval for marketing is equivalent to the promotion of best clinical practice, in the same way that the DSM-IV and -5 are also not regulated or approved by FDA. Is FDA device approval equivalent to the designation 'empirically supported'? Based on the extant literature, the use of the NEBA device as an assessment aid for ADHD is not empirically supported. The sine qua non of scientific replication and empirical validation has clearly not been met for the association between the TBR and ADHD, as illustrated above. The diagnostic ambiguity and lack of clarity regarding clinical endpoints in the Snyder et al. (2015) study gives rise to further uncertainty as to whether the NEBA device is of limited, or no clinical utility in identifying complicating/Criterion E conditions.

As noted above, CDRH is responsible for reviewing an extremely diverse set of devices spanning genetic, cellular, neurologic, psychiatric, dermatologic, urologic and gynecologic (to name just a few) areas of expertise. It may not be reasonable to expect a level of expertise in all the areas for which device requests are submitted, and yet the public relies on FDA regulators to be the experts who can adequately identify effectiveness issues for devices. In the case of NEBA, the focus in creating the TBR cutoffs was to maximize specificity, which will increase the likelihood of false negatives. The effects of a missed ADHD diagnosis, particularly given the significant impairment typically associated with ADHD diagnosis in the absence of treatment, is a significant risk and problem with the effectiveness determination.

In conclusion, we have used the NEBA device as an example to clarify the difference between FDA de novo device marketing approval and claims about best clinical practice, on the basis of empirically supported, scientifically validated and replicated findings. It is understood that the aims of each differ; however, for many, including the lay public as well as some mental health professionals, these terms may be treated as though they are synonymous. Given this we recommend the attitude of caveat emptor (let the buyer beware!) when considering the use of ADHD diagnostic tests with FDA approval for marketing.

Supporting information

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

Figure S1. Decreaseing effect size (ES) of the theta to beta ratio (TBR). A clear trend for decreased TBR-ES across the years (size of the circle reflects the relative sample size of the study) emerges (with ES reflecting the difference between ADHD and non-ADHD groups). Note the large difference in ES for the two Snyder studies (black circles) from ES = 1.1 in 2008 (Snyder et al., 2008) to ES = 0.4 in 2015 (Snyder et al., 2015). [This figure is a modified and updated version of the findings from the meta-analysis of Arns et al. (2013).]

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Note

1. DSM-5, ADHD diagnostic criteria, criterion E: The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

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