Quantitative Electroencephalography as a Diagnostic Aid for Attention-Deficit/Hyperactivity Disorder

Description

Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) may have alterations in their brain wave patterns that can be measured by quantitative electroencephalography (QEEG). A commercially available system, the Neuropsychiatric EEG-based ADHD Assessment Aid (NEBA®), measures the resting theta/beta ratio of the EEG. This technology is being evaluated to aid in the diagnosis of ADHD in adolescents and children for whom there is a clinical suspicion of ADHD.

Background

Attention-Deficit/Hyperactivity Disorder is a common disorder in children, adolescents, and adults defined by pervasive symptoms of inattention and/or hyperactivity-impulsivity which can lead to impairment in at least 2 domains of the work school or home environments. Stimulant medications reduce symptoms associated with ADHD, although there are concerns about the potential for over diagnosis and overprescribing of medication. Presently, ADHD is diagnosed clinically by assessing behavioral symptoms and impairment via interviews and standard questionnaires. Diagnosis can be challenging, as the core symptoms are non-specific. They may be present in other psychiatric disorders (e.g., learning disabilities, conduct disorders, or affective disorders) or result from environmental influences such as a lack of discipline. In addition, ADHD is a heterogeneous disorder with multiple subtypes and frequently co-exists with other psychiatric disorders.

There has been a substantial amount of research over the last several decades on whether EEG-derived brain wave patterns in patients with ADHD differ from those without ADHD. EEG patterns are typically categorized into 4 frequency ranges, delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-25 Hz). The largest focus of research on brain wave patterns in ADHD has been on whether there is increased theta wave activity and an increased theta/beta ratio in ADHD patients.

The NEBA® system is a specific QEEG system that measures the resting theta/beta ratio of the EEG with an electrode located at the central midline position (referred to as position CZ in the international 10-20 EEG system). QEEG uses computer analysis with mathematical transformation from the time domain into the frequency domain (fast Fourier transform) to determine the total power at each
frequency. Relative power of the waveform can then be calculated in relation to the total power of the 4 frequency ranges. The NEBA system uses proprietary cut offs to generate an estimate of the likelihood of ADHD based on the resting theta/beta ratio.

It is proposed that the NEBA system can be used to confirm a clinical diagnosis or support further testing in children and adolescents with ADHD. The system is not intended to evaluate patients in whom the clinician’s diagnosis of ADHD is negative, and the system does not generate an interpretive report in this situation. It is also proposed that the clinician’s diagnostic impression plus the results generated by the NEBA system may reduce the potential for overdiagnosis of ADHD, and thereby reduce the risks of administering unnecessary pharmacologic therapy in the intended use population.

Regulatory Status

In 2011, the U.S. Food and Drug Administration (FDA) approved a de novo 510k classification (class II, special controls, product code: NCG) for the generic device: Neuropsychiatric Interpretive Electroencephalograph Assessment Aid. According to the FDA documentation, a Neuropsychiatric Interpretive Electroencephalograph Assessment Aid is a device prescribed by a physician that uses a patient’s EEG to provide an interpretation of the patient’s neuropsychiatric condition. In addition to the general controls, approval of these devices is subject to a number of special controls, including the following:

- Clinical performance testing must demonstrate the accuracy, precision, and reproducibility of the EEG-based interpretation, including any specified equivocal ones (cut-offs).
- Clinical performance testing must demonstrate the ability of the device to function as an assessment aid for the medical condition for which the device is indicated. Performance measures must demonstrate device performance characteristics per the intended use in the intended use environment. Performance measurements must include sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) per the device intended use. Repeatability of measurement must be demonstrated using interclass correlation coefficients and illustrated by qualitative scatter plots.
- The device design must include safeguards to prevent use of the device as a stand-alone diagnostic.
- The labeling must bear all information required for the safe and effective use of the device.

