

MAINTAINING STRONG BONES: STRONG OPINIONS, LITTLE EVIDENCE

Two Randomized Vitamin D Trials in Ambulatory Patients on Anticonvulsants: Impact on Bone. Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan Gel-H. *Neurology* 2006;67(11):2005–2014. **OBJECTIVE:** To investigate the effects of two doses of vitamin D given over 1 year on bone density in ambulatory patients on long-term antiepileptic drug (AED) therapy. **METHODS:** We conducted two parallel, randomized, controlled trials in 72 adults (18–54 years old) and 78 children and adolescents (10–18 years) on long-term AED therapy. They received either low-dose vitamin D 400 IU/day or high-dose vitamin D 4,000 IU/day (adults) and 2,000 IU/day (children/adolescents). Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry. **RESULTS:** In adults, baseline BMD was lower than that of age- and gender-matched controls vs either a Western or an ethnically identical population. After 1 year, there were significant increases in BMD at all skeletal sites compared to baseline in the high-, but not in the low-dose treatment group. However, BMD at 1 year remained below normal. In children, baseline BMD was normal vs age- and gender-matched controls and showed significant and comparable increases in both treatment groups. **CONCLUSIONS:** In ambulatory adults on antiepileptic drugs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites. In children, both doses resulted in comparable increases in bone mass.

COMMENTARY

Over the past several years, much attention has been paid to the maintenance of bone health in patients with epilepsy who are taking antiepileptic drugs (AEDs) (1). Studies suggesting a higher risk of bone loss in such patients were first published over 35 years ago but were largely ignored by the medical community (2). The best-documented risks for reduced bone density are associated with enzyme-inducing AEDs, with enhanced vitamin D metabolism being the generally accepted mechanism. But more direct effects of AEDs on bone homeostasis also have been proposed, and reduced bone mass has been observed in patients taking long-term valproate, which is not a cytochrome P enzyme inducer (3). Until recently, however, no serious attempts to quantify the risk of osteoporosis or to reduce it had been made.

Maintenance of normal bone mass depends on proper functioning of a complex network of enzymes, vitamins, and minerals, to ensure an accurate homeostasis of ongoing bone resorption and new bone formation. This process requires adequate dietary calcium and its normal absorption and use, which are facilitated by normal vitamin D serum levels. Vitamin D is derived from the diet, but cutaneous metabolism into its active form is a photosensitive process, normally facilitated through exposure to sunlight.

Osteoporosis (i.e., a bone density T score <-2.5) and osteopenia (T score between -1.0 and -2.5) are remarkably common, with prevalence increasing with age. Other risk factors include female gender, sedentary lifestyle, thin body habitus, Caucasian race, and a positive family history. Extreme inactivity and indoor life (common in those with cerebral palsy or residency in assisted living facilities) are powerfully associated with bone loss; the reported prevalence of osteoporosis is up to 97% in this population (4). The prevalence of osteoporosis in the largely sedentary, general U.S. population is also remarkably high: the lifetime incidence of osteoporosis-related fracture is 30% to 50% in women and 15% to 30% in men (5).

The significant impact of bone loss on the population with epilepsy has been well demonstrated. Already at risk for fractures from falls related to seizures, drug toxicity, and associated neurological disease, patients with epilepsy on enzyme-inducing AEDs or valproate are at a slightly higher fracture risk than the general population, with a detectable dose-response effect (6). However, even as the connection between AEDs and bone loss has become more firmly established, there has been little to guide the clinician hoping to reduce the risk of osteopenia and osteoporosis in patients with epilepsy, who often take AEDs for many years. Confirmation of the efficacy of supplementing vitamin D and calcium to prevent osteoporosis in the general population is scanty (7,8), yet various clinicians writing about long-term exposure to AEDs have recommended supplements of up to 1,500 mg of extra calcium daily. However, there is no evidence-based guidance for the prescribing physician about the efficacy of dietary supplements or the appropriate amounts to recommend.

Even more disturbing is the lack of guidance for the practitioner wanting to monitor the bone health of patients. The National Osteoporosis Foundation and the United States Preventive Services Task Force guidelines stipulate bone density scans for all women over the age of 65. Those women with risk factors, such as a family history of osteoporosis, fractures, low body weight, and smoking, are considered for scanning after age 50 years. No consistent guidelines are available for males, neither are there data that indicate when to measure bone density in patients with epilepsy exposed to years of enzyme-inducing or other types of AEDs.

Mikati et al. decided to examine the effects of vitamin D supplementation in adults and children taking AEDs. Their study has the advantages of relative long duration (1 year), prospective design, well-balanced comparison groups, a community-based population, and carefully measured vitamin D serum and bone density levels. Its shortcomings include an unblinded study design and a high subject dropout rate (25%), with only a vague description of the reasons for the latter. It seems largely to be attributed to gastrointestinal distress in those on high-dose vitamin D. In addition, the study is underpowered for the detection of any dosage effect in the pediatric group, thus offering no grounds for a rational method of choosing a dose for vitamin D supplementation. Finally, the formulation of the supplement (liquid rather than tablet), probably chosen for easier acceptance by the pediatric group, would unlikely to be adopted for daily use by adults.

After 1 year of therapy with vitamin D, the percentage of adult patients with normal serum levels increased from 20% to 69% and the percentage of children from 41% to 50%. The more clinically significant value of bone density increased significantly at three of five bone sites in the treated adult group. In the pediatric group, lumbar spine bone density, total body bone mineral content, and total body bone mineral density all increased in treated subjects; however, all of the children started the study with normal bone mineral densities. In contrast, the adult group as a whole had lower bone mineral density at all sites at the beginning of the study.

