

## Current Literature

In Clinical Science



## Regulation or Rising Cream?

**Historical Control Monotherapy Design in the Treatment of Epilepsy.**French JA, Wang S, Warnock B, Temkin N. *Epilepsia* 2010;51:1936–1943.

**PURPOSE:** Monotherapy approvals have been difficult to obtain from the U.S. Food and Drug Administration (FDA), and have almost all been achieved using a trial design entitled “withdrawal to monotherapy” in treatment-resistant patients, which employs a so-called “pseudo-placebo” as a comparator arm. The authors submitted a white paper to the FDA advocating use of a virtual placebo historical control as an alternative to pseudo-placebo. Such an approach reduces patient risk that would result from exposure to pseudo-placebo. In this article, we present the data submitted to the FDA to justify a historical control. **METHODS:** We analyzed individual patient data from eight previously completed withdrawal to monotherapy studies, which we determined had similar design. All studies employed percent meeting predetermined exit criteria (denoting worsening of seizure control) as the outcome measure. Kaplan-Meier estimates of the percent exiting were calculated at 112 days. **RESULTS:** The percent meeting exit criteria were uniformly high, ranging from 74.9–95.9%. The eight studies appear to meet the criteria set forth for use of historical control. The estimate of the combined percent exit based on the noniterative mixed-effects model is 85.1%, with a lower bound of the 95% prediction interval of 65.3%, and 72.2% for an 80% prediction interval. **CONCLUSION:** There is justification for proposing that these data can serve as a historical control for future monotherapy studies, obviating the need for a placebo/pseudo-placebo arm in trials intended to demonstrate the efficacy of approved drugs as monotherapy in treatment-resistant patients.

**Commentary**

Clinical trials are designed and meant to bring safe and effective treatments to patients. The pathway to antiepileptic drug (AED) approval from preclinical and animal model studies to use in humans is long, arduous, and expensive. It is estimated that the cost of bringing a new chemical entity from early development through to the clinic is approximately \$800 million. A randomized placebo-controlled trial involving 300 patients can cost in the order of 8 million dollars. In epilepsy, in the vast majority of cases, initial approval is for add-on treatment in refractory focal epilepsy. However, the holy grail for many pharmaceutical companies following initial release for use as adjunctive therapy is subsequent regulatory approval for use in monotherapy, ideally in newly diagnosed patients as well as in patients who have previously failed other AEDs, for whatever reason.

The priorities for the different stakeholders along these approval routes overlap but have different emphases. The regulatory body wants to be comfortable that, first and foremost, the new drug is safe, and that it is more effective than no treatment (placebo). The sponsoring pharmaceutical company wants to ensure that its drug is used appropriately and safely in as many patients as possible, thus ensuring a return for its

investment in the development of the drug. The trial investigator team is motivated by the opportunity to contribute to knowledge in clinical science, give its most refractory patients the chance to improve on a new promising treatment, and also to enhance the reputation of its department. Following the release of the new AED, treating physicians in the real world of everyday practice will want to be comfortable that the drug will or may bring benefits to their patients, initially trying the drug in patients who have not done well on many or most previously available AEDs. New AEDs are generally first used by epileptologists in specialist clinic settings, then used by general neurologists, and finally used by other nonspecialist physicians and family practitioners. In parallel with this evolution of clinical use, newer AEDs begin to be used by pediatric neurologists and other specialists such as psychiatrists. With clinical experience and postmarketing surveillance (both formal and informal), a new AED might rise up the pecking order and be used earlier by more physicians for more patients. Finally, the priority of the patient and his or her family is to be seizure-free on a well-tolerated medication prescribed by a doctor they trust. This natural maturation of the real-life use of new AEDs might be referred to as the *rising cream* process—over time, the most efficacious drugs will be used earlier and earlier in the treatment hierarchy.