The Neuropsychiatric EEG-based Assessment Aid (NEBA®, Lexcor Medical Technology, LLC, Augusta, Ga) for ADHD was cleared for marketing in 2013 as a de novo 510(k) device indicated to measure the theta/beta ratio of the EEG at electrode CZ on patients 6-17 years of age, combined with a clinician’s evaluation, to aid in the diagnosis of ADHD (K112711). NEBA should only be used by a clinician as confirmatory support for a completed clinical evaluation or as support for the clinician’s decision to pursue further testing following a clinical evaluation. The device is not intended to be used as a stand-alone in the evaluation or diagnosis of ADHD.
The Lexicor QEEG system is marketed as a diagnostic aid for ADHD. Lexicor Medical Technology provides an internet analysis service of the QEEG, producing a DataLex report. Lexicor Medical Technology also developed the NEBA system.

FDA Product Code: NCG

Related Policies

None

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Quantitative electroencephalographic based assessment of the theta:beta ratio is considered not medically necessary as a diagnostic aid for attention-deficit/hyperactivity disorder.

Benefit Application

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.

Rationale

Assessment of a diagnostic technology typically focuses on 3 domains: 1) technical performance (test-retest reliability or inter-rater reliability); 2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes. Subsequent use of a technology outside of the investigational setting may also be evaluated.

BCBSA TEC Assessment Overview

A Blue Cross and Blue Shield Association (BCBSA) TEC Assessment published in February 2014 evaluated the evidence related to the use of quantitative electroencephalography (QEEG) with the NEBA system in the diagnosis of attention-deficit/hyperactivity disorder (ADHD). (1) This evidence was submitted to the FDA in 2013 and subsequently published by Snyder et al (of NEBA Health) in 2015. (2, 3) The evidence related to the diagnostic accuracy of NEBA for the diagnosis of ADHD consisted of data submitted to the U.S. Food and Drug Administration (FDA) from 275 children and adolescents (6-18 years) who presented with attention and/or behavioral concerns to one of 13 clinics in the United States. The evidence related to the technical performance of NEBA for the diagnosis of ADHD included test-retest reliability of the NEBA theta/beta ratio for electroencephalography (EEG) data from 198
patients who had recordings on 2 different days. These studies are described in greater detail in the sections next on technical performance and diagnostic accuracy. No studies were identified that assessed whether the reclassification of patients suspected of having ADHD, as reported to FDA, improves health outcomes.

**Technical Performance**

Data submitted to FDA for the NEBA system included test-retest reliability of the theta/beta ratio for EEG data from 198 patients who had recordings on 2 different days (≈2.5 weeks apart on average). (2) EEG data were collected for 10 minutes with patients seated in a chair with eyes open and fixed with attention to a point at eye level on the wall. Epochs (30 seconds in duration) with substantial artifact were screened out by EEG processing technicians at a central facility. Analysis of EEG data required at least 15 epochs of data with little to no artifact. There were 198 patients with 2 sessions of data out of the per protocol set of 275. The theta/beta cutoffs were revised prior to the blind break based on data from a prior study. (4) The intraclass correlation coefficient of repeated NEBA theta/beta ratio was 0.83, which is considered to be high.

**Diagnostic Accuracy**

A number of studies have been published that measured theta activity or the theta/beta ratio in children and adolescents with ADHD compared to non-affected controls. The most commonly reported alteration in EEG is an increase in the theta/beta ratio. However, some studies have reported that other patterns such as increased beta wave activity are found in some patients, and several recent studies have found no significant difference in theta activity in a clinical vs. non-clinical population.

A 2005 systematic review included 17 studies evaluating theta activity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). (5) Meta-analysis found a weighted mean effect size of 0.59 for an absolute increase in theta activity and a mean effect size of 0.91 for theta relative to total EEG activity. A 2006 systematic review by Snyder and Hall included 9 studies (N=1498) that used DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria and screening tests in a clinical setting. (6) Meta-analysis identified a mean increase of theta power of 32% and a pooled effect size of 3.08 for the theta/beta ratio in patients with ADHD compared with unaffected children, adolescents, and adults. It was noted that the included studies often had retrospectively set limits and that an increase in the theta/beta ratio has also been identified in other conditions. A 2001 study by Monastra et al found a change in QEEG at CZ in a large study (N=469) of children and adolescents who were diagnosed as ADHD versus controls, although this study used an attention index measured across 4 different tasks (eyes fixed, silent reading, listening, drawing). (7)