Possible variations in risk arising from different AEDs were not detected in this study, which simply divided the drugs into enzyme inducers and all the other agents, leaving open the question of whether the results would change significantly if those taking valproate were reassigned to the enzyme-inducing

group. The study was not powered to detect significant differences among individual enzyme-inducing AEDs. Furthermore, the element that makes the study least applicable to ordinary clinical practice is the omission of calcium supplementation—despite the judgment that dietary calcium in the study subjects was judged to be “suboptimal.” Perhaps the improvements in bone density that were seen in the treated groups would have been more significant had calcium intake been supplemented as well.

This paper includes a revealing tabulated literature review, exposing the bewildering variations, contradictions, and limitations of previous studies of calcium and/or vitamin D supplementation for patients with epilepsy. The neurology community and their patients must still wait for a study that may help determine the utility of such supplements, the most appropriate time to introduce them, and the most useful dosages.

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NOW WE KNOW THE DRUG OF FIRST CHOICE—OR DO WE?

The SANAD Study of Effectiveness of Carbamazepine, Gabapentin, Lamotrigine, Oxcarbazepine, or Topiramate for Treatment of Partial Epilepsy: An Unblinded Randomised Controlled Trial. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaidis P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. *Lancet* 2007;369(9566):1000–1015. **BACKGROUND:** Carbamazepine is widely accepted as a drug of first choice for patients with partial onset seizures. Several newer drugs possess efficacy against these seizure types but previous randomised controlled trials have failed to inform a choice between these drugs. We aimed to assess efficacy with regards to longer-term outcomes, quality of life, and health economic outcomes. **METHODS:** SANAD was an unblinded randomised controlled trial in hospital-based outpatient clinics in the UK. Arm A recruited 1,721 patients for whom carbamazepine was deemed to be standard treatment, and they were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate. Primary outcomes were time to treatment failure, and time to 12-months remission, and assessment was by both intention to treat and per protocol. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN38354748. **FINDINGS:** For time to treatment failure, lamotrigine was significantly better than carbamazepine (hazard ratio [HR] 0.78 [95% CI 0.63–0.97]), gabapentin (0.65 [0.52–0.80]), and topiramate (0.64 [0.52–0.79]), and had a non-significant advantage compared with oxcarbazepine (1.15 [0.86–1.54]). For time to 12-month remission carbamazepine was significantly better than gabapentin (0.75 [0.63–0.90]), and estimates suggest a non-significant advantage for carbamazepine against lamotrigine (0.91 [0.77–1.09]), topiramate (0.86 [0.72–1.03]), and oxcarbazepine (0.92 [0.73–1.18]). In a per-protocol analysis, at 2 and 4 years the difference (95% CI) in the proportion achieving a 12-month remission (lamotrigine-carbamazepine) is 0 (–8 to 7) and 5 (–3 to 12), suggesting non-inferiority of lamotrigine compared with carbamazepine. **INTERPRETATION:** Lamotrigine is clinically better than carbamazepine, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures.

The SANAD Study of Effectiveness of Valproate, Lamotrigine, or Topiramate for Generalised and Unclassifiable Epilepsy: An Unblinded Randomised Controlled Trial. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaidis P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. *Lancet* 2007;369(9566):1016–1026. **BACKGROUND:** Valproate is widely accepted as a drug of first choice for patients with generalised onset seizures, and its broad spectrum of efficacy means it is recommended for patients with seizures that are difficult to classify. Lamotrigine and topiramate are also thought to possess broad spectrum activity. The SANAD study aimed to compare the longer-term effects of these drugs in patients with generalised onset seizures or seizures that are difficult to classify. **METHODS:** SANAD was an unblinded randomised controlled trial in hospital-based outpatient clinics in the UK. Arm B of the study recruited 716 patients for whom valproate was considered to be standard treatment. Patients were randomly assigned to valproate, lamotrigine, or topiramate between Jan 12, 1999, and Aug 31, 2004, and follow-up data were obtained up to Jan 13, 2006. Primary outcomes were time to treatment failure, and time to 1-year remission, and analysis was by both intention to treat and per protocol. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN38354748. **FINDINGS:** For time to treatment failure, valproate was significantly better than topiramate (hazard ratio 1.57 [95% CI 1.19–2.08]), but there was no significant difference between valproate and lamotrigine (1.25 [0.94–1.68]). For patients with an idiopathic generalised epilepsy, valproate was significantly better than both lamotrigine (1.55 [1.07–2.24]) and topiramate (1.89 [1.32–2.70]). For time to 12-month remission valproate was significantly better than lamotrigine overall (0.76 [0.62–0.94]), and for the subgroup with an idiopathic generalised epilepsy 0.68 (0.53–0.89). But there was no significant difference between valproate and topiramate in either the analysis overall or for the subgroup with an idiopathic generalised epilepsy. **INTERPRETATION:** Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies. However, because of known potential adverse effects of valproate during pregnancy, the benefits for seizure control in women of childbearing years should be considered.

COMMENTARY

The two studies reviewed here—one done with patients with newly diagnosed epilepsy for whom carbamazepine

would have been considered standard treatment (SANAD A, mostly partial) and the other with patients for whom valproate would have been considered standard treatment (SANAD B, mostly generalized or unclassified epilepsy)—are clearly landmark. It could be argued that no study since the Veterans Administration cooperative studies in the 1970s and 1980s has been designed with such intent to perform clinically meaningful (and therefore clinically useful) randomized, controlled trials to assess best treatment options for these patient populations (1,2). It is important to appreciate that the stated purpose of the studies was (i) to determine the “effectiveness” of each of the drugs tested and (ii) to assess which agent was the best option for the treatment of newly diagnosed epilepsy.