It is remarkable to reflect that only two of the many new AEDs approved for use in the United States over the last 20 years have been granted regulatory approval for use as initial monotherapy, that is, oxcarbazepine and topiramate,

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and only two other drugs, felbamate and lamotrigine, have regulatory monotherapy approval following withdrawal of another AED. The basis for this is the well-known fact that the FDA has not accepted equivalence when a new AED has been compared with an older standard AED (usually carbamazepine). This subsequently led to the design of *withdrawal-to-monotherapy* studies comparing the new agent with a usually suboptimal dose of a standard comparator (so-called *pseudo-placebo*), with specified exit criteria. Ethical and safety concerns have led French and colleagues to develop a historical control monotherapy trial design based on the placebo or pseudo-placebo response in eight previously published withdrawal-to-monotherapy trials. The white paper outlining this new design was accepted by the FDA in July 2010, and a summary paper has recently been published in *Epilepsia* (1). On the basis of this, several new AED conversion-to-monotherapy trials using this new paradigm are currently underway.

The pathway to regulatory monotherapy drug approval in Europe is different than that of the United States. The European Medicines Agency allows for active control equivalence trials where the new AED is compared with a well-established AED that has *substantial evidence* of effectiveness. The fundamental difference in monotherapy AED approval between the United States and Europe is contrary to the goals of global harmonization in the drug-approval process. Lamotrigine, levetiracetam, oxcarbazepine, and topiramate are licensed for monotherapy in Europe. Moreover, the SANAD studies from the United Kingdom, two large pragmatic randomized, nonblinded, monotherapy studies comparing a number of different older and newer AEDs in both newly diagnosed focal and generalized epilepsy, have provided information that has generally underscored prior clinical practice (2, 3). SANAD 2 is planned to start later this year, if funded, comparing lamotrigine, levetiracetam, and zonisamide in newly diagnosed focal epilepsy, and comparing levetiracetam with valproate in generalized (and unclassified) epilepsy (A. Marson, MD, in writing, February 2011).

French and coworkers are to be congratulated for helping to find newer, safer, and more acceptable ways of bringing newer AEDs to monotherapy approval. However, there are a number of practical and logistical difficulties in this new conversion-to-monotherapy trial design. There are now more than 15 AEDs available which may be prescribed for focal epilepsy syndromes. This makes enrolment in clinical trials of

new AEDs increasingly challenging, even in patients with recognized drug-refractory partial epilepsy, as treating physicians might be somewhat reluctant to *expose* their patients to an unfamiliar agent when other AEDs are already available to prescribe. This concern will be particularly acute in a conversion-to-monotherapy trial design, which is likely to include patients with less severe epilepsy who are on one or at most two AEDs at time of enrolment and who have previously failed a smaller number of drugs. In addition, there are also concerns regarding the availability or not of the test AED—many trials now recruit patients from many different countries, some of which may have already granted approval of the new AED, and in some of which the drug may not be available. Therefore, in the former it will likely be more difficult to recruit patients into the trial, whereas in the latter, recruitment will be easier and might be seen as a way of getting newer drugs faster for individual patients. In this scenario, patient characteristics (and patient recruitment numbers) from countries with and without drug availability are likely to be very different.

Any clinical trial methodology and indeed the *industry* of clinical trial medicine is itself not without its problems and critics. The *rising cream* process of drug maturation in the therapeutic use of AEDs utilizes the combined clinical wisdom, attained and honed over time, of many specialists treating different types of patients with epilepsy (each with their own unique genetic background and illness narrative), and shared by word of mouth, meeting presentations, and publications in the peer-reviewed literature. This accumulated knowledge about each drug likely has much more influence over appropriate prescribing patterns than does regulatory-driven monotherapy trials, no matter how well-intentioned.

by Norman Delanty, MD, FRCPI

#### References

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## *Epilepsy Currents Journal*

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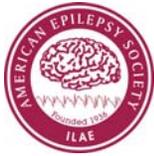
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