# How to get the answer to nearly everything; using the Internet for epilepsy research.

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**Abstract**

Although we now have many drugs to treat patients with epilepsy, we often do not know which of these drugs are the best to use, or whether specific combinations of drugs are of particular value. We propose that the epilepsy community establish an Internet-based research programme to address these questions. This would be a multi-centre programme, open to neurologists anywhere in the world who have sufficient expertise and interest in epilepsy, and access to the Internet. A series of prospective, pragmatic, randomised research protocols would run in parallel. Recruitment, randomisation and subsequent data collection would be via the Internet. Studies could be focussed on patients with specific seizure types, specific epilepsy syndromes or particular aetiologies. The process would be flexible, so that new studies could be started whenever new syndromes are identified, or new information regarding the aetiology of a syndrome (such as genetic mutations) are discovered. Studies would be independent of pharmaceutical companies, and would not be designed to assess new drugs. Instead, studies would be designed to determine which of the drugs we have in our armanetarium are best for a particular patient group. Patients could be randomised whenever the treating doctor is uncertain regarding the optimal treatment. Different drug selections could be compared in different countries, depending on availability in the particular country. Although patients would be randomised, neither they nor the treating doctors would be blinded. Recruitment would be simple and would take just a few minutes. Doctors would not be paid to enrol subjects.

# How to get the answer to nearly everything; using the Internet for epilepsy research.

It is surprising how little we know regarding the optimal treatment of patients with epilepsy. This lack of information has been highlighted recently in this journal with respect to management of patients with newly diagnosed epilepsy (Glauser et al, 2006). There is probably even less evidence regarding the optimal management of patients who have failed the first drug tried (Kwan and Brodie, 2000). In this article we would like to propose a new approach to determining how patients with epilepsy should be managed.

## Overview

We propose that the epilepsy community establish an internet-based research programme. This would be a multi-centre programme, open to any neurologist anywhere in the world who has sufficient expertise and interest in epilepsy. A series of prospective, pragmatic, randomised research protocols would run in parallel. Recruitment, randomisation and subsequent data collection would be via the Internet. Although patients would be randomised, neither they nor the treating doctors would be blinded. Recruitment would be simple and would take just a few minutes. Doctors would not be paid to enrol subjects.

**The Problem**

Most of us who treat people with epilepsy see patients whose management is difficult. Often, we do not know which of several treatment options offers the best prospect of seizure control. In some circumstances, we know that several drugs may be effective. However, we may not know which drug has the best chance of rendering the patient seizure-free with the lowest likelihood of side effects. If a patient has failed to respond to a first or second treatment, we often have very little evidence to guide our subsequent therapeutic choices. In practice, we usually have to rely on the recommendation of experts and our previous experience (Karceski et al, 2005).

Relatively few studies have been performed in which different drugs have been directly compared. Pharmaceutical companies appear to have little interest in comparing their drug with an anti-epileptic drug produced by another company; why would they want to take the risk of showing that their drug is less effective than a rival’s product?

There is also very little data comparing specific combinations of drugs. At present, there are over 100 possible combinations of two different drugs which could be prescribed in most Western countries. Again, we have remarkably little information to guide us when trying to choose a specific combination. There is some information from animal studies suggesting that particular combinations are likely to be synergistic (Borowicz et al, 2002; Luszczki and Czuczwar, 2004) but little controlled data from humans. We do not even know whether we should be treating patients who have failed a first drug with alternative monotherapy, or a combination of two drugs (Kwan and Brodie, 2000; Deckers 2002). The conventional approach is to try a second drug as monotherapy before combining drugs (Karceski et al, 2005), but there is limited data to suggest that, at least in some circumstances, combinations may be more effective (Deckers et al, 2001; Kwan and Brodie, 2006).

Most studies have grouped together patients according to the seizure type, rather than the underlying pathology. In particular, patients with partial seizures tend to be grouped together while it is possible (and in our opinion likely) that patients with different aetiologies may respond differently to particular anti-epileptic drugs or drug combinations. Is it reasonable to assume that a patient who has seizures secondary to a cavernous haemangioma, where there is haemosiderin staining of the brain, will necessarily respond in the same way as a patient whose seizures are due to a malformation of cortical development or mesial temporal sclerosis?

**The Solution**

An internet-based research programme, open to neurologists throughout the world, could answer many of these questions. We are aware that internet based programmes are underway to prospectively collect data on patients with epilepsy; we are suggesting that this approach be developed further and used for conducting randomised controlled trials. Eucare, for instance, intends following patients with newly diagnosed epilepsy who are being treated throughout Europe (Brodie 2003). We are proposing a complementary programme in which the epilepsy community uses the Internet to randomise patients to different treatment arms, and thus also obtain prospective randomised efficacy data.

In the scheme we are proposing, doctors would log onto a website whenever they are unsure of the optimal management for a patient. The doctor would answer questions regarding the seizure type, seizure syndrome and aetiology. Information would be sought regarding previous drug use and intercurrent illnesses. This information would be entered into a database, and a computer algorithm would determine immediately if the particular patient’s characteristics matched those required for any of the controlled trials being undertaken. If an appropriate trial was underway, randomisation would be offered.

If enough neurologists chose to participate, it would be possible to enrol large numbers of patients relatively rapidly. This approach would enable epileptologists to organise trials that would be focused on patients with specific syndromes or aetiologies, as well as those with particular seizure types.

We propose that the project belong to the entire community of epileptologists, so that anybody could propose a research protocol; obviously, he or she would have to provide some justification for the proposal. Equally obviously, it would not be possible to conduct all possible trials simultaneously. We would envisage that a panel of experts in a particular syndrome would decide on the optimal research protocol.