Recently, a great deal of discussion has centered on the ability of a trial to determine effectiveness rather than efficacy. “Efficacy” is defined as the ability of a treatment to obtain a prespecified outcome (e.g., seizure reduction) over the course of a prespecified (usually short) time frame. A drug can be highly efficacious yet not very clinically useful, that is, not clinically effective. For example, a drug could produce a 50% reduction in seizures but cause vomiting in all patients; could require four times a day dosing, which is likely to reduce compliance; or could be useful only in the narrow spectrum of patients eligible for the trial but not the larger population who would receive it, once approved. Effectiveness, in contrast to efficacy, is meant to be a more pragmatic measure that addresses the utility of a drug as it is actually employed in practice. To measure effectiveness, it is necessary to mirror a real-world environment as much as possible. Thus, the SANAD trials were performed primarily by general neurologists and not in highly specialized epilepsy centers. Physicians were offered guidance on titration schemes and maximal doses but were then permitted to treat patients according to their own assessment. They could discontinue treatment when they wished. To prevent an artificial environment and simplify the trial, the study was performed without blinding; these trial design aspects clearly add to the ability of the study to provide clinically useful data. Thus, the trial results likely adequately address the question of the effectiveness of each AED, as assessed in the hands (and minds) of neurologists in practice in the United Kingdom.

Let us now turn to the other question the authors claim to have addressed, namely, “Which drug should be first-line treatment?” This one is more difficult to definitively answer. Why? One reason is that almost by their nature, effectiveness trials sacrifice rigor. For example, since physicians were permitted to treat without strict guidance, it is not clear whether all of them used long-acting formulations (which would impact the effectiveness of carbamazepine). The clinicians might not have reached maximum dose in all cases, and titration schedules might have been too fast or too slow. They also very well might have been influenced by knowing which drug the patient

was receiving during the trial. Thus, the drug that was favored by a physician before the trial began might have a substantial advantage over a drug that he or she felt had problems with either efficacy or safety, thus producing a self-fulfilling prophecy. Preconceived notions and habits of use might have enough impact, in fact, that the “winner” could have been different if the same study were performed in the United States or elsewhere in Europe, rather than in the United Kingdom.

Other pertinent issues include the fact that the outcome was determined for “all comers.” For instance, in the SANAD B trial, all generalized syndromes were lumped together, as were all seizure types. Thus, if one drug, such as lamotrigine, was very effective for generalized tonic-clonic seizures, but less effective or even aggravating for myoclonic seizures, as some believe, this distinction would be lost in the analysis (3,4). Perhaps most important, one must consider whether a drug of first choice can be selected based only on the variables—namely, time to drug failure, time to 1-year remission, health economic assessment, and quality of life—that were tested (and testable) in these trials. In truth, this designation often rests on other issues as well. For example, felbamate is a very well-tolerated and effective drug that might have fared well if included in either arm of this study; however, it is considered a drug of last resort, based on idiosyncratic reactions (aplastic anemia and hepatic failure) that occur at a frequency of 1/3,000 (5). The number of patients included in SANAD was large yet not large enough to evaluate serious idiosyncratic events. Valproate can cause pancreatitis at a rate of 1/300 patients as well as hepatic failure, which has a high frequency rate in some subgroups (polytherapy under age 10 and any use under age 2) (6), yet it was chosen as drug of first choice. And, what of other variables not measured? How can one determine their “relative value” in selection of a drug of first choice? In a study performed in the 1970s, which is similar to the present one except that blinded, newly diagnosed patients were randomized to one of the four drugs commonly prescribed at the time, no differences were found between carbamazepine and phenytoin with respect to either safety or tolerability (1). So, why is phenytoin currently considered an inferior choice when compared with carbamazepine? Indeed, a number of other characteristics ultimately stood out, including bone health, long-term side effects (e.g., gum hyperplasia and neuropathy), as well as the difficulty of using a drug that respects zero-order kinetics at higher dosages. The phenytoin example highlights important issues that color drug choice, such as long-term side effects, safety, pharmacokinetics, and potential for teratogenicity, that cannot be easily evaluated, even in the best-designed randomized trial.

In conclusion, the epilepsy community should welcome the data provided by this trial. Picking a drug of first choice, however, may not yet be within our grasp.

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COMPARATIVE MONOTHERAPY TRIALS AND THE CLINICAL TREATMENT OF EPILEPSY

Comparison of Levetiracetam and Controlled-Release Carbamazepine in Newly Diagnosed Epilepsy. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ; Levetiracetam Monotherapy Study Group. *Neurology* 2007;68(6):402–408. **OBJECTIVE:** We report the results of a prospective study of the efficacy and tolerability of levetiracetam, a new antiepileptic drug with a unique mechanism of action, in comparison with controlled-release carbamazepine as first treatment in newly diagnosed epilepsy. **METHODS:** Adults with 2 partial or generalized tonic-clonic seizures in the previous year were randomly assigned to levetiracetam (500 mg twice daily, $n = 288$) or controlled-release carbamazepine (200 mg twice daily, $n = 291$) in a multicenter, double-blind, noninferiority, parallel-group trial. If a seizure occurred within 26 weeks of stabilization, dosage was increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or carbamazepine 600 mg twice daily. Patients achieving the primary endpoint (6-month seizure freedom) continued on treatment for a further 6-month maintenance period. **RESULTS:** At per-protocol analysis, 73.0% (56.6%) of patients randomized to levetiracetam and 72.8% (58.5%) receiving controlled-release carbamazepine were seizure free at the last evaluated dose (adjusted absolute difference 0.2%, 95% CI – 7.8% to 8.2%) for 6 months (1 year). Of all patients achieving 6-month (1-year) remission, 80.1% (86.0%) in the levetiracetam group and 85.4% (89.3%) in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with carbamazepine. **CONCLUSIONS:** Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy at optimal dosing in a setting mimicking clinical practice. This trial has confirmed in a randomized, double-blind setting previously uncontrolled observations that most people with epilepsy will respond to their first-ever antiepileptic drug at low dosage.

