

Current Literature

In Clinical Science



Predicting Seizures: Are We There Yet?

Prediction of Seizure Likelihood with a Long-Term, Implanted Seizure Advisory System in Patients with Drug-Resistant Epilepsy: A First-in-Man Study.

Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, D'Souza W, Yerra R, Archer J, Litewka L, Hosking S, Lightfoot P, Ruedebusch F, Sheffield WD, Snyder D, Leyde K, Himes D. *Lancet Neurol* 2013;12:563–571.

BACKGROUND: Seizure prediction would be clinically useful in patients with epilepsy and could improve safety, increase independence, and allow acute treatment. We did a multicentre clinical feasibility study to assess the safety and efficacy of a long-term implanted seizure advisory system designed to predict seizure likelihood and quantify seizures in adults with drug-resistant focal seizures. **METHODS:** We enrolled patients at three centres in Melbourne, Australia, between March 24, 2010, and June 21, 2011. Eligible patients had between two and 12 disabling partial-onset seizures per month, a lateralised epileptogenic zone, and no history of psychogenic seizures. After devices were surgically implanted, patients entered a data collection phase, during which an algorithm for identification of periods of high, moderate, and low seizure likelihood was established. If the algorithm met performance criteria (ie, sensitivity of high-likelihood warnings greater than 65% and performance better than expected through chance prediction of randomly occurring events), patients then entered an advisory phase and received information about seizure likelihood. The primary endpoint was the number of device-related adverse events at 4 months after implantation. Our secondary endpoints were algorithm performance at the end of the data collection phase, clinical effectiveness (measures of anxiety, depression, seizure severity, and quality of life) 4 months after initiation of the advisory phase, and longer-term adverse events. This trial is registered with ClinicalTrials.gov, number NCT01043406. **FINDINGS:** We implanted 15 patients with the advisory system. 11 device-related adverse events were noted within four months of implantation, two of which were serious (device migration, seroma); an additional two serious adverse events occurred during the first year after implantation (device-related infection, device site reaction), but were resolved without further complication. The device met enabling criteria in 11 patients upon completion of the data collection phase, with high likelihood performance estimate sensitivities ranging from 65% to 100%. Three patients' algorithms did not meet performance criteria and one patient required device removal because of an adverse event before sufficient training data were acquired. We detected no significant changes in clinical effectiveness measures between baseline and 4 months after implantation. **INTERPRETATION:** This study showed that intracranial electroencephalographic monitoring is feasible in ambulatory patients with drug-resistant epilepsy. If these findings are replicated in larger, longer studies, accurate definition of preictal electrical activity might improve understanding of seizure generation and eventually lead to new management strategies.

Commentary

Efforts to predict impending seizures before they actually occur have been the focus of extensive lines of research over decades. Successful seizure prediction would offer the possibility of immediate treatment to preempt the seizure, as well as to provide an opportunity for the patient to take precautionary measures and reduce risk. There is even evidence that simply reducing the unpredictability of seizures would significantly reduce the burden of epilepsy (1). Despite the tremendous potential benefits and years of impressive research, there are still no highly reliable, clinically useful methods available to predict and preempt impending seizures in patients with

epilepsy (2). This fact underscores the complexity of epileptogenic networks, the neurophysiology of seizure generation, and preictal/peri-ictal physiology.

Upon this backdrop, Cook et al. studied a "long-term implanted seizure advisory system." The system—utilizing intracranial electrodes connected to an implanted telemetry unit—was designed to predict seizure likelihood and inform the subject of this likelihood using colored advisory lights. While the primary outcome was the safety of the device, the authors developed reliable advisory algorithms for seizure occurrence, representing a significant advance in neurophysiologic seizure prediction.

The term "seizure advisory" adds to a list of terms including seizure anticipation, seizure prediction or seizure detection, describing attempts to reliably identify seizures in advance of behavioral manifestations. The time period from the identification of the state of high seizure risk and actual seizure onset is considered the pre-ictal period; identification of the "preictal"

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period provides the best opportunity to preemptively treat and prevent the transition to the ictal state (3). In addition to intracranial EEG, other candidate approaches to identifying the preictal state include cellular physiological changes, and patient-based clinical reports (4). The “preictal” period ranges from seconds to hours or even days, depending upon the methodology and the patient. The timing of the seizure prediction has to align with the time required to administer and realize the benefits of treatment. If the intervention is direct cortical stimulation, a time window of seconds may suffice. If the intervention is taking an oral benzodiazepine a warning of minutes to hours may be required.

In this feasibility study, cortical strip electrodes were placed unilaterally over the quadrant felt to be the most epileptogenic (including patients with bilateral temporal lobe onset seizures). The leads were tunneled down the neck and connected to a telemetry unit placed subclavicularly, similar to vagal nerve stimulator placement. Sixteen channels of iEEG (intracranial EEG) were transmitted wirelessly to a handheld advisory device capable of delivering information to the subject. An algorithm previously tested in canines (5) was applied to the continuous iEEG which characterized epochs of EEG as high likelihood, moderate likelihood or low likelihood for seizure. When the algorithm met performance criteria (sensitivity of high-likelihood warnings greater than 65%, and performance better than chance for prediction of randomly occurring events), subjects proceeded to the advisory phase where they would receive feedback about seizure likelihood. Most subjects were “enabled” for high or moderate seizure likelihood; some were also enabled for low likelihood advisory feedback.

