

SPECIAL ISSUE

Medication Prediction with Electroencephalography Phenotypes and Biomarkers

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This article reviews current medication practices for the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, diagnostic category of attention-deficit hyperactivity disorder. A wide range of medication classes are in use clinically, based on divergent pharmacological mechanisms, from stimulants to anticonvulsants to antidepressants, and including even more esoteric medications such as oxytocin and the various channel blockers. The author proposes that quantitative electroencephalography (EEG) patterns can provide a more reliable basis for medication selection than diagnostic category. The EEG's neurophysiological indicators for these medication classes are summarized and reviewed based not only on 41 years of experience in the field but also on outcomes from psychiatric practices, in an evidence-based approach to medication prediction.

Historically, EEG Has Been Used to Predict Medication Efficacy

The intersection of the fields of pharmacology and electroencephalography (EEG) has a relatively brief history, with pioneering work by Max Fink and Turan Itil that dates to the 1960s with two channels of digital analysis of the EEG (Itil, Shapiro, & Fink, 1968). Pharmaco-EEG has an organization that formed early in the history of the field. The International Pharmaco-EEG Group (IPEG) is a small, dedicated group that meets every 2 years at various international venues, such as at New York University early in 2012 and at the University of Leipzig, Germany, in fall 2014. This truly international group has active members in Europe, Asia, Australia, the United States, Iceland, and other countries. IPEG seems to have new interest from the academic and research laboratories in Europe, with advanced techniques being applied to the issue of selecting the right medication for the individual.

There are also now commercial companies with computer algorithms that are used to predict medication options, such as Daniel Hoffman's company, CNS Re-

sponse. This work is based on the pioneering work by Suffin and Emory (1995) in predicting medication response with the EEG/quantitative EEG (QEEG).

Even with these historic findings and the international organization, the application of EEG to medication selection remains clearly outside the normal realm of clinical practice standards in psychiatry. This may be changing with the rapid abandonment of the classical *Diagnostic and Statistical Manual of Mental Disorders* (DSM) approach and the current race to find predictors of treatment efficacy, which seems now more salient as a goal than mere administrative categorization of the symptoms.

Applying EEG/QEEG Markers to a Specific Disorder: Attention-Deficit Hyperactivity Disorder

In this section, I will introduce the application of EEG and QEEG markers by a discussion of a typical child patient with attention-deficit hyperactivity disorder (ADHD). The situation I pose is a common one: the initial presentation of a 7-year-old patient who was correctly behaviorally diagnosed by the physician as having ADHD. This determination would be based on impulsive, inattentive, and hyperactive behaviors across a period of time. The current clinical standard requires that this diagnosis of ADHD be based on behavioral observations, as detailed in the new DSM-V, even though the National Institute of Mental Health has declared the DSM to be invalid in that it fails to predict effective therapy (Frances, 2013).

Following the behaviorally based diagnosis, the next real question for the attending physician might be how to treat the patient effectively. For medical professionals, the choices are too often limited to the question, "Which medication will be effective in treating the ADHD behaviors?" Unfortunately, other effective treatment options including neurofeedback (NF)/neuromodulation are often overlooked.

Will the effective medication approach be one of the early classical stimulants (Kuczenski and Segal, 1997), such as the dopamine reuptake inhibitor class represented by methylphenidate (Ritalin, Concerta, etc.), or will this client be one who responds better to one of the amphetamine-related norepinephrine (NE) agonists such as Vyvanse or Adderall? Or should it be a “nonstimulant” NE-reuptake inhibitor such as Strattera?

If the client does not respond to stimulants, then is the right drug perhaps one of the newer approaches (Van Der Kolk, 1987) with an ion-channel blocker such as Clonidine, Intuniv, or Prazosin (Boehnlein and Kinzie, 2007)? Or is this one of the 10%–24% of the ADHD population who has unexpected epileptiform or paroxysmal EEG activity who will respond to anticonvulsant medication, and if so, which one? For some cases of ADHD, there is even a chance a client will respond to the selective serotonin reuptake inhibitor (SSRI) class of drugs including Prozac and Zoloft (Dumont, de Visser, Cohen, & van Gerven, 2005) or to the serotonin and norepinephrine (SNRI) drugs such as Effexor or its newer isomer Pristiq. Occasionally, lithium may be provided for hyperkinetic behavior, as though it were related to bipolar disorder. In some circumstances, the presence of a comorbid sleep issue may even find the client prescribed a stimulant such as Provigil/Nuvigil, applied to maintain daytime vigilance.