COMMENTARY

With the exception of oxcarbazepine and felbamate, all of the new antiepileptic drugs were approved initially as adjunctive therapy for partial epilepsy; approval was based on placebo-controlled, add-on trials involving patients with refractory epilepsy. In these trials, the main outcome measures were improvement in seizure frequency over baseline and the proportion of patients with 50% or greater reduction in seizure frequency. Superiority over placebo in add-on trials does not necessarily predict that an antiepileptic drug will be effective

and well tolerated as an initial monotherapy. Confirmation for use of an antiepileptic drug as first-line treatment requires a sound monotherapy trial with newly diagnosed patients. In addition, the practicing physician would need to feel assured that the new antiepileptic drug is not less effective than established, standard therapy. Large, comparative antiepileptic drug trials are necessary to provide that assurance. The two large, cooperative VA comparative trials have played a major role in developing guidelines for the older antiepileptic drugs and propelled carbamazepine to the position of being the favored initial agent for the treatment of partial epilepsy (1,2). Consequently, carbamazepine has become the customary active control used for comparative, first-line, monotherapy trials of lamotrigine, oxcarbazepine, and gabapentin (3–6).

Levetiracetam is one of the most widely used add-on antiepileptic medications. Some of its advantages include rapid

and almost complete absorption, initiation at an effective dose, absence of hepatic metabolism, absence of enzyme induction, absence of clinically significant interactions, and the availability of an intravenous formulation (7,8). Several published open-label reports of successful initial monotherapy administration of levetiracetam begged for a formal, blinded, and randomized trial to support this practice. The current study by Brodie et al. addresses this issue, is well powered, and also distinguishes itself from previous comparative trials by using a controlled-release preparation of carbamazepine as well as flexible dosing. Controlled-release carbamazepine is better tolerated owing to less fluctuation in plasma levels. Levetiracetam and controlled-release carbamazepine were equally effective with respect to seizure freedom at 6 months and 1 year of treatment. With both antiepileptic drugs, most patients became seizure free at the lowest dose level. Overall, more patients discontinued therapy because of adverse experiences in the carbamazepine group, but the difference did not reach significance, and the two drugs showed a similar proportion of patients who had at least one adverse experience. The levetiracetam-treated group more often reported depression and insomnia, while the carbamazepine group more often reported back pain, which is hard to explain. There also was greater weight gain with carbamazepine than levetiracetam.

The results of this trial earned levetiracetam approval as a first-line monotherapy in the treatment of partial epilepsy in the European Union, but not in the United States. Approval of antiepileptic drugs by the U. S. Food and Drug Administration (FDA) requires demonstration of superiority over another treatment or over placebo and may not be based on equivalent efficacy. In adjunctive trials, demonstration of superiority is straightforward, with placebo used as a comparator, and since baseline antiepileptic medications are continued, there are no ethical issues involving the use of placebo. In contrast, the use of placebo as monotherapy for epilepsy does raise ethical concerns, and superior efficacy has never been demonstrated for a new antiepileptic drug in comparison with the old antiepileptic drugs. As a result of these difficulties, few drugs have earned initial monotherapy indication in the United States. One concern raised by the FDA in relation to equivalence trials is that it is possible that in a specific population studied, equivalence could be due to equal lack of efficacy (9). However, the proportion of seizure-free patients should help evaluate this possibility. One epidemiologic study suggested that the risk of seizure recurrence at 1 year is 57%, after two unprovoked seizures, and 61%, following three unprovoked seizures (10). Most patients in this epidemiologic study received treatment, and the chance of remaining seizure-free for 1 year without treatment must be less than 40%. The 1-year seizure-free rate of 56.6% to 58.5% in the study by Brodie and colleagues is significantly better

than expected ($p = 0.001$) and represents evidence that both antiepileptic drugs were effective.

The Therapeutics and Technology Assessment Subcommittee and the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society accepted large, blinded, and randomized comparative studies in its assessment of the new antiepileptic drugs (11). Its 2004 recommendation was that patients with recently diagnosed partial epilepsy who require treatment can be initiated on lamotrigine, gabapentin, oxcarbazepine, or topiramate (11). The current trial likely will add levetiracetam to that list. As a result of the growing list of antiepileptic drugs that can now be considered for first-line treatment, there is a need to develop guidelines. Such guidelines ideally should be determined by comparative trials that evaluate relative efficacy and tolerability of the new antiepileptic drugs. However, choice of first-line antiepileptic drugs also should take into consideration factors such as the acuteness of the epilepsy, the need for rapid titration, the need to avoid interactions, as well as associated comorbid conditions. In the future, an important criterion in the selection of the first antiepileptic drug for a patient may be its antiepileptogenic potential, which is the ability of a drug to arrest, delay, or reverse the development of epilepsy. Some antiepileptic drugs, such as valproate and levetiracetam, demonstrated an antiepileptogenic action in animal models of epilepsy, particularly suppressing the development of kindling. However, valproate failed to demonstrate an antiepileptogenic effect in patients with head trauma or brain tumors (12), and no drug has been demonstrated to have an antiepileptogenic effect in human epilepsy. In recent onset epilepsy, it is possible that epileptogenesis could still be active. An antiepileptogenic drug could potentially influence the course of the epilepsy, perhaps to the degree that seizures do not recur after antiepileptic drug withdrawal. If seizure-free patients in the trial of Brodie and colleagues continue to be followed after drug discontinuation, this trial may help provide data on whether levetiracetam has antiepileptogenic effects in recently diagnosed partial epilepsy. If treatment with levetiracetam is associated with less seizure recurrence on discontinuation, this finding could be evidence of an antiepileptogenic effect and potentially be a very important factor in choosing the first treatment for epilepsy.

