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# Do You Believe in Magic (Bullets)?

**Commentary on: French JA. Response to First AED. *Epilepsy Curr.* 2002;2(3):72-73. doi: 10.1046/j.1535-7597.2002.t01-1-00026.x**

In 2000, Patrick Kwan and Martin Brodie wrote their seminal *New England Journal of Medicine* paper on treatment response to the first antiseizure medicine (ASM).[1] The data derived from observation of approximately 500 patients seen in their new-onset epilepsy clinic in Glasgow. Although others had stated it before, this article firmly established the concept that newly treated epilepsy could be controlled approximately two-third of the time, while one-third of individuals would be treatment resistant. A second article in 2001, which formed the basis of my Epilepsy Currents commentary written the same year[2], further clarified that treatment sensitive individuals were usually controlled by their first ASM, and that this medicine could usually be given at modest doses.[3] Moreover, if the first ASM was ineffective at controlling seizures, a second ASM had only a dismal 10% likelihood of conferring seizure control. Notably at that time 80% of their patients were receiving 1 of 3 popular ASMs, namely carbamazepine, valproic acid, or lamotrigine.

What has happened since? In the ensuing 2 decades, a dozen more ASM's found their way to the clinic. These ASM's have exerted their anti-seizure effect with a myriad of novel mechanisms, including the first AMPA antagonist (perampanel), the first potassium channel opener (retigabine) and the first marijuana extract (cannabidiol).[4] Much has changed, for sure, but despite what might be the expected benefits from such a sea change, several articles have been written about the absence of substantial improvement for people who suffer from uncontrolled seizures. In other words, we failed to find the elusive "magic bullet." In 2012 when Brodie et al returned to the same clinic and reanalyzed the likelihood of seizure freedom, the numbers who had been rendered seizure free had increased only from 64% to 68% by the last clinic visit.[5] The investigators again noted that a second regimen only conferred a 13% additional likelihood of seizure freedom. The likelihood of seizure freedom went down dramatically after 2 regimens. In 2009, the International League Against Epilepsy defined treatment resistance as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[6] The implication of this definition is that although we have over 25 ASMs to choose from, they are so similar in their efficacy that they are essentially interchangeable. In other words, "If you have tried two, you have tried them all."

There has been a great deal of teeth-gnashing and consternation over the apparent absence of progress in controlling treatment-resistant epilepsy.[7] Many have blamed the use of animal models that exhibit acute seizures rather than ones that simulate seizures arising from an epileptic brain. The standard models, it is argued, might always pick drugs that act similarly, and might reject drugs that could represent true progress for the treatment-resistant population.[8] Some have argued that the maximal electroshock (MES) test, while a "gold standard" for base screening, is not "fit for purpose" for discovering drugs to improve patients with treatment-resistant epilepsy.[9] This concept has taken hold to the point that the NINDS anticonvulsant screening program (newly named the Epilepsy Therapy Screening Program) has changed its screening paradigm, adding a "high hurdle" of entry based on standard models (success in both MES and 6 Hz electrical stimulation, the latter of which is resistant to many standard ASMs) and also adding chronic in vitro and in vivo epilepsy models.[10]

Thus far, the new seizure/epilepsy animal models have not led to a breakthrough therapy, but perhaps it is early days. Such models make a great deal of sense for assessing disease modifying therapies, which might be completely ineffective against acute seizures, and clearly require chronic models to demonstrate an effect and to identify any incremental benefits that might accrue over time. Moreover, chronic models clearly might be better for identifying additional benefits such as reduction of or improvement in comorbidities. Unfortunately, other than possibly everolimus for Tuberous Sclerosis complex,[11] no novel disease modifying epilepsy therapy has yet been entered into clinical trials.

But what of anti-seizure drugs? These drugs in many cases can be thought of as symptomatic treatments. To test a drug for tuberculosis, you need an animal model of tuberculosis. But to test a very strong cough suppressant, you need an animal model which produces a cough. A drug that suppresses a cough produced by multiple different underlying causes is surely more likely to be universally successful

than one that suppresses cough due to a single etiology. Epilepsy is a disease caused by many etiologies, and for many patients the cause is still unknown. Therefore, a standard seizure model may indeed help us find a better drug. In fact, there have been 2 recent examples of the dangers of "novel" models and the (perhaps) potential for the standard models. The first example is the drug padsevonil, which was developed by UCB, the creators of the very successful drug levetiracetam, and the follow-on drug brivaracetam. The company was heavily focused on the concept that their next drug development program had to make a dent in treatment-resistant epilepsy, and padsevonil was engineered specifically for that purpose. The drug, which has a combined mechanism, binding