One of the more recent options is the use of oxytocin, the hormone related to emotional bonding, to improve social “presence” (Perry et al., 2010). This medication intervention is hypothesized to operate through an increased engagement of the mirror neuron system, as reflected in the related EEG rhythm: Mu. Mu is a normal EEG variant in the alpha frequency band, which can be seen in the EEG bicentrally in the absence of movement, intention to move, or even “engagement.”

This long and varied listing of medications has a wild swing of various underlying mechanisms, although all of them can be applied to a specific clinical case with a solid personalized medicine rationale and all are commonly seen in clinical practice today. The real trick is picking the right one the first time, or at least avoiding the obvious contraindications.

“Try This (and See If It Works)”

The range of pharmaceutical choices in this single diagnostic cluster is diverse, and the mechanisms of action for these drug classes cover a wide range of physiological systems. The prescribing physician may have the patient “try one,” and if that doesn’t work, then “try another,” as they go through the list of various classes of drugs, one

after another, eventually maybe even trying a combination of these drugs. If the doctor’s first best guess does not work, then the patient can try another; however, side effects occasionally can be expected. This is especially true if drugs are mismatched with the client’s underlying neurophysiological profile, in which case side effects are absolutely expected. The current standard of practice with the physician “guessing” what class of drugs will work is not always without consequence, and iatrogenic issues are common, but often they can be treated with other drugs.

Precipitating Adverse Events

Providing a stimulant to a patient who has an undiscovered or untreated epileptiform EEG burst of spike activity, with sharper and slower content, which typically emerges from the background with a sudden onset and cessation, may exacerbate the discharges. These epileptiform/paroxysmal EEG patterns, if treated with stimulant medications, may precipitate the first clinical event, as we have observed many times in the past 40 years of EEG monitoring. Another contraindicated drug when paroxysms are present is prescribing an antipsychotic drug, which lowers the discharge threshold and can have a severe side effect if it is done without also treating the underlying paroxysmal discharge. Proceeding carelessly may precipitate a “break-through event” for a client with an existent convulsive disorder or even initiate convulsions or altered function (temporal lobe epilepsy often mimics psychiatric conditions such as auditory hallucinations) in previously asymptomatic individuals. Stimulants or SSRIs given to those with beta spindles may often kindle the beta activity into symptomatic side effects associated with cortical overarousal.

It should be obvious that the “try one” method is not an optimal approach to personalized medicine! For those requiring proof that the current standard of practice is inadequate, I would point to the rate of intractable epilepsy or intractable depression. In the case of depression, the “Star-D” study, with more than 3,000 patients tracked, showed that this “try one” method had only a 38.6% initial trial efficacy, and further, after the fourth set of trials, a residual 33% of those complaining of clinical depression still remained ineffectively treated for their depression with pharmaceuticals (Gordon, 2007). In my opinion, if the current DSM-based system were working to treat patients effectively, there would be far fewer bottles of medicine turned in when pharmacies accept old unused drugs, and the wild polypharmacy I often see would not be seen as often.

Grandma Was Right

I would suggest that we all actually follow my grandmother's sagacious advice: "Don't dive into the water unless you know what is under the surface!" If clinical practitioners wish to "look" before they just try one of this long list of medications, then they should look at the brain's function prior to prescribing a medication to treat a client. The need to "look first" is due to the multiplicity of neurophysiological patterns that can be seen as the same behaviorally defined clinical DSM entity, such as ADHD (Johnstone, Gunkelman, and Lunt, 2005).

