Current Review

In Clinical Science

Translating Nature to Nurture: Back to the Future for “New” Epilepsy Therapies

Steven C. Schachter, MD

Professor of Neurology, Harvard Medical School, Boston, MA

Address correspondence to Steven C. Schachter, MD, 125 Nashua Street, Suite 3228, Boston, MA E-mail: sschacht@bidmc.harvard.edu

An emerging strategy for finding new epilepsy therapies is focused on botanicals (as illustrated by recent attention to medical marijuana), given their centuries-old traditions of use in treatment of convulsive seizures, contemporary anecdotal reports of efficacy in persons with epilepsy, and identification of underlying mechanisms of action that are relevant to epilepsy. Hundreds of plant extracts have been found to block seizures in acute animal seizure models, with actions that include effects on GABA receptors and voltage-gated ion channels as well as anti-inflammatory and neuroprotective effects. While existing published clinical studies of botanicals and seizure control are generally of inadequate quality to determine safety and efficacy, recent developments at the FDA may encourage sponsors to develop and commercialize botanicals for epilepsy.

Thanks to the “buzz” generated by the recent intense media coverage of medical marijuana for treatment of children desperately ill with epilepsy, the concept of using botanical products to control seizures is now quite familiar to physicians and the lay public. However, many people may be unfamiliar with the rich and age-old history of botanical use to treat epilepsy, as exemplified by a recently published description of botanicals used for epilepsy in Traditional Chinese Medicine (TCM) by Xiao and colleagues from Sichuan University in Chengdu, China (1).

Here, I highlight the emergence of botanicals and the related topics of unmet needs in epilepsy, the historical and current use of botanicals around the world, scientific and clinical aspects of botanicals for epilepsy, and regulatory considerations.

Unmet Needs in Epilepsy

It is widely acknowledged that nearly one in three patients with epilepsy (PWE) who have access to antiepileptic drugs (AEDs) continue to have seizures despite the large and growing number of available AEDs. Further, similar proportions of PWE experience unacceptable AED-related side effects and life-limiting cognitive and psychiatric comorbidities, which are under-recognized and undertreated; even when treated, symptoms may respond incompletely and further complicate seizure management (2, 3). Even more troubling, among the tens of millions of PWE around the world who live in developing countries (4), the vast majority are not treated with AEDs due to a number of barriers (5–8). This situation is not unique to epilepsy; as a consequence, according to the World Health Organization, most persons in developing countries rely on botanicals for medical treatment (9).

In recent years, incremental rather than transformative progress in the treatment of epilepsy has led to new strategies for the identification, development, and testing of epilepsy treatments (3, 10, 11). One such “new” strategy centers on botanicals, drawing interest from their traditions of use in the treatment of convulsions, contemporary anecdotal reports of efficacy in PWE, identification of underlying mechanisms of action that are relevant to epilepsy, and, especially, the recent attention garnered by cannabis and its constituent compounds such as cannabidiol.

Historical and Current Use of Botanicals Around the World

Botanical products from plants—specifically herbs and herbal materials—may include any parts from the roots to the leaves and are prepared and administered in numerous ways. Botanicals were apparently used to treat convulsive seizures dating from 6000 B.C. in India (12) and from 3000 B.C. in China and Peru. The oldest Chinese document that details the treatment of epilepsy, *The Yellow Emperor’s Classic of Internal Medicine*, attributed to Huang Di Nei Jing, was written from 770 to 221 B.C. Regions within Africa and South America also have longstanding traditions in the use of botanicals for convulsions.

Written and oral histories of these cultures’ use of botanicals clearly lack the level of evidence required today to prove the safety and efficacy of AEDs. However, the dramatic appearance of convulsions—which would likely include primary as well as secondarily generalized seizures—is such that the therapeutic effects of a botanical treatment could reasonably be expected to be observable by PWE and family members and then reported to healers/herbalists (irrespective of the theories used by these practitioners to explain their effects), much the same as today when physicians rely on self-reports by PWE and family members to determine the effectiveness of AEDs.

Epilepsy Currents, Vol. 15, No. 6 (November/December) 2015 pp. 310–312
© American Epilepsy Society

OPEN ACCESS Freely available online

Researchers and clinicians generally associate the use of botanicals with TCM, Ayurveda (a system of traditional Hindu medicine), and other ancient systems of healthcare, but herbal therapies were widely used and studied in the West for the treatment of epilepsy until these therapies were replaced by compounds (whether derived from plants or synthesized) in the mid-to-late 19th and early 20th centuries. For example, Sir William Gowers, whose clinical descriptions of seizures is unequaled even today, wrote extensively about his use of a number of different botanicals to treat PWE, including *Cannabis indica* and digitalis, the latter derived from the Foxglove plant (*Digitalis purpurea*; 14).

