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Federal Employee Program®
1310 G Street, N.W.
Washington, D.C. 20005
202.942.1000
Fax 202.942.1125

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Section:	Mental Health	**Effective Date:**	January 15, 2014
Subsection:		**Original Policy Date:**	December 6, 2013
Subject:	Quantitative Electroencephalography as a Diagnostic Aid for Attention-Deficit/Hyperactivity Disorder	**Page:**	1 of 9

Last Review Status/Date: December 2013

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 (EEG). 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.

Background

Attention-Deficit/Hyperactivity Disorder is a common disorder in children, adolescents, and adults. ADHD is defined as involving pervasive symptoms of inattention and/or hyperactivity-impulsivity. The behaviors, which are frequently considered to be age-inappropriate, can lead to impairment in the school and home environment. Stimulant medications have been shown to reduce symptoms associated with ADHD, although there are concerns about the potential for overdiagnosis 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 be a result of environmental influences such as a lack of discipline. In addition, ADHD may be a heterogeneous disorder with multiple subtypes.

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 is 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 quantitative EEG system (QEEG) that measures the resting theta/beta ratio of the EEG with an electrode located at the central midline position (CZ). QEEG uses computer analysis with

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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.

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®) for ADHD was cleared for marketing in 2013 as a *de novo* 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.

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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.

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 (EEG)-based assessment that reports the strength, pattern and/or ratios of brain waves is considered **not medically necessary** as a diagnostic aid for neuropsychiatric disorders, including but not limited to attention-deficit/hyperactivity disorder.

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. These domains, although not always evaluated in sequence, can be considered similar to the 4 phases of therapeutic studies:

- **Phase I – Technical Performance**
  - Test-retest reliability
  - Agreement among multiple readers
- **Phase II – Diagnostic Accuracy**
  - Sensitivity (False Negatives) and Specificity (False Positives) for detecting disease compared to the reference standard *in a population with the disease* (often the first step)
  - Sensitivity (False Negatives) and Specificity (False Positives) for detecting disease compared to the reference standard *in a population either with the disease or definitely without the disease* (often the second step)
  - Sensitivity (False Negatives) and Specificity (False Positives) for detecting disease compared to the reference standard in a population covering the spectrum of disease, as encountered *in clinical practice* (required step)
- **Phase III – Effect on Patient Outcomes**
  - Ideally shown in a randomized controlled trial, but difficult to conduct and not always required

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- o Demonstrate tightly linked chains of evidence from diagnostic accuracy to outcomes
- **Phase IV – Post Adoption Use/Safety**
  - o Generalizability
  - o Overuse
  - o Downstream testing
  - o Does use conform to established Appropriateness Criteria?

There are no published peer-reviewed studies that evaluate the accuracy of the commercially available device (NEBA) in the diagnosis of ADHD. The currently available evidence consists of studies that report quantitative EEG (QEEG) results using standard EEG equipment and results of the pivotal FDA studies that led to approval of the NEBA system, which is available through the FDA website and is included in this evidence review.

Technical Performance

What is the reliability of the NEBA system?

Data submitted to the FDA included test-retest reliability of the NEBA theta/beta ratio for EEG data from 198 patients who had recordings on 2 different days (about 2 ½ weeks apart on average). (1) The intraclass correlation coefficient of repeated NEBA theta/beta ratio was 0.83, which is considered to be high. In the published studies, there were no reports identified that measured the reliability of QEEG.

Diagnostic Accuracy

Do patients with ADHD have an increased theta/beta brainwave ratio when measured by quantitative EEG?

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). (2) 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=1,498) that used DSM-IV [*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition] criteria and screening tests in a clinical setting. (3) 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 to 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. In 2008, Snyder et

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al. reported a significant increase in the theta/beta ratio in patients with ADHD compared to other conditions when prospectively assessed with a predefined threshold. (4) 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). (5)

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 that were matched for age, gender, and IQ. (6) Resting EEG was measured separately for the 3 midline electrodes (frontal - FZ, central - CZ, and 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 to controls. There was no evidence for a maturational lag in patients with ADHD. In 2012, Ogrim and colleagues 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. (7) The overall accuracy at CZ was 63% for theta and 58% for the theta/beta ratio compared to non-affected controls. Elevations of theta were found in 25.8% of patients compared to 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. (8, 9)

What is the 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. (1) 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 gold standard diagnosis of ADHD. A separate group of investigators who were unaware of the clinical diagnosis collected the EEG data (NEBA system). When compared to the consensus diagnosis, NEBA was found to have a sensitivity of 89%, specificity of 87%, positive predictive value (PPV) of 81% and negative predictive value (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%.

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%.

Section Summary. 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 EEG compared to clinical diagnosis. In these studies, sensitivity ranges from 79-89% and specificity ranges from 87-97%.

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.

Can quantitative EEG accurately reclassify patients with an initial clinical diagnosis of ADHD into the correct diagnostic categories?

Material submitted to the FDA in support of this claim included reclassification tables from the multi-center study described above to determine whether NEBA provides additional information beyond the clinician's initial diagnosis. (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.

Consensus ADHD		Clinician Alone		
		+	-	Total
NEBA	+	95	11	106
	-	21	3	24
	Total	116	14	130

Consensus Non-ADHD		Clinician Alone		
		+	-	Total
NEBA	+	8	1	9
	-	85	51	136
	Total	93	52	145

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Section Summary. The results of reclassification from the FDA study raise the possibility that QEEG might be used to decrease the overdiagnosis 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 this study 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.

Practice Guidelines and Position Statements
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). (10) Assessment by QEEG is not mentioned in these guidelines.

Summary
The Neuropsychiatric electroencephalography (EEG)-based ADHD Assessment Aid (NEBA) is a quantitative EEG system that measures the resting theta/beta ratio of the EEG at position CZ. NEBA is being evaluated to aid in the diagnosis of children and adolescents with attention-deficit/hyperactivity disorder (ADHD). The system is indicated when there is a clinical suspicion of ADHD, and is not to be used as a primary diagnostic test.

Current evidence includes numerous studies that have evaluated quantitative EEG at CZ with standard EEG equipment, and one pivotal trial submitted to the U.S. Food and Drug Administration (FDA) that used the NEBA system to assess test-retest reliability, sensitivity, specificity, and reclassification analysis in an appropriate population of patients. In the FDA pivotal trial, the specificity and positive predictive value of QEEG was high, although the reclassification analysis showed little benefit of a positive NEBA over clinical assessment alone. 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. Further research is needed to evaluate the potential impact of NEBA on management of ADHD. In addition, the effect of the test on patient outcomes, such as rates of medication use, would allow greater certainty regarding the usefulness of NEBA.

The larger body of evidence also raises questions about the utility of measuring the theta/beta ratio in patients suspected of ADHD, as this has not been a consistent finding across studies. Recent studies show low accuracy (58%) and no significant increase in the theta/beta ratio in children and adolescents with ADHD compared to age- and sex-matched controls. Other studies show an increase in beta (rather than a decrease) in a subgroup of affected children and adolescents. Given the uncertainty of an increase in the theta/beta ratio in children and adolescents with ADHD, additional

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study is needed to determine how strongly the theta/beta ratio is associated with ADHD. Therefore, quantitative EEG as a diagnostic aid for ADHD is considered investigational.

Medicare National Coverage
No national coverage decisions identified.

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Policy History

Date	Action	Reason
December 2013	New Policy	

Keywords

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

This policy was approved by the FEP Pharmacy and Medical Policy Committee on December 6, 2013 and is effective January 15, 2014.

Signature on File
Deborah M. Smith, MD, MPH