Matching the Medication to EEG and Neurotransmitter Patterns

For each EEG profile, there is a neurotransmitter mix correlate (Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990), and getting the right neurochemistry mix when using pharmaceuticals can be guided by actually looking at the neurophysiological signals the brain emanates. This can be illustrated with the ADHD case.

Excessive frontal theta is a common presentation for the EEG of a client with ADHD (Monastra, Monastra, & George, 2002). Another EEG pattern is frontal slower frequency alpha, which looks like theta to a fixed-band analysis. Frontal age-appropriate frequency alpha represents even another pattern seen in ADHD clients. Other variants of the EEG include the presence of beta spindles and even paroxysmal or epileptiform discharges affecting the frontal lobe (Arns, Gunkelman, Breteler, & Spronk, 2008). All of these patterns can disturb the frontal lobe's function, resulting in the same behavioral manifestation of the multiple physiological patterns, each representing a very differing pathophysiology and predicting very different pharmacotherapeutic approaches.

If the EEG has a frontal theta pattern noted, the medication "lock and key" match is methylphenidate, to increase the striatal levels of dopamine with this dopamine reuptake inhibitor class of medication (Kuczenski & Segal, 1997). In ADHD, this frontal theta pattern is generally due to altered dopamine transporter genetics, which functionally depletes the client's dopamine levels. Ritalin (methylphenidate) is a short-acting form of this dopamine reuptake inhibitor; Concerta® is a longer-acting extended release version of methylphenidate.

Slower-frequency alpha seen frontally needs to have more NE released from the brainstem, to slightly speed up the thalamic alpha frequency pacemaker as well as to stimulate the frontal cortex via the brainstem's ascending reticular activating system, which feeds into the frontal lobe through the diffuse thalamic projections. The diffuse

projection system stimulates the cortex more anteriorly than the posterior specific sensory relay nuclei of the thalamus. The thalamic sensory relays via the medial and lateral geniculate and pulvinar innervate cortical sensory areas, occipitally, parietally, and in the temporal-parietal junction, but not frontally. With some stimulant medications, the production of more NE is accomplished with direct agonists, as seen in amphetamine-based stimulants such as Adderall or Vyvanse (Rothman et al., 2001), and with a somewhat less powerful effect, this can also be accomplished using NE-reuptake inhibitors such as Strattera (Kooij, 2013).

If the frontal lobe has regular frequency alpha seen in excess, especially with eyes-closed frontal alpha hypercoherence, then in our experience, an SSRI or an SNRI may be used to increase frontal function. The SSRI does this by increasing serotonin, and with SNRIs, there is also a small NE effect (a 10:1 ratio of SSRI to SNRI effects are seen in Effexor). Remeron is a tetracyclic antidepressant and has the action of both an NE agonist and reuptake inhibitors for serotonin, doubling up on the mechanism of action. Trazadone is a serotonin antagonist and reuptake inhibitor (SARI), which enhances serotonin levels more prominently as well as provides a mild hypnotic effect for sleep-onset enhancement (Cipriani, et al., 2009)

Beta spindles are also a possible EEG pattern in ADHD, with disturbed function due to what Fred and Erna Gibbs originally described in the 1930s as an easily "kindled" or triggered and "irritable" cortex (Gibbs, Davis, & Lennox, 1935). These are generally seen from 18 to 25 Hz, with a sinusoidal morphology, and need to be differentiated from compensatory beta spindling at lower frequencies (<http://www.brainclinics.com/eeg-voorbeelden-low-voltage-beta-spindles>). These irritable cortex beta spindles respond well to ion channel blockers, as well as to anticonvulsants. Beta spindles were initially described by Gibbs and Gibbs in the 1930s in epileptics, although this neural pattern is also seen in other conditions, such as ADHD and bipolar depression, and is not considered specific to epilepsy, although it suggests an irritable or easily kindled cortex.