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IMAGING DEPRESSION IN EPILEPSY: HINTS AT THE BIOLOGY OF DESPAIR

Major Depression in Temporal Lobe Epilepsy with Hippocampal Sclerosis: Clinical and Imaging Correlates. Briellmann RS, Hopwood MJ, Jackson GD. *J Neurol Neurosurg Psychiatry* 2007 Jan 26; [Epub ahead of print] PURPOSE: Refractory temporal lobe epilepsy (TLE) is often associated with hippocampal sclerosis (HS). Patients with Major Depression (MD) may also show structural abnormalities in the limbic system. Co-occurrence of TLE with HS and MD is not uncommon. We investigate clinical and morphological characteristics of TLE patients in relation to MD. METHODS: Thirty-four TLE patients with HS were assessed at a Comprehensive Epilepsy Program. All relevant clinical data were obtained, including the history of antecedent events to epilepsy. MD was diagnosed based on detailed psychiatric investigation. MRI was used to measure the volume and tissue signal (T2-relaxometry) of the hippocampus and amygdala. The imaging data were expressed as percentage of the values obtained in a series of 55 controls. RESULTS: A history of MD was present in 15 (44%) of the 34 patients. Patients with MD had a longer duration of their epilepsy ($p < 0.05$), and a lower frequency of antecedent events (13% with MD, 58% without MD, $p < 0.05$). Both groups had a similar degree of ipsilateral HS (small hippocampal volume, increased hippocampal T2-relaxation time), and demonstrated bilateral amygdaloid atrophy. However, the contralateral amygdala showed lower signal in presence of MD (97 ± 9 msec; no MD: 103 ± 8 msec, ANCOVA, $p < 0.05$). CONCLUSION: The integrity of the amygdala may influence mood disturbances in TLE patients with HS, as depression was associated with a relative preservation of the contralateral amygdala. In contrast, hippocampal abnormalities were not related to the presence of depression.

Hippocampal 1H-MRSI Correlates with Severity of Depression Symptoms in Temporal Lobe Epilepsy. Gilliam FG, Maton BM, Martin RC, Sawrie SM, Faught RE, Hugg JW, Viikinsalo M, Kuzniecky RI. *Neurology* 2007;68(5):364–368. OBJECTIVE: To investigate the association of an indicator of hippocampal function with severity of depression symptoms in temporal lobe epilepsy. METHODS: We evaluated 31 patients with video/EEG-confirmed temporal lobe epilepsy using creatine/*N*-acetylaspartate ratio maps derived from a previously validated ¹H magnetic resonance spectroscopic imaging (¹H-MRSI) technique at 4.1 T. We also assessed depression symptoms, epilepsy-related factors, and self-perceived social and vocational

disability. We used conservative nonparametric bivariate procedures to determine the correlation of severity of depression symptoms with imaging and clinical variables. RESULTS: The extent of hippocampal ^1H -MRSI abnormalities correlated with severity of depression (Spearman $\rho = 0.65$, p value < 0.001), but other clinical factors did not. CONCLUSION: The extent of hippocampal dysfunction is associated with depression symptoms in temporal lobe epilepsy and may be a more important factor than seizure frequency or degree of disability.

COMMENTARY

Depression is increasingly recognized as an important comorbid condition for patients with epilepsy. It is more common in people who have epilepsy than in either the general population or people who have other chronic medical conditions. While much of the focus of a physician's clinical visits tends to be on seizure control and medication side effects, mood status overwhelmingly drives quality-of-life measures for individuals with epilepsy (1). The mounting interest in epilepsy-associated depression has spawned two recent reports in which investigators attempt to relate functional and structural imaging findings to mood status in patients with temporal lobe epilepsy (TLE).

Prior studies have documented the importance of limbic structures in depression. Patients with major depressive disorder may have reduced hippocampal volumes compared to the general population (2). Since hippocampal volumes are even more profoundly reduced in patients with TLE, Briellmann and colleagues sought to determine whether the hippocampal volume loss might be an important predisposing factor for depression in patients with TLE. They used a 3-T MRI scanner to obtain volume and T2 relaxation measurements of both the epileptogenic and contralateral medial temporal structures. As expected, the structures demonstrated varying degrees of volume loss and prolonged T2-relaxation times, with the most prominent findings on the side of the seizure focus. The only finding that was associated with depression, however, was relative sparing (at least with regard to the T2 signal) of the amygdala contralateral to the seizure focus. They speculate that a preserved amygdala allows for abnormal processing of negative emotions. Patients in this study were classified according to a history of depression—either past or present. In fact, many of these patients were not depressed at the time of the imaging study. Accordingly, the authors acknowledge that an intact amygdala may be a *predisposing factor* for depression, although the person is not depressed much of the time.

Since patients with normal MRI scans were not included in this study, it is not possible to exclude hippocampal sclerosis as a risk factor for major depression. Investigators have found that MRI evidence of mesial temporal sclerosis increases the risk for both moderate depressive symptoms (3) and drug-induced depression (4) in patients with epilepsy. Patients were selected for the current study based on the presence of mesial temporal

sclerosis on clinical MRI examinations. If patients with normal MRI were also included in this study, it is possible that the authors would have found that, as in patients with major depression who do not have epilepsy, the presence of a hippocampal MRI abnormality is a risk factor for depression, although the degree of the abnormality is not important (2).