Other studies find no significant difference in theta activity in a clinical population with ADHD. For example, in 2013, Liechti et al reported the theta/beta ratio in 32 children and 22 adults with ADHD compared with healthy controls who were matched for age, gender, and IQ. (8) Resting EEG was measured separately for the 3 midline electrodes (frontal [FZ], central [CZ], parietal [PZ]) and for frontal, central, and parietal regions. The study found a decrease in theta with age, but no consistent increase
in theta or theta/beta ratio in patients with ADHD compared with controls. There was no evidence for a maturational lag in patients with ADHD. In 2012, Ogrim et al assessed differences in theta activity measured at CZ in 62 children and adolescents with a tentative diagnosis of ADHD compared with 39 sex- and age-matched controls. (9) The overall accuracy at CZ was 63% for theta and 58% for the theta/beta ratio compared with non-affected controls. Elevations of theta were found in 25.8% of patients compared with 2.6% of controls. None of the EEG measures reached statistical significance in separating patients from controls. In other studies, subgroups of children with ADHD have been shown to have an increase of beta activity instead of a decrease in beta or increase in the theta/beta ratio. (10,11) In a study of QEEG in combination with the Connors’ Continuous Performance Test and the Test of Variables of Attention in the diagnosis of ADHD in 157 children, 85 with and 72 without ADHD based on Diagnostic Interview Schedule for Children (Version IV), Kim et al reported that the ADHD group had significantly higher values for theta waves in 13 positions, while for the theta/beta ratio, the ADHD group had higher values for only 1 position (right frontal lobe). (12)

### Sensitivity, Specificity, and Predictive Value of the Theta/Beta Ratio in the Diagnosis of ADHD

Data submitted to the FDA regarding diagnostic accuracy were from a multi-center study of 275 children and adolescents (6-18 years) who presented with attention and/or behavioral concerns to one of 13 clinics in the U.S. (2, 3) An additional 89 children and adolescents were recruited but did not complete the study, and of these, 67 had incomplete EEG recordings. (3) Diagnostic evaluation for ADHD and other disorders was conducted with clinical interview and rating scales that included behavior rating scales, IQ and achievement testing, and scales of severity and dysfunction. A consensus best-estimated diagnosis was determined by a multidisciplinary clinical team composed of a clinical psychologist, a neurodevelopmental pediatrician, and a child/adolescent psychiatrist. The clinical team had access to de-identified patient files, but did not conduct an interview or have access to the parent rating scales, features which are considered critical for a criterion standard diagnosis of ADHD. A separate group of investigators who were unaware of the clinical diagnosis collected the EEG data (NEBA system). When compared with the consensus diagnosis, NEBA was found to have a sensitivity of 89%, specificity of 87%, PPV of 81% and NPV of 93% for adolescents (12-17 years). For children (6-11 years), NEBA had sensitivity of 79%, specificity of 97%, PPV of 96% and NPV of 82%. The investigators calculated that the addition of NEBA to the clinician’s ADHD evaluation would have improved the clinician’s diagnostic accuracy from 61% to 88%. This calculation is based on the 275 patients who completed the protocol, rather than the intention-to-treat population. The results of this FDA-regulated study suggest that QEEG might be used to decrease the overdiagnosis of ADHD by identifying patients who may not have the disorder. Strengths of this study include that it is multicenter and the reclassification analysis of data was obtained from a blinded analysis. Limitations of this study are lack of patient interview by the consensus team and lack of intent-to-treat analysis.

Snyder and colleagues reported the accuracy of the theta/beta ratio for diagnosis of ADHD in an industry sponsored, investigator-blinded, multi-center study from 2008. (4) Patients (n=159) aged 6 to 18 who had presented to 1 of 4 psychiatric and pediatric clinics with suspected attention and behavioral symptoms were evaluated in a standardized semi-structured manner according to DSM-IV criteria by a clinical team that had been trained on the study instruments. Rating scales were distributed to parents
and teachers and held in sealed envelopes until the blind was broken. EEG was collected separately by investigators who were blinded to the clinical diagnosis, using a 19-electrode cap according to the 10-20 system with eyes open and eyes shut. A threshold of 1.5 standard deviations of the theta/beta ratio from normative database values (according to age) at electrode CZ was used to determine ADHD versus non-ADHD. With a prevalence of ADHD of 61% based on clinical diagnosis, the theta/beta ratio had a sensitivity of 87%, specificity of 94%, PPV of 95% and NPV of 82%. The rating scales provided sensitivity of 38-79% and specificity of 13-61%. Results from this study were used to set a new theta/beta threshold for analysis of data from the FDA-regulated study of the NEBA device. (2, 3)