Obviously, when paroxysms and even frankly epileptiform discharges are seen, the clear medication choice is an anticonvulsant (Sasa et al., 1988). Just selecting this general class still leaves a wide array of various anticonvulsant drugs from which to choose. The presence of paroxysms may also alter the choice for other drugs because of concern for lowering the discharge threshold, allowing a more clinically significant discharge to occur (Centorrino, 2002). Although stimulants can be provided to individuals with a treated paroxysmal EEG, where anticonvulsant drugs are

being used, it is much better to utilize short-acting stimulants rather than long-acting forms of stimulant. Paroxysms also suggest discontinuation of lithium or any antipsychotic or atypical antipsychotic drugs due to the commonly observed lowering of the discharge threshold.

Speaking in gross generalities about classical anticonvulsant treatment, Depakote (divalproex sodium) and Depakene (valproic acid) are more commonly used with children as well as classically with bipolar depression, along with or in place of lithium. Keppra (levetiracetam) is more commonly prescribed for temporal lobe epilepsy as well as with generalized seizures. Tegretol (carbamazepine) or Lamictal (lamotrigine) are best used with clients with a normal peak frequency alpha; however, Trileptal (oxcarbazepine) is a better match with those showing a slower peak frequency alpha, as it speeds up the background rhythmicity. Zarontin (ethosuximide) is used for children with 3-spike and wave absence spells. Topamax is an anticonvulsant used for migraine clients who have paroxysmal EEGs (Sasa et al., 1988).

Neurontin (gabapentin) is a secondary-level anticonvulsant that reduces the central nervous system arousal level (Rijnbeek, de Visser, Franson, Cohen, & van Gerven, 2003). Klonopin (clonazepam) is used for only short-term acute management, as it is highly addictive, with higher dependency potential, and introduces dramatic EEG beta spindles, interfering with the underlying EEG analysis. Ativan (lorazepam) or Valium (diazepam) are also used only for acute anticonvulsant treatment (Visser et al., 2003), such as for status epilepticus (an ongoing epileptiform discharge in an apparently comatose person). In these cases, these drugs are given as an injection in a hospital or emergency setting, or even as a pen-style injection with Diastat, similar to epinephrine for bee sting being done with a pen injector.

Phenobarbital is used in infants for febrile seizures or as initial treatment, although this is quite sedating and is not generally used for longer-term care. Dilantin is an older-style anticonvulsant with serious periodontal side effects. Tegretol is a classical anticonvulsant, much like Trileptal, but Tegretol does not speed up alpha.

Withdrawal Is Not Always Easy

If a drug class has been tried and found to be ineffective or to have too many side effects to be tolerated, then discontinuing the drug is required. Unfortunately, rapid withdrawal from many of these drugs can cause significant side effects. Withdrawing from SSRIs is commonly associated with dizziness, weakness, nausea, headache, lethargy, insomnia, anxiety, poor concentration, and even

occasionally paresthesias. Withdrawing from an NE-related reuptake inhibitor causes urinary urgency and increased gastrointestinal motility and diarrhea. When discontinuing anticonvulsant drugs, there is a likelihood of increased mood instability, anxiety, agitation, and occasionally visceral or autonomic changes. People withdrawing from anticonvulsants often report sleep-onset problems and other sleep disturbances as cortical excitability increases.

Withdrawal from some drugs can alter the metabolic processing of remaining drugs. As an example, with Tegretol (carbamazepine) and Trileptal discontinuation, other drugs have an increased risk of toxicity, which is due to decreased liver metabolism and increased drug blood levels. Conversely, when stopping Depakote/Depakene-related anticonvulsants, there may be less clinical efficacy from other drugs due to increased liver metabolism and decreased blood levels.

With all this difficulty during withdrawal from various drugs, the importance of picking the right medication the first time becomes all the more apparent. Unfortunately, the DSM provides no guidance at all.

DSM's Efficacy Illusion: "Diagnosis, Therefore Therapy"

To stay grounded, this discussion has focused on a simple clinical presentation and the drug selection, specifically for an ADHD child's treatment with medication. The variety of divergent neurophysiological presentations seen in this simple example, as well as the variety of pharmaceutical approaches that are appropriate for each of the underlying "causes" of the clinical behavioral presentation, in my opinion, points to the core flaw of the DSM approach to selecting pharmaceutical treatment.