In contrast to the study by Briellmann et al., Gilliam and colleagues used proton spectroscopy, a functional rather than anatomical measure of hippocampal integrity, to assess the relationship between the integrity of medial temporal structures and the presence of ongoing depressive symptoms. They measured creatine/*N*-acetylaspartate (Cr/NAA) ratios, which increase (as the neuronal marker NAA decreases) and found that the degree of hippocampal dysfunction (as assessed by proton spectroscopy) was strongly associated with depressed mood. At first glance, the strong correlation between mood and hippocampal function seems surprising, if not contradictory, given the finding of Briellmann et al. that hippocampal volume is not related to depression. However, Gilliam and colleagues point out that anatomical (5) and functional (6) hippocampal measures are not always tightly correlated in TLE. In fact, many patients with TLE and normal MRI scans have profoundly reduced NAA measurements (5). The current studies suggest that brain function, rather than structure, determines a person's mood status.

The strong association between hippocampal function and depression reported by Gilliam and colleagues provides powerful support for the involvement of limbic structures in depression in patients with epilepsy. It is surprising, then, that another measure of cerebral function, glucose metabolism, as measured by ^{18}F -fluorodeoxyglucose PET (^{18}F -FDG PET), fails to demonstrate this relationship (7). The authors speculate that glucose metabolism might be affected by the neuron/glia ratio, which is known to be extremely variable in TLE, making NAA synthesis a better measure of hippocampal function. Other PET ligands may more effectively evaluate hippocampal function than ^{18}F -FDG for this purpose, however. Recent studies suggest that hippocampal serotonin receptor binding, as assessed by [^{18}F]FCWAY PET, correlates well with depressive symptoms in patients with and without epilepsy (8).

While these studies do not provide conclusive evidence for the involvement of limbic structures in epilepsy-related depression, they do point to its being a strong possibility. The current body of knowledge suggests that hippocampal

function is likely important in epilepsy-related mood disorders. In addition, other limbic structures probably play a role. These reports represent an initial attempt to understand depression as an important comorbidity in patients with epilepsy. Wisely, neither group makes a strong case for the imaging findings being causally related to depression. Rather than providing a call for changing diagnostic or treatment strategies, each group of investigators illustrate the fact that depression is a complex condition that will require further research to elucidate the mechanisms involved. It is hoped that an understanding of the biological processes will help to develop better ways to address patients' depression. Perhaps more important, these studies are a blunt reminder to screen patients for depression in order to provide the best treatment currently available.

by Paul A. Garcia, MD

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NOCTURNAL FRONTAL LOBE EPILEPSY: THERE IS BAD, GOOD, AND VERY GOOD NEWS!

Surgical Treatment of Drug-Resistant Nocturnal Frontal Lobe Epilepsy. Nobili L, Francione S, Mai R, Cardinale F, Castana L, Tassi L, Sartori I, Didato G, Citterio A, Colombo N, Galli C, Lo Russo G, Cossu M. *Brain* 2007;130(Pt 2):561–573. Of the cases with nocturnal frontal lobe epilepsy (NFLE) 30% are refractory to antiepileptic medication, with several patients suffering from the effects of both ongoing seizures and disrupted sleep. From a consecutive series of 522 patients operated on for drug-resistant focal epilepsy, 21 cases (4%), whose frontal lobe seizures occurred almost exclusively (>90%) during sleep, were selected. All patients underwent a comprehensive pre-surgical evaluation, which included history, interictal EEG, scalp video-EEG monitoring, high-resolution MRI and, when indicated, invasive recording by stereo-EEG (SEEG). There were 11 males and 10 females, whose mean age at seizure onset was 6.2 years, mean age at surgery was 24.7 years and seizure frequency ranged from <20/month to >300/month. Nine patients reported excessive daytime sleepiness (EDS). Prevalent ictal clinical signs were represented by asymmetric posturing (6 cases), hyperkinetic automatisms (10 cases), combined tonic posturing and hyperkinetic automatisms (4 cases) and mimetic automatisms (1 case). All patients reported some kind of subjective manifestations. Interictal and ictal EEG provided lateralizing or localizing information in most patients. MRI was unrevealing in 10 cases and it showed a focal anatomical abnormality in one frontal lobe in 11 cases. Eighteen patients underwent a SEEG evaluation to better define the epileptogenic zone (EZ). All patients received a microsurgical resection in one frontal lobe, tailored according to pre-surgical evaluations. Two patients were operated on twice owing to poor results after the first resection. Histology demonstrated a Taylor-type focal cortical dysplasia (FCD) in 16 patients and an architectural FCD in 4. In one case no histological change was found. After a post-operative follow-up of at least 12 months (mean 42.5 months) all the 16 patients with a Taylor's FCD were in Engel's Class Ia and the other 5 patients were in Engel's Classes II or III. After 6 months post-surgery EDS had disappeared in the 9 patients who presented this complaint pre-operatively. It is concluded that patients with drug-resistant, disabling sleep-related

seizures of frontal lobe origin should be considered for resective surgery, which may provide excellent results both on seizures and on epilepsy-related sleep disturbances. An accurate pre-surgical evaluation, which often requires invasive EEG recording, is mandatory to define the EZ. Further investigation is needed to explain the possible causal relationships between FCD, particularly Taylor-type, and sleep-related seizures, as observed in this cohort of NFLE patients.

COMMENTARY

Nocturnal frontal lobe epilepsy (NFLE) is a heterogeneous epileptic seizure disorder that affects all age groups. It presents with various clinical manifestations ranging from brief seizures, consisting of stereotypic sudden arousals that recur throughout the night in a periodic pattern, to more elaborate seizures, with complex dystonic and dyskinetic phenomena, or to longer seizures consisting of aimless wandering, simulating somnambulant behavior (1,2). While in most patients NFLE is considered a cryptogenic epilepsy, a familial variant has been identified with an autosomal dominant transmission, known as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (2,3).