Scientific and Clinical Aspects of Botanicals for Epilepsy

The pendulum is now swinging back, fueled by modern methods of scientific inquiry. The understanding of botanicals and the rationale for their development for use in PWE are expanding as modern laboratory techniques increasingly reveal their biological properties. Hundreds of plant extracts have demonstrable anticonvulsant activity in acute animal seizure models (including models of focal seizures), and many of these actions have been attributed to the effects of flavonoids, furanocoumarins, phenylpropanoids, and terpenoids on GABA receptors and voltage-gated ion channels (15). In addition, many botanical extracts have been shown to have anti-inflammatory, neuroprotective, and cognition-enhancing activities in laboratory studies (15).

The clinical study of botanicals in PWE for seizure control is far less developed than the basic science, and the evidence is generally anecdotal and of poor quality (16). Somewhat more substantial clinical evidence exists for the use of botanicals in the treatment of epilepsy-related comorbidities in PWE, including depression, anxiety, and attentional disorders (17). Several challenges unique to herbal medicines must be overcome before conducting the clinical trials necessary for approval by regulatory agencies such as the US Food and Drug Administration (FDA). To this end, recommendations for conducting and reporting randomized clinical trials of botanical products have been published by experts in clinical trial methodology, pharmacognosy, and herbal products, who emphasized the importance of completely describing the herbal product with regard to name, manufacturer, plant part used, type of preparation, source and authentication of the herbal material, pharmaceutical quality, dosage regimen, and purity testing (17).

Regulatory Considerations

Governmental regulations vary globally concerning the approval of herbal therapies for treatment of diseases. In the United States, prescription drugs are regulated by the Federal Food, Drug, and Cosmetic Act, whereas herbal therapies are covered separately under the 1994 Dietary Supplement and Health Education Act (DSHEA). DSHEA defines *dietary supplement* as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites (https://ods.od.nih.gov/About/dshea_wording.aspx. Accessed 8/9/15).

Two developments have significantly impacted the role of the FDA in overseeing the manufacturing and labeling of herbal therapies. First, in June 2007, the FDA issued “Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements” (<http://www.fda.gov/ohrms/dockets/98fr/cf0441.pdf>. Accessed 8/9/15), which significantly tightens manufacturing standards for dietary supplements, including herbal therapies, stating that they should substantially improve their quality. Second, in 2004, the FDA issued a policy guidance for the evaluation of the safety and efficacy of herbal therapies (referred to as *botanical drug products*) in mitigating, treating, curing, or diagnosing a disease. Depending in part on a particular product’s route of administration, form/formulation, safety, and intended use, this guidance provides the regulatory pathway for FDA approval of herbal therapies for specific medical indications, potentially including epilepsy. Two botanical drugs have since been approved by the FDA: Veregen (sinecatechins; ointment, 15%; Medigene, Planegg/Martinsried, Germany), which is an extract of green tea (*Camellia sinensis* Kuntze) for the topical treatment of genital and perianal warts, and Fulyzaq (crofelemer; Salix Pharmaceuticals, Raleigh, NC), a proprietary oral extract of the blood-red latex of the South American croton tree (*Croton lechlerii* Müll. Arg), for the relief of diarrhea in patients with HIV/AIDS taking antiretroviral therapy (18).

Example of Traditional Chinese Medicine

To help move this field forward, recent publications have synthesized a vast amount of preclinical and clinical information concerning botanicals (often from journals and other sources not readily available to Western researchers), and authors often provide the information in the contexts of both the associated traditional medical system as well as modern medical bioscience (1, 13, 15). For example, Xiao et al. (1) started their review by describing the TCM classification of epilepsy and how the principles of TCM are applied to patients in combining herbs with other treatment modalities, such as acupuncture, massage, diet, and therapeutic exercise. They then provided a comprehensive overview of botanicals in current use in TCM based on an extensive search of PubMed and numerous Chinese databases, as well as hand searches of numerous Chinese journals and the latest Chinese pharmacopeia. Twenty-three botanicals were thereby identified, with detailed information given about each one, if available, with respect to their generic name, scientific name, Chinese name, traditional use, current clinical use, mechanisms of actions, results of animal studies, known chemical components, main active component, and side effect profiles. The authors conclude that plants with medicinal properties have “the potential to be a rich source for the identification of safer and more effective antiepileptic agents” (1).

Conclusion

Like Xiao and colleagues (1), a number of research groups around the world are actively pursuing the study and development of botanicals for treatment of epilepsy. One published approach starts by identifying botanicals with a tradition of use over centuries in medical systems such as TCM and then applying modern methods to provide the scientific rationale for moving the study of these herbal therapies into clinical

studies (19). In this way, herbal therapies and compounds isolated from them that have promising activity in animal epilepsy models and relevant in vitro assays are then further assessed in preclinical studies that are necessary to proceed to early-stage clinical studies as per FDA regulations (19).