The unspoken statement defining the core of this flaw is that the DSM diagnosis does not predict therapeutic efficacy for any psychiatric drug or even really significantly narrow the drug selection for the prescribing physician to consider. Although clinical work is not random, it is also not a hard science. There is no clinical logic flow and decision tree chart describing a flow diagram that gives predictable outcomes. In this author's opinion, clinical work, especially the prediction of medication, remains an art not yet meeting the ideal of a scientist/practitioner model.

For those with expertise in analysis and interpretation of the EEG/QEEG, the data help get past the DSM/behavioral-based diagnosis flaw, and rather than focusing of categorization, the neurophysiological findings identified with the underlying EEG biomarkers can help predict medication responses. The original basis for these observations is the EEG phenotype model proposed in 2005, which makes

specific predictions, which, when tested, have performed well, as seen in the ability of the original model to predict stimulant efficacy in a large group of children with ADHD (Arns et al., 2008). Data on 126 depressive and 126 matched controls predicting SSRI efficacy are also being compiled for submission. I also have a contact (Ronald Swatzyna, PhD, Houston, TX) who is trying to publish a summary of 400 clients with QEEG evaluations, which predicts their medication failure (submitted to the journal *Clinical EEG and Neuroscience*). This remains an active and emerging area of neuroscience.

Biomarkers and Phenotypes Transcend the DSM

This document represents an extension of the original 2005 phenotype paper and points to EEG biomarkers that can be used to guide medication selection (Johnstone et al., 2005). The EEG patterns and predictions used to illustrate this simple ADHD diagnosis case will be consistent, even if these patterns are seen in other DSM categories. The phenotype model predictions and these biomarker observations are independent of the DSM, transcending the old behavioral definitions to look at the underlying physiological systems involved, using these biological metrics to help direct medication selection as well as dose titration based on objective criteria, and avoiding the many pitfalls associated with unexpected findings.

The EEG indicators for the medications in the single case of ADHD are the same indicators seen in all other DSM categories, so the limitation imposed at the start of the article was not really very restrictive, as seen easily in the very broad spectrum of medications represented in the discussion. In other words, each of these specific neural patterns—excessive frontal theta, slower frequency alpha, and so on—can be found in patients with multiple disorders; the neural patterns overlap several diagnoses. The neural activation pattern provides a better guide in selecting medications than does the DSM diagnosis. As seen earlier in this article, from the various stimulant subclasses to the SSRI/SSNR/SARI and other antidepressants, to ion channel blockers, anticonvulsants, and even hormones, to the range of various contraindicated medications when paroxysms are noted; all of these findings suggest that significant guidance can be provided by the EEG for pharmaceutical selection. As this article suggests, medication guidance using EEG patterns can be more stable and targeted than comparable medication selection guided by the current DSM criteria.

With these general components for guidance, many psychiatrist customers have become quite insistent on

seeing the EEG/QEEG results from their psychiatric patients prior to considering their medication. Once a good clinician sees how murky the water is when guided by behavior and the DSM, becoming aware of the dangerous features that can be discovered with the “try one” approach, the clinicians generally become a fan of my grandmother’s approach of really looking before just diving in.

Mix and Match?

Medications work well in conjunction with NF, as seen in work published by Monastra et al. (2002), in which NF and stimulants were given to one group and medication only to another. Both groups did well clinically with their ADHD behaviorally, with only the NF plus medication group staying well when medications were withdrawn. Occasionally, the behavioral need is acute, and the NF learning curve is not of immediate assistance, so medication for the short-term benefits and NF for long-term improvement can be a good match for the client’s needs.

The exception to this is the use of channel blockers, which can impede alpha/theta training according to those doing post-traumatic stress disorder work with soldiers (D. Hagedorn, personal communication, 2012).

I encourage others to start to look at the EEG/QEEG prior to starting medications to gain insight into the underlying neurophysiology and hopefully guide their medication selection and to expand the emerging area of pharmaco-EEG.

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