The bad news: NFLE is often misdiagnosed as a sleep disturbance, as it consists of recurrent paroxysmal episodes that occur primarily or exclusively during sleep. The diagnostic confusion often stems from the absence of recorded epileptiform activity in scalp recordings either interictally and/or during the ictal events (1–4). For example, in the largest case series published so far (100 consecutive patients), Provini et al. found an absence of ictal pattern in 44% of patients, while in 51% interictal recordings failed to show any epileptiform discharges. Similarly, in a series of 40 consecutive patients with ADNFLE, Oldani et al. found that a correct diagnosis of epilepsy had been reached in only 18.4% of patients (3).

Unfortunately, there is often reluctance on the part of patients and physicians alike to push for the achievement of total seizure freedom in the 25% to 30% of patients with persistent seizures (1–3). Such complacency results from the assumption that patients can function normally, lead an independent life, and maintain their driving privileges, since the occurrence of seizures is restricted to the sleep state. Yet, contrary to the common belief that NFLE is a benign epilepsy, it is not the case for all patients. Indeed, the persistence of nocturnal seizures has a significant negative impact on the quality of life of these patients because of excessive daytime somnolence, which often can be incapacitating and interfere with patients' school, work, or social activities.

The excessive daytime somnolence results from a seizure-induced sleep disturbance that consists of sleep fragmentation and reduced sleep efficiency. Vignatelli et al. administered a questionnaire on daytime sleepiness-related symptoms and subjective sleep quality to 33 patients with NFLE and 20 controls

(4). Tiredness and spontaneous sleep awakening were significantly more frequent in epilepsy patients than controls (36.4% vs. 11.1% and 50% vs. 22%, respectively). In a study on the macro- and microstructure of sleep in patients with ADNFLE, Zucconi et al. found a relationship between sleep fragmentation as well as nocturnal motor seizures and daytime symptoms (5).

The good news: NFLE can be well controlled with antiepileptic drug (AED) therapy (1–3). For example, in the Oldani et al. series of 40 patients with ADNFLE, seizures had remitted completely in 73% of patients who were administered an AED (3), while in Provini's series, AED therapy remitted seizures in 70% of patients (1). Among the patients with drug-resistant NFLE, surgical treatment is considered a potential option. To date, failure to refer patients in a timely manner for presurgical evaluation and surgery remains an obstacle in the treatment of these patients—an obstacle that can be easily overcome with better patient and physician education. The localization of the seizure focus in NFLE has been facilitated by the significant advances in neuroimaging studies, such as high-resolution MRI with stronger magnets and of functional neuroimaging studies, such as ictal SPECT and subtraction ictal SPECT.

The absence of reported cognitive and behavioral disturbances in patients with NFLE is another item of good news related to this type of epilepsy. Indeed, such disturbances are commonly encountered in other types of frontal lobe epilepsy, including learning disabilities (preceding and/or following the seizure onset), attention-deficit hyperactivity, and impulsivity (6).

The better news: Patients with drug-resistant NFLE appear to be good candidates for surgical treatment, as suggested by the data of the Nobili et al. study. Indeed, the seizure-freedom rates are significantly higher (up to 75%) than those reported in other types of frontal lobe epilepsy surgical series, which have yielded a 40% to 50% seizure-free rate. In a recent study of 70 patients who underwent a frontal lobectomy, Jeha et al. estimated the probability of complete seizure-freedom to be 55.7% (95% confidence interval [CI] = 50–62) at 1 postoperative year, 45.1% (95% CI = 39–51) at 3 years, and 30.1% (95% CI = 21–39) at 5 years (7). The better surgical outcome in NFLE, demonstrated by Nobili et al., was associated with the presence of focal cortical displasias of the Taylor type. Other investigators also have reported favorable postsurgical outcomes following the resection of seizure foci associated with Taylor focal cortical displasia in partial epilepsies that are different from

NFLE. For example, two studies with at least 1-year follow-up found a seizure-free state in 75% and 69% of patients, respectively (8,9). Whether a Taylor FCD is a cause of drug-resistant NFLE is yet to be established.

In conclusion, an investigation of excessive daytime somnolence should be an integral part of each visit in patients with NFLE. When present, it ought to serve as a “red flag,” suggestive of an unsuccessful treatment and of the need to consider further in-depth evaluations to establish the need for alternative pharmacotherapy with AEDs or more aggressive treatments, including surgery.

by Andres M. Kanner, MD

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WHEN BASIC RESEARCH DOESN'T TRANSLATE TO THE BEDSIDE—LESSONS FROM THE MAGNESIUM BRAIN TRAUMA STUDY

Magnesium Sulfate for Neuroprotection After Traumatic Brain Injury: A Randomised Controlled Trial. Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, Lucas T, Newell DW, Mansfield PN, Machamer JE, Barber J, Dikmen SS. *Lancet Neurol* 2007;6(1):29–38. **BACKGROUND:** Traumatic brain injuries represent an important and costly health problem. Supplemental magnesium positively affects many of the processes involved in secondary injury after traumatic brain injury and consistently improves outcome in animal models. We aimed to test whether treatment with magnesium favourably affects outcome in head-injured patients. **METHODS:** In a double-blind trial, 499 patients aged 14 years or older admitted to a level 1 regional trauma centre between August, 1998, and October, 2004, with moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within 8 h of injury and continuing for 5 days. Magnesium doses were targeted to achieve serum magnesium ranges of 1.0–1.85 mmol/L or 1.25–2.5 mmol/L. The primary outcome was a composite of mortality, seizures, functional measures, and neuropsychological tests assessed up to 6 months after injury. Analyses were done according to the intention-to-treat principle. This trial is registered with Clinicaltrials.gov, number NCT00004730. **FINDINGS:** Magnesium showed no significant positive effect on the composite primary outcome measure at the higher dose (mean = 55 average percentile ranking on magnesium vs. 52 on placebo, 95% CI for difference –7 to 14; $p = 0.70$). Those randomly assigned magnesium at the lower dose did significantly worse than those assigned placebo (48 vs. 54, 95% CI –10.5 to –2; $p = 0.007$). Furthermore, there was higher mortality with the higher magnesium dose than with placebo. Other major medical complications were similar between groups, except for a slight excess of pulmonary oedema and respiratory failure in the lower magnesium target group. No subgroups were identified in which magnesium had a significantly positive effect. **INTERPRETATION:** Continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury.

