



## This Is Your Brain on Drugs: Predicting Anticonvulsant Effect Using Transcranial Stimulation

### Predicting Seizure Control: Cortical Excitability and Antiepileptic Medication.

Badawy RAB, Macdonell RAL, Berkovic SF, Newton MR, Jackson GD. *Ann Neurol* 2010;67:64–73.

**OBJECTIVE:** Approximately 30% of patients with newly diagnosed epilepsy do not respond to antiepileptic drugs (AEDs), but this is not predictable. We used transcranial magnetic stimulation to determine the effect of AEDs on cortical excitability in patients with epilepsy and correlated this with a successful response to treatment. **METHODS:** Ninety-nine drug-naïve patients with newly diagnosed epilepsy (55 idiopathic generalized epilepsy, 44 focal epilepsy) were evaluated. Motor threshold and cortical excitability on recovery curve analysis were measured before and 4 to 16 weeks after starting medication. After 1 year of treatment, 43 of 55 idiopathic generalized epilepsy and 26 of 44 focal epilepsy patients were seizure free. **RESULTS:** A decrease in cortical excitability occurred in the seizure-free group as indicated by an increase in motor threshold ( $p < 0.05$ ) and intracortical inhibition on recovery curve analysis, maximum at the 250-millisecond interstimulus interval ( $p < 0.01$ ) compared with pretreatment values. These changes were not present in the group with ongoing seizures. **INTERPRETATION:** Seizure freedom is marked by a reduction in transcranial magnetic stimulation measures of cortical excitability, evident shortly after beginning therapy. This virtual normalization of cortical excitability occurred regardless of the seizure characteristics or AED used. Failure to show this response to AED treatment may be valuable as an early predictor of pharmacoresistance in individual patients.

### Commentary

The term *biomarker*, proffered so knowingly in contemporary medical research, shows up rarely in the epilepsy literature, mainly because we don't have any. For the unfamiliar, a biomarker is something that is measured as an indicator of a biologic process, usually a pathologic one. It is not an assessment of the clinical endpoint of the disease itself; rather, it is a measure that moves in the direction in which the disease moves, be it better or worse. The very best biomarkers are so highly reliable and reproducible in their correlation with clinical consequences that they become established as surrogate endpoints; cholesterol and coronary artery disease is a prime example.

So why do we need them? If the purpose of medical treatment is to prevent adverse outcomes, why not just measure those outcomes directly? In some conditions—for example, stroke—said outcomes may be severe and irreversible, so that waiting for them to occur makes it too late to intervene to help the patient. Thus, therapeutic outcomes are greatly improved by measuring a biomarker—for example, carotid intima-media thickness—rather than waiting for patients to develop permanent ischemic deficits. In other cases—say, multiple sclerosis—disease progression is slow enough that assessment

of outcomes is a protracted affair. In this case, the measurement of a more quickly responsive biomarker—say, MRI lesion burden—greatly facilitates the assessment of therapies. These considerations apply both to individual patients and to a field as a whole. It is no coincidence that the areas of neurology in which active therapeutic progress is being made tend to be those in which there are useful biomarkers.

What could be done with biomarkers in epilepsy? At the individual level, imagine having a tool to determine whether a drug was likely to prevent a patient's seizures without having to wait many anxious months—how much aggravating, fruitless trial-and-error could be avoided! At a greater level, having a reliable biomarker for seizure recurrence could greatly facilitate the process of developing new therapies by reducing the time, and likely the sample size, for assessment of candidate drugs and devices. The benefit to physicians, pharmaceutical companies, and patients would be considerable.

So why is there such a void in biomarkers for epilepsy? In general, developing a biomarker requires an understanding of the pathophysiology underlying the condition, and in this respect we are greatly limited. The chief concept we have available is that epilepsy involves an imbalance between cortical excitation and inhibition, beyond which the specifics remain, for the time being, intractably obscure.

Enter Badawy et al., who cleverly leverage the simple notion of excitation/inhibition imbalance using a noninvasive tool. They studied a group of 59 adolescent and adult patients with new-onset epilepsy using transcranial magnetic stimula-



tion (TMS) both before and after initiation of anticonvulsant treatment, along with a control group. TMS is a well-established method for assessing cortical excitability (1, 2), and, theoretical risks notwithstanding, can be safely used in patients with seizures (3). The authors assessed both motor threshold and the cortical recovery curves to paired pulse stimulation at various interstimulus intervals (ISIs), with the goal of determining whether drug treatment alters these parameters, and whether these alterations relate to drug response.

The study is complex because of a number of dichotomies: the authors studied both generalized and focal epilepsy patients; they stimulated both hemispheres; they constructed both short ISI and long ISI recovery curves; and they distinguished between patients who were rendered seizure free by their treatment and those who were not. But, after boiling it all down, the meat of the findings is as follows:

- Confirming their previous work, baseline cortical excitability as measured by short- and long-ISI recovery curves was elevated in both focal epilepsy (ipsilateral to the presumptive seizure focus) and generalized epilepsy (bilaterally) relative to controls (2).
- Motor thresholds in patients with epilepsy are normal prior to treatment and rise significantly when treatment is successful; but in those who do not become seizure free with treatment, motor thresholds remain unchanged.
- Analogously, both long- and short-ISI recovery curves become less abnormal after treatment and more like controls—in fact, almost superimposable upon the controls—but only when treatment is successful. In patients with ongoing seizures after treatment, these curves barely change at all.

Punctuating the latter point are the results in a group of treatment-failure patients who were tried on a second anticonvulsant and then studied with TMS the third time: once again, those who became seizure free had increases in motor threshold and normalization of recovery curves, while those with resistant seizures had no change.

So are we ready to take TMS into the clinic? Not quite. When the authors did dichotomous analyses to find a clinical cutoff, applying it to the patients with idiopathic generalized epilepsy yielded a very high positive predictive value (PPV = 0.97) but a very low negative predictive value (NPV = 0.42). In other words, passing the “TMS test” predicted seizure freedom very strongly, but failing it didn’t tell us much. For the focal epilepsy patients, the story was even worse: NPV was about the same, while PPV was substantially lower (0.69).

So the authors’ protocol appears to be much more useful at the population level than the individual level. But this makes it no less scientifically intriguing and opens the door to some potentially important uses. First, other drugs must be studied, as the authors’ patients were all treated with one of three drugs (valproate, lamotrigine, or carbamazepine), and it would be important to know whether drugs of different structure and presumptive mechanism yield the same results. Should their findings be validated, pharmaceutical companies might find TMS highly useful as a screening tool for early stage drug development. Furthermore, at least one investigation has shown a correlation between carbamazepine level and cortical excitability; if this relationship is validated among multiple drugs, TMS might even be useful for phase II dose-finding studies (4).

And it’s not just industry who might find this helpful; anticonvulsant action has been ascribed to a number of compounds, from thiazide diuretics to fluoxetine to verapamil (5-7). Might TMS be a “quick and dirty” way to tell if these compounds really show promise in seizure prevention?

Perhaps further work will reveal other TMS protocols with higher PPV and NPV that will be useful for individual patients. In any case, this work will hopefully serve to stimulate interest in biomarker development in epilepsy, which is critical to accelerate what has been a frustratingly slow pace of empirical progress.

By Scott Mintzer, MD

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