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Review

Issues and promise in clinical studies of botanicals with anticonvulsant potential

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ABSTRACT

Botanicals are increasingly used by people with epilepsy worldwide. However, despite abundant preclinical data on the anticonvulsant properties of many herbal remedies, there are very few human studies assessing safety and efficacy of these products in epilepsy. Additionally, the methodology of most of these studies only marginally meets the requirements of evidence-based medicine. Although the currently available evidence for the use of cannabinoids in epilepsy is similarly lacking, several carefully designed and well controlled industry-sponsored clinical trials of cannabis derivatives are planned to be completed in the next couple of years, providing the needed reliable data for the use of these products. The choice of the best botanical candidates with anticonvulsant properties and their assessment in well-designed clinical trials may significantly improve our ability to effectively and safely treat patients with epilepsy.

This article is part of a Special Issue entitled "Botanicals for Epilepsy".

1. Introduction

Epilepsy is a very common neurological disease, and despite the introduction of more than a dozen new antiepileptic drugs (AEDs) during the last 25 years, about 30% of the people with epilepsy (PWE) continue to suffer from drug-resistant seizures [1]. Over the past few decades, the use of complementary and alternative medicine (CAM) by inhabitants of western countries has significantly increased, as exemplified by the 2007 American National Health Interview Survey of 23,393 adults and 9417 children, where 38.3% of adults and 11.8% of children reported using CAM therapies [2]. The most commonly utilized form of CAM was natural products, which were used by 17.7% of the adults. Studies that assessed the consumption of CAM by PWE reported that 24 to 56% of the adults and 12 to 32% of children have used CAM therapies, that 2 to 44% of these patients have used these products specifically for control of seizures, and that many patients do not report the use of CAM to their physicians [3]. People with epilepsy reported consuming CAM therapies for treating known comorbidities of epilepsy and common adverse events of AEDs, such as depression and impaired memory. However, despite the significant use of botanicals by PWE and the vast and increasing number of preclinical studies demonstrating efficacy of herbal products as anticonvulsants in animal models of seizures and epilepsy, there is still a lack of human trials providing evidence for clinical utilization of botanicals in PWE.

The current status of published clinical trials of botanicals with anticonvulsant potential is reviewed here, as well as the studies planned for the next few years, and the challenges and promise for obtaining evidence-based data for the use of herbal medicines in epilepsy are then discussed.

2. Clinical studies of botanicals in epilepsy

There are no English-language publications of randomized clinical trials (RCTs) of botanicals for the treatment of epilepsy. The last Cochrane review of TCM for epilepsy, published in 2009, found seven Chinese trials of herbal products given as monotherapy and compared with AEDs [4]. In all these trials, epilepsy was diagnosed according to the International League Against Epilepsy (ILAE) classifications. Two of the seven studies were excluded from the review due to unclear design and an unusual allocation of 6:1 between the study and control arms. The other five studies were of single center, parallel design and had a control group. Although randomization was mentioned, the randomization procedures were unclear, and none of the studies were blinded. The duration of the studies varied between two months and three years. No meta-analysis of the results could be performed, due to variation of the baseline patients' characteristics, the herbal formulations, and the administered control AEDs between the studies. Although the studies did report some benefit, a high probability of selection, detection, and performance bias precluded drawing reliable conclusions on the effect of TCM for epilepsy. A study published after this Cochrane review, available in English in abstract form only, reported on Dianxianning (a mixture of 22 natural products) treatment as add-on to conventional

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AEDs [5]. This was a multicenter, prospective, randomized, placebo-controlled trial, with 137 patients with epilepsy in the treatment arm and 69 in the control group. After three months of treatment, a 37.84% reduction in seizure rate was reported in the group of patients who received Dianxianning and only 13.18% reduction in the placebo group ($p < 0.05$).

In contrast to the lack of reliable data on the use of botanicals for treating epilepsy, the available clinical information on the treatment of some of the most common comorbidities of epilepsy is slightly more substantial. Evidence supports the use of St. John's wort in treating mild to moderate depression [6] and the use of kava in the treatment of generalized anxiety [6,7]. Rosenroot was found to improve attention, fatigue, mild depression, and mental performance [8]. A recently-published clinical trial assessed the ability of *Xylaria nigripes* (Wu Ling capsule) to treat depression in patients with epilepsy [9]. This double-blind, placebo-controlled, randomized, superiority study was performed in eight medical centers in China and recruited 104 patients with epilepsy and depression. After 12 weeks of treatment, a 51.3% improvement was found by Hamilton Depression Rating Scale in the Wu Ling group, as compared with only 35.7% improvement in the placebo group ($p = 0.002$). Additionally, the quality of life, assessed by QOLIE-31, improved in the treatment group in comparison to control ($p < 0.05$). No difference was found between the two groups with regard to frequency and severity of seizures and in the reported adverse events [9].

Search of ClinicalTrials.gov on clinical studies for epilepsy revealed 791 interventional studies with known recruitment status. Out of these trials, 18 assessed treatment with botanicals. The majority (15) of them planned treatment with cannabis and its compounds, primarily cannabidiol (CBD). Two studies, both marked as completed, assessed interactions between botanicals and antiepileptic drugs (carbamazepine and St. John's wort and phenytoin and gingko biloba) in healthy volunteers. The study of carbamazepine and St. John's wort comedication has subsequently been published and reported no influence from 17 days of St. John's wort administration on the blood concentration of carbamazepine [10]. Another completed study assessed the efficacy of Wu Ling capsule in treating depression in patients with epilepsy (the same study described in the previous paragraph). Among the trials with unknown recruitment status, only one planned to evaluate a herbal remedy — a phase II trial to assess safety and anticonvulsant efficacy of *Passiflora incarnata* extract in patients with partial epilepsy (last updated in 2011). No report on the results of this trial was found by searching PubMed and Google.