COMMENTARY

One of the most important areas of epilepsy research is the search for antiepileptogenic therapies. Treatments that reduce development of chronic epilepsy after a brain injury or forestall progression to medication resistant epilepsy could minimize or eliminate seizure-related disability in many individuals. In this search, posttraumatic epilepsy is one of the most studied conditions, not only because it is common, often severe, and resistant to medications, but also because it is temporally well defined—a time window exists before the development of chronic seizures in which intervention could be attempted. Clinical trials of potential antiepileptogenic therapies are inevitably linked to the search for neuroprotective treatments because head injury often results in severe neurological and cognitive impairment, although it should not be assumed that neuroprotective agents would necessarily prevent epilepsy.

Prior clinical trials, whether using various antiepileptic agents (including phenytoin and valproate) or any other treatment, have failed to show neuroprotection or antiepileptogenesis (1). Therefore, the choice of magnesium sulfate for a new clinical trial of neuroprotection was based on the hypothesis that an agent with multiple proven beneficial actions at the cellular level may have neuroprotective or antiepileptogenic effects. These cellular-level effects of magnesium sulfate include hyperpolarization, action as an ATP cofactor, inhibition of presynaptic excitatory neurotransmitters, blockade of NMDA and voltage-gated calcium channels, potentiation of presynaptic adenosine, vasodilatation by relaxation of smooth muscle, and others. Multiple experimental rodent studies have demonstrated decreased brain magnesium after injury (2), with worse outcome associated with magnesium deficiency (3). Indeed, magnesium supplementation before or after injury has been shown to improve outcome in rodents (3–6). A pilot human head injury study also suggested that magnesium supplementation improves outcome after head injury (7). Most of these preclinical studies were based on models of focal cortical injury (2–4) or impact acceleration diffuse brain injury (5,6).

The clinical trial by Temkin and colleagues was a single-site, parallel-group, randomized, double-blind study. Approximately half the patients were victims of motor vehicle accidents, and 5% had penetrating brain injuries. In the great majority, there was radiological evidence of cortical and/or diffuse axonal injury as well as subdural and epidural hematomas and skull fractures. It should be noted that the current standard of care is to correct magnesium deficiency, and this intervention therefore was allowed in both the magnesium and placebo groups. At the suggestion of the grant review study section, a target serum magnesium range of 1.25 to 2.5 mmol/L was initially used for randomization of 118 patients. At this dosage range, mortality

in the magnesium group was twice that of placebo, while blood pressure and cerebral perfusion pressure were lower than in the placebo group. After an interim analysis, the study was restarted with randomization of 381 patients, using a serum magnesium target range of 1.0 to 1.85 mmol/L, which did not produce significant differences from placebo in mortality, blood pressure, or cerebral perfusion pressure, but did show a significantly worse outcome than placebo in an analysis of a composite of 39 outcome markers. Early seizures were rare, although there was no screening for subclinical electrographic seizures, and late seizures were slightly lower in the placebo group, though not significantly. The negative results of this study are convincing and echo the findings of another large clinical trial assessing whether magnesium is neuroprotective for stroke (8). The head injury study of Temkin et al. had adequate statistical power, 93% follow-up at 6 months, and demonstrated no benefit in any of the 39 individual outcome measures with either magnesium concentration ranges.

In spite of its known beneficial properties, magnesium may have deleterious effects for patients with brain injury that offset any favorable effects. There could be a narrow concentration or time window to produce neuroprotective benefits, although these circumstances were not demonstrated by animal studies. All experimental work was done in the rat, but there could be species differences, for example, in magnesium's effect on vascular tone. One study has indicated that peripheral elevation of serum magnesium levels in humans results in only very modest increases in CSF concentration (9), which means that peripheral effects of magnesium infusion in humans (consisting of vasodilatation, with decreased blood pressure and cerebral perfusion) might predominate and potentially have negative effects on injured tissue. Finally, animal studies used fluid percussion and impact-acceleration models of injury, which are very good models of brain contusion and blood–brain barrier opening but do not reproduce the heterogeneous injuries of different severities that occur in the human. Indeed, human head injury often entails a large, diffuse axonal injury component in the absence of blood–brain barrier opening, which is not easily modeled in rodents (10). In the absence of sufficient blood–brain barrier opening in brain areas with diffuse axonal injury, magnesium may not have readily penetrated as it did in the preclinical models.

The fact that this carefully conceived and well-designed clinical study did not discover effective neuroprotective or antiepileptogenic treatments with magnesium infusion must be considered an indication of the extent to which the success of clinical trials is rooted in the completeness and soundness of the prior preclinical studies performed with experimental animals. Accordingly, it would be of great benefit if the laboratory studies identifying and investigating candidate agents became more comprehensive and more closely modeled the etiology of

human disease. Multiple models and different species need to be analyzed to probe the various aspects of the human pathology, and a close match must exist between the type of injuries being presented by patients entering a trial and the injuries reproduced by the preclinical models—of both neuroprotection and antiepileptogenesis—that are used for drug development.

by John W. Miller, MD, PhD, and Raimondo D'Ambrosio, PhD

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