Other studies have reported lower accuracy of QEEG in the diagnosis of ADHD. In the Kim et al study reported above, on receiver operator curve analysis, QEEG theta wave amplitude showed low accuracy for the diagnosis of ADHD (56.4%), and theta/beta wave amplitude did not significantly predict ADHD diagnosis.(12) Sangal et al evaluated the discriminatory power of QEEG measurements during auditory and visual tasks requiring selective attention in 28 control children and 58 children with ADHD.(13) Subjects with ADHD had significantly higher average theta/beta ratios (2.6 vs 2.25; P=0.007) and lower average beta-I amplitudes (3.66 vs 4.22; P=0.01). The average theta/beta ratio had sensitivity and specificity in diagnosing ADHD of 69% and 50%, respectively, while the theta/beta ratio at the CZ position had sensitivity and specificity of 69% and 43%, respectively.

**Section Summary: Diagnostic Accuracy**

Patients with ADHD may have altered brain wave patterns on EEG compared to patients without ADHD. While an increased theta/beta ratio is the most common alteration reported, not all studies have found this association, and some report other brain wave patterns in ADHD patients. A few studies report on sensitivity and specificity of quantitative EEG compared to clinical diagnosis. In these studies, sensitivity ranges from 69% to 89% and specificity ranges from 43% to 97%. However, a weakness of these studies is the lack of a true criterion standard for diagnosis of ADHD.

**Effect on Clinical Outcomes**

A proposed benefit of the NEBA system is a reduction in the overdiagnosis of ADHD, thereby reducing the risks of administering unnecessary pharmacologic therapy in children and adolescents. There were no published studies that directly reported on clinical outcomes, such as measures of disease activity and/or medication use. The pivotal FDA study reported reclassification of diagnosis following NEBA; this may be considered an indirect measure that may impact outcomes.

The evidence related to the question of whether QEEG improves the clinical diagnosis of patients with suspected ADHD consists of the material submitted to FDA as part of the NEBA’s approval process, as previously described. (2, 3) The study included reclassification tables to demonstrate whether NEBA provides additional information beyond the clinician’s initial diagnosis, which are summarized in Table 1 based on the BCBSA TEC Assessment. (1) Use of NEBA resulted in little change in categorization for patients diagnosed with ADHD by both the initial clinical diagnosis and the consensus diagnosis. For example, 95 of 130 children and adolescents (73%) who were considered to have ADHD by the
consensus diagnosis were classified as ADHD by both the clinician alone and NEBA. Greater reclassification was observed when using NEBA for patients diagnosed by retrospective consensus as non-ADHD. For example, there were 145 children and adolescents who had a non-ADHD diagnosis by the consensus. Of the 145, 93 had received an initial clinical diagnosis of ADHD but 85 (91%) of these were negative by NEBA.

Table 1: NEBA Reclassification of Patients With Consensus ADHD Diagnosis

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<tr>
<th>Consensus Diagnosisa</th>
<th>Initial Clinical Diagnosis</th>
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<td>ADHD</td>
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<td>NEBA interpretationb</td>
<td>+</td>
<td>95 (81.9)</td>
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<td></td>
<td>-</td>
<td>21 (18.1)</td>
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<tr>
<td>Total</td>
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<td>NEBA interpretationb</td>
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<tr>
<td></td>
<td>-</td>
<td>85 (91.4)</td>
</tr>
<tr>
<td>Total</td>
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<td>93</td>
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NEBA: Neuropsychiatric EEG-Based Assessment Aid for Attention Deficit Hyperactivity Disorder (ADHD); NEBA interpretation: NEBA results plus initial clinical diagnosis.

a The consensus diagnosis is assumed to be the reference standard (ie, correct). Two categories are included in the ADHD consensus diagnosis: diagnosed with ADHD or referred for more testing for the condition. Similarly, the “not ADHD” diagnosis included those diagnosed as not having ADHD or as needing more testing for other conditions.
b The NEBA interpretation is a composite of both the initial clinical diagnosis and the NEBA results, like a dichotomized posttest probability. The performance measures are presumably calculated assuming that a negative NEBA result can override a positive initial clinical diagnosis, but in the FDA summary, it is stated that a negative diagnosis can only result from a negative initial clinical diagnosis (ie, the NEBA interpretation cannot override it).

Section Summary

The evidence related to the question of whether NEBA, or QEEG more generally, leads to improved accuracy of ADHD diagnosis consists of a single study, with results presented to FDA. The results of this FDA study suggest that QEEG might be used to decrease the over diagnosis of ADHD, by identifying patients with an initial clinical diagnosis who may not have the disorder. Strengths of this study include that is multicenter and the reclassification analysis of data was obtained from a blinded analysis. However, a weakness of this study is the lack of a true gold standard for diagnosis of ADHD. It cannot be determined from the study description whether the initial diagnosis by the single clinician according to DSM-IV criteria or the consensus diagnosis (conducted without interview or parent rating scales) was more accurate. No studies were identified that address whether QEEG improves clinical outcomes for patients with suspected ADHD by improving diagnosis.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.
2011 Practice guidelines for the diagnosis, evaluation, and treatment of ADHD by the American Association of Pediatrics (AAP) state that to make a diagnosis of ADHD, the primary care clinician should determine that Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria have been met (including documentation of impairment in more than 1 major setting), and information should be obtained primarily from reports from parents or guardians, teachers, and other school and mental health clinicians involved in the child’s care. The primary care clinician should also rule out any alternative cause (quality of evidence B/strong recommendation). (14) Assessment by QEEG is not mentioned in these guidelines.

A report from the American Academy of Neurology and the American Clinical Neurophysiology Society on the assessment of digital EEG, quantitative EEG, and EEG brain mapping was reaffirmed in 2013. The report states that:

“On the basis of current clinical literature, opinions of most experts, and proposed rationales for their use, QEEG remains investigational for clinical use in postconcussion syndrome, mild or moderate head injury, learning disability, attention disorders, schizophrenia, depression, alcoholism, and drug abuse. (Class II and III evidence, Type D recommendation).” (15)

U.S. Preventive Services Task Force Recommendations

Quantitative electroencephalography is not a preventive service.

Summary

The evidence on QEEG in individuals who are suspected of having ADHD includes a number of studies on brain wave patterns, particularly the theta/beta ratio. Relevant outcomes include test accuracy, symptoms, functional outcomes, and medication use. Numerous studies have evaluated brain wave patterns with standard EEG equipment, and there is a pivotal trial that was submitted to the U.S. Food and Drug Administration (FDA) that measured the theta/beta ratio with the NEBA system. In the pivotal trial, the specificity and positive predictive value (PPV) of QEEG was high. The reclassification analysis suggests that a negative NEBA might make ADHD less likely, although it is not clear from this study whether the consensus diagnosis was more accurate than the initial clinical diagnosis that included patient interview and parent rating scales. The larger body of evidence also raises questions about the utility of measuring the theta/beta ratio, as this has not been a consistent finding across studies. Given the uncertainty of an increase in the theta/beta ratio in patients with ADHD, additional study is needed to determine whether a low theta/beta ratio can identify children and adolescents who are unlikely to have ADHD. In addition, the effect of the test on patient outcomes would allow greater certainty regarding the usefulness of this test. The evidence is insufficient to determine the effect of the technology on health outcomes.

Medicare National Coverage
No national coverage decisions identified.

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Quantitative Electroencephalography as a Diagnostic Aid for Attention-Deficit/Hyperactivity Disorder TEC Assessments. 2014;Volume 29, Number 1.


Policy History

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<tr>
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<td>Update Policy</td>
<td>Policy updated with literature review through September 8, 2014. References 1, 11, 12, and 14 added. Policy statements unchanged.</td>
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Keywords

Attention-Deficit/Hyperactivity Disorder, Assessment
ADHD
DataLex
Lexicor EEG
NEBA
Neuropsychiatric EEG-based ADHD Assessment

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 4, 2015 and is effective January 15, 2016.

Signature on File
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