Another herbal product, not yet registered at ClinicalTrials.gov but mentioned for several consecutive years as part of the future epilepsy pipeline at Eilat Conferences of new antiepileptic drugs, is Huperzine A [11]. This is a small alkaloid, derived from the Chinese herb *Huperzia serrata*, which showed anticonvulsant and neuroprotective properties in preclinical studies. A phase I study conducted by Biscayne Pharmaceuticals revealed only cholinergic dose-dependent adverse events, attributed to the rapid rise in serum concentrations of the immediate release formulation, but no cardiovascular alterations, similarly to the safety data published in a clinical trial of Huperzine A in doses up to 0.8 mg/day for Alzheimer's dementia [12]. Biscayne Pharmaceuticals plans to use a new extended release formulation of Huperzine A in a pilot clinical trial in children with Dravet syndrome and in a phase II trial in adults with refractory complex partial seizures [11].

3. Safety of botanicals in epilepsy

The reports of adverse events of herbal medicines in clinical trials of botanicals for epilepsy are even fewer than the reports on efficacy. Only minimal GI discomfort was reported in the TCM clinical trials of herbal products for treatment of epilepsy [4], in line with the common belief that natural remedies are safe. One of these trials reported the actual incidence of adverse effects in the 'antiepilepsy capsule' and phenobarbital groups. The Peto odds ratio was 0.04 (99% CI 0.01 to 0.12, $P < 0.00001$), favoring the antiepilepsy capsule [4]. No report of adverse events was provided in the English-language abstract of the clinical trial on the efficacy of Dianxianning treatment for epilepsy [5].

Case reports of association between epileptic seizures and use of herbal remedies for various indications have been published, involving ephedra, caffeine, gingko biloba seeds, star anise, star fruit, and evening primrose [13,14]. A review of the 65 cases of dietary supplement-associated seizures reported to the FDA between 1993 and 1999 determined that 20 seizures were probably related to the dietary supplement (19 of them involved ephedra and 14 involved caffeine), 13 were possibly related (7 involved ephedra, 5 involved caffeine, and creatine, St. John's wort, and ginkgo biloba were also implicated), and 10 were unrelated [15].

Many botanicals are known to influence liver metabolism and intestinal absorption, and interactions between herbal remedies and AEDs have been broadly reported in animal studies. However, these clinically important interactions have only marginally been studied in humans [13,14,16,17]. Chronic treatment with St. John's wort, which is known to affect the cytochrome P450 system, was reported to decrease the bioavailability of benzodiazepines in healthy subjects [18–20]. However, the decrease in the plasma concentration did not induce pharmacodynamic effects in one of the studies [19]. Gingko biloba was reported as probably responsible for the decrease in plasma concentrations of phenytoin and valproic acid in a patient with epilepsy with fatal seizures who had been using herbal supplements [21]. Piperine was found to significantly increase the mean plasma concentration of phenytoin, when given in two different doses in 20 patients with uncontrolled epilepsy [42] and when coadministered with phenytoin in 6 healthy volunteers [22]. Grapefruit juice increased carbamazepine bioavailability in patients with epilepsy [43] and increased the serum concentration of diazepam in healthy volunteers [23]. Finally, psyllium was found to decrease the plasma concentration of carbamazepine when taken together by 4 healthy subjects [24].

4. Methodology pitfalls of botanical clinical trials

Publications of botanical clinical trials for the treatment of epilepsy usually have encouraging results. However, the methodology used in these trials is most often not sufficiently adherent to the requirements of modern evidence-based medicine. In many cases, the implementation of these requirements is precluded by the very basic principles of the traditional medical systems making use of the herbal remedies. For example, these systems generally involve a holistic, personalized approach to treating patients rather than a disease-focused one and, therefore, are not applied in the same way to all patients characterized by a specific disease. Additionally, cultural differences between western and traditional populations may raise ethical issues which make the incorporation of evidence based principles for RCTs difficult [25].

The Consolidated Standards of Reporting Trials (CONSORT) statement is a guide on the essential information required in reports of two-group parallel RCTs [26,27]. Specific recommendations for reporting RCTs of herbal medicines were prepared by a consortium that included experts in clinical trial methodology, pharmacognosy, and herbal products [28]. Nine out of the 22 items of the CONSORT statement were elaborated for relevance to RCTs of botanicals. Specific attention was given to the precise description of the intervention to include all the details of the name, manufacturer, plant part used, type of preparation, source and authentication of the herbal material, pharmaceutical quality, dosage regimen, and purity testing. Follow-up recommendations for reporting RCTs of TCM interventions [29], outcomes [30], and adverse events [31] were subsequently proposed by Chinese researchers. A study that examined the implementation of the herbal medicines' CONSORT recommendations in 406 RCTs up to the end of 2007 found that the reports improved in the more recent years, albeit only 38% of the required information was reported [32]. A recent study reported on the adherence to the CONSORT statement in clinical