Protocols would be published on the Internet with explicit instructions regarding the introduction of the appropriate drugs. Introduction of drugs would be flexible, reflecting what is done in real life, and would not be excessively regimented. Doctors would download and print information sheets regarding the protocols and the drugs for their patients. Subsequent data collection would also be on line.

It would not be necessary to establish protocols for all epilepsy syndromes at the outset. Initially, there may be protocols established for the more common problems, and other protocols could be added as the need became apparent. If it became clear (or if we already have the evidence) that a particular treatment is the optimal treatment in a given condition, then this information could be made available to the doctor when he or she logs onto the website.

The whole approach would need to be flexible, so that it could adapt to ongoing developments. We are aware that we do not yet have definitive classification systems for either seizures or epileptic syndromes (Engel, 2006). At the outset, we would use the currently accepted ILAE classifications, but it would be possible to alter these categories if new classifications are adopted. Likewise, it would be possible to set up new study protocols when new information becomes available. For instance, if a genetic mutation was discovered that is common in a particular syndrome, then it would be possible to subdivide patients depending on whether or not they have had the appropriate test, and if so, whether the test was positive or negative.

It would also be possible to collect data regarding outcomes of patients even if there was no study protocol suitable for them. In this way, observational studies could be included in the project. It would be possible to collect other valuable information about patients, including information on sudden death in epilepsy and outcomes of pregnancy. Because of the potential to enrol large numbers of subjects relatively rapidly, this project could provide an excellent opportunity to co-ordinate large prospective studies when there is a low likelihood of a particular outcome. For instance, it would be possible to use this network of epileptologists to undertake prospective studies of possible strategies to prevent sudden death in epilepsy.

**Potential Difficulties**

There are potential difficulties with this proposal. However, we do not think any of them are insurmountable.

1. **Funding**

In the project we are proposing, epileptologists would not be paid to enrol patients, but they would do so because they could see the potential of this research. Obviously, the process would have to be simple and rapid if this were to succeed. The drugs themselves would not be funded by the project, but patients would be randomised to drugs that are already available in the particular country. We think it is important that the project remain independent of pharmaceutical companies, and we would not envisage that they would provide the drugs free of charge.

The website and associated database that we are envisaging would clearly be complex, and would need ongoing refinements. There would be a cost in establishing and maintaining these. A large amount of data that would be collected, and there would be costs involved in analysing it. A funding source would need to be identified for these costs.

1. **Encouraging Participation**

For the project to succeed, it would require that doctors actually enrol subjects. In the fullest development of this idea, doctors would be able to enrol (almost) any patient about whose management they are uncertain. It would take some time before this stage could be reached. Initially, it would require a concerted effort to bring the project to doctors’ attention and to continually remind them of the studies that are being undertaken. However, once the project had obtained a certain level of momentum, we would hope that this project would remain at the forefront of epileptologists’ minds. In addition, of course, the projects would start providing all of us with important and clinically relevant information. Doctors could check the website to see what the current best evidence is for the treatment of a patient with a particular syndrome.

1. **Accuracy of data collected**

It is essential that all data collected is accurate. It would also be critical that follow up data be entered reliably. It would, therefore, be necessary that the data entry be kept as simple as possible. We envisage that regular e-mails would be issued to update participants on the studies’ progress and to remind them of the need to provide data at the appropriate times. This could be done automatically by the computer software.

To ensure that appropriate patients were recruited into the various studies, protocols would contain checklists to ensure a ‘pure culture’ of subjects was recruited. A doctor would have to review a checklist for each specific patient before that patient could be recruited. Clearly, it would be necessary that the doctors are knowledgeable about epilepsy. For example, it may be that doctors would need to be members of the International League Against Epilepsy or their national neurological association before they could recruit patients to a study.

The studies we are proposing would not be blinded, although patients would be randomised. For non-blinded studies to be worthwhile, there needs to be a robust and reliable end-point that is not subjective. In the current context, we envisage that the end-point would be seizure freedom. Information would also be collected regarding seizure frequency and drug side effects, but these would be secondary analyses.

1. **Ethics Committee approvals**

In most centres there would be separate ethics committees who would need to give approval before patients could be recruited. It is likely that each separate randomisation procedure would require separate approval. This could significantly slow the uptake of the project. However, it is not necessary that all centres or countries start simultaneously. Centres could join as the ethics committees give approval. Some countries have national ethics committees which could give approval for doctors throughout the entire country to enter patients into a particular study; this is now the case in New Zealand. We are envisaging that all the medication used would have proven effective and have been approved for use in epilepsy. The studies we are envisaging would be designed to determine whether one drug or combination of drugs is superior to another in a particular condition.

1. **Personal security**

The website would be secure, using the same mechanisms used for conducting business transactions.

## Moving forward

There may be other problems that we have not considered. Some of these problems may not become apparent until the approach is tested. The New Zealand chapter of the International League against Epilepsy is therefore planning to undertake a pilot study to look at the feasibility of internet-based recruitment. In the first instance, we will be looking at the management of patients who have failed to respond to the first drug that has been prescribed. However, New Zealand is not a sufficiently large country to answer many questions, so the pilot study will aim to test the concept of internet-based recruitment and data collection.

We believe that the approach outlined here has the potential to systematically answer a number of questions regarding the management of patients with epilepsy. We are proposing the idea in this forum to gauge how much enthusiasm there is amongst the wider epilepsy community. It seems appropriate that the International League against Epilepsy would co-ordinate and promote the project, but this role could be undertaken by some other international organisation. We would like to determine how much interest there is throughout the world, and we would invite readers to contact us with their responses and ideas.

Please contact us with your responses at [pbergin@adhb.govt.nz](mailto:pbergin@adhb.govt.nz).

Acknowledgements:

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