Herbal therapies have the potential to yield new treatment options for patients whose seizures are uncontrolled despite available AEDs. They may also represent more affordable, culturally acceptable treatments for the tens of millions of people around the world with untreated epilepsy who do not have access to AEDs. Theoretically, herbal therapies could also be investigated for their potential to prevent epilepsy, seizure worsening, or progressive psychological changes (e.g., memory loss). Further, some of these extracts and their constituent compounds active in animal models of epilepsy may be found to have novel mechanisms of action that could lead to the identification of new molecular targets, thereby encouraging the development of additional pharmacological interventions for epilepsy (19).

To facilitate the research community's efforts in this area, a publically available wiki will soon launch under the auspices of the ILAE that will constitute the most comprehensive repository available of current scientific and medical knowledge regarding botanical products in epilepsy, written and updated by credentialed experts who have published relevant research in peer-reviewed journals.

The traditions of use of botanicals for epilepsy throughout history provide a reasonable basis for their systematic evaluation using the latest scientific methods (20), and as noted by Xiao et al. (1), together with rigorous clinical trials, these traditions will ensure that “the legacy of botanicals . . . gains more impact and recognition.” History certainly supports this contention, suggesting that the current mantra of “bench to bedside” for development of epilepsy treatments from botanicals should be expanded to “tradition to bench to bedside” to fully translate nature to nurture.

References

- Xiao F, Yan B, Chen L, Zhou D. Review of the use of botanicals for epilepsy in complementary medical systems – Traditional Chinese Medicine [published online ahead of print June 5, 2015]. *Epilepsy Behav* 2015;pii: S1525-5050(15)00219-X. doi: 10.1016/j.yebeh.2015.04.050.
- Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med* 2011;365:919–926.
- Sørensen AT, Kokaia M. Novel approaches to epilepsy treatment. *Epilepsia* 2013;54:1–10.
- Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. *Epilepsia* 2010;51:883–890.
- Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: A systematic review of the magnitude, causes, and intervention strategies. *Epilepsia* 2008;49:1491–1503.
- Meinardi H, Scott RA, Reis R, Sander JW; ILAE Commission on the Developing World. The treatment gap in epilepsy: The current situation and ways forward. *Epilepsia* 2001;42:136–149.
- Newton CR, Garcia HH. Epilepsy in poor regions of the world. *Lancet* 2012;380:1193–1201.
- Winkler AS, Mayer M, Ombay M, Mathias B, Schmutzhard E, Jilek-Aall L. Attitudes towards African traditional medicine and Christian spiritual healing regarding treatment of epilepsy in a rural community of northern Tanzania. *Afr J Tradit Complement Altern Med* 2010;7:162–170.
- World Health Organization. *WHO Traditional Medicine Strategy: 2014–2023*. Geneva: WHO, 2013.
- Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma. *Epilepsia* 2011;52:657–678.
- Bialer M, White HS. Key factors in the discovery and development of new antiepileptic drugs. *Nat Rev Drug Discov* 2010;9:68–82.
- Jain S. Ayurveda: The ancient Indian system of medicine. In: *Complementary and Alternative Therapies for Epilepsy*. (Devinsky O, Schachter S, Pacia S, eds.) New York, NY: Demos Medical Publishing, 2005:123–128.
- Kakooza-Mwesige A. The importance of botanical treatments in traditional societies and challenges in developing countries [published online ahead of print August 17, 2015]. *Epilepsy Behav*. doi:10.1016/j.yebeh.2015.06.017.
- Gowers WR. Epilepsy and other chronic convulsive diseases: Their causes, symptoms, & treatment. London: Churchill, 1881:264–268, 271.
- Sucher NJ, Carles MC. A pharmacological basis of herbal medicines for epilepsy [published online ahead of print June 11, 2015]. *Epilepsy Behav* 2015;pii: S1525-5050(15)00263-2. doi: 10.1016/j.yebeh.2015.05.012.
- Li Q, Chen X, He L, Zhou D. Traditional Chinese medicine for epilepsy. *Cochrane Database Syst Rev* 2009: CD006454.
- Ekstein D. Issues and promise in clinical studies of botanicals with anticonvulsant potential [published online ahead of print September 1, 2015]. *Epilepsy Behav*. doi:10.1016/j.yebeh.2015.07.042.
- Hoffman FA. Botanicals as “new” drugs: US development [published online ahead of print August 26, 2015]. *Epilepsy Behav*. doi:10.1016/j.yebeh.2015.07.028.
- Schachter SC. Herbal therapies for epilepsy. In: *Encyclopedia of Basic Epilepsy Research*. (Schwartzkroin PA, ed.) Oxford: Academic Press, 2009:1450–1454.
- Schachter SC. Herbs and botanicals. In: *Epilepsy: Mechanisms, Models, and Translational Perspectives*. (Rho JM, Sankar R, Strafstrom CE, eds.) Boca Raton, FL: CRC Press, 2010:403–411.