The primary endpoint was adverse events associated with the device at 4 months after implantation. Of 15 subjects who received the implantable device, the investigators reported 11 adverse events in total, of which 4 were considered serious, requiring procedural interventions. In two subjects, units had to be explanted prior to study completion. The secondary endpoints relate to the success of the prediction algorithms and sustainability over time. In total, 11 of 14 subjects met criteria following the baseline phase and proceeded to the advisory phase, and 8 remained in the advisory phase past the 4 designated study months. For 2 of the 10 subjects who completed the advisory phase, prediction was excellent, with all seizures occurring during high likelihood periods. Sensitivity in the other subjects ranged from 17 to 77% with 6 of 10 achieving a sensitivity of greater than 50%. While the amount of time in high advisory periods is provided, the authors did not provide positive predictive values (PPV) of high or moderate advisory. Additionally, “low advisory” was tested in 5 subjects, and nearly all achieved a negative predictive value (NPV) of 100.

As a “proof of concept” approach, this study certainly succeeds in proving that seizure prediction with high sensitivity is possible. This is a major step towards the development of preemptive therapy in epilepsy. In addition, the device was very successful at predicting low-risk seizure times, thus providing reassurance that may be an important contribution to quality of life. From a risk benefit ratio, it is difficult to assess the impact of successfully predicting some but not all seizures for most subjects, with a device that certainly carries ongoing risk.

Is this algorithm more successful than many reported approaches utilizing EEG? Most published seizure prediction

methodologies are derived from EEG data obtained during inpatient epilepsy monitoring. The investigators point out the known limitations related to use of this largely inpatient iEEG data to generate prediction algorithms, including the effects of medication changes, sleep states, and surgery. Thus, the long-term outpatient iEEG “real life” recording described in this study may be an important approach toward overcoming these limitations. However, even with this outpatient-based methodology, there was an “EEG signal drift” described for varying times up to months following the device implantation that delayed successful implementation of the algorithm.

The paper raises some difficult issues: The investigators found that patient report frequently underestimated “clinically equivalent seizures,” defined as electrographic patterns with a similar appearance, propagation, and spread as reported seizures. Of course, without a clinical correlate, these may represent electrographic seizure patterns and not electroclinical seizures. It remains to be determined if treating these EEG patterns would provide clinical benefits. The authors raise a previously noted concern about such disparities between patient-reported and EEG-recorded seizures (6), suggesting that this disparity has important implications for clinical epilepsy research. While these concerns are valid, patient report is the only available methodology for the majority of patients with epilepsy who will not undergo long-term intracranial monitoring. Therefore, for the foreseeable future—with a few notable exceptions—clinical trials and clinical care in epilepsy will likely continue to rely on patient report.

Studies such as this also raise concerns about the appropriate sensitivity and predictive values for proposed interventions. If seizure prediction/preictal state detection is to realize its therapeutic promise, predictions have to be accurate. High sensitivity is required so that most seizures can be detected and a high PPV is required so that treatment is delivered only when seizures are very likely. Methodologies linked to taking a preemptive medication during high-risk or high advisory conditions would require a rigorous PPV to avoid excessive medication use. Even an advisory system with precautionary measures as the sole intervention might worsen stress levels and quality of life if applied out of proportion to the frequency of actual seizures. While possibly disappointing to the investigators, it might actually be reassuring that anxiety and quality of life measures appeared unchanged over the course of this study, despite fair amounts of time spent in high seizure advisory.

Are we there yet? While the future of this particular device is uncertain due to funding limitations, the high sensitivity of prediction in this study is encouraging. Bold and innovative approaches—be they implanted devices, use of large collaborative international EEG databases (7, 8), or even smartphone based e-diaries (9)—steadily move us closer to solving the difficult problem of “unpredictability,” with the hope of reducing the burden of epilepsy.

by Sheryl Haut, MD

References

1. Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, Walker S. The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. *Epilepsy Res* 2000;41:39–51.



2. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: The long and winding road. *Brain* 2007;130: 314–333.
3. Haut SR, Lipton RBL. Predicting seizures: A behavioral approach. *Neurol Clinics* 2009;27:925–940.
4. Binder D, Haut SR. Towards new paradigms of seizure detection. *Epilepsy Behav* 2013;26:247–252.
5. Davis KA, Sturges BK, Vite CH, Ruedebusch V, Worrell G, Gardner AB, Leyde K, Sheffield WD, Litt B. A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG. *Epilepsy Res* 2011;96:116–122.
6. Tatum WO, Winters L, Gieron M, Passaro EA, Benbadis S, Ferreira J, Liporace J. Outpatient seizure identification: Results of 502 patients using computer-assisted ambulatory EEG. *J Clin Neurophysiol* 2001;18:14–19.
7. Klatt J, Feldwisch-Drentrup H, Ihle M, Navarro V, Neufang M, Teixeira C, Adam C, Valderrama M, Alvarado-Rojas C, Witon A, Le Van Quyen M, Sales F, Dourado A, Timmer J, Schulze-Bonhage A, Schelter B. The EPILEPSIAE database: An extensive electroencephalography database of epilepsy patients. *Epilepsia* 2012;53:1669–1676.
8. Schulze-Bonhage A, Feldwisch-Drentrup H, Ihle M. The role of high-quality EEG databases in the improvement and assessment of seizure prediction methods. *Epilepsy Behav* 2011;22(suppl 1):S88–93.
9. Haut SR, Hall CB, Borkowski T, Tennen H, Lipton RB. Modeling seizure self-prediction: An e-diary study. *Epilepsia* 2013; Sept 20 epub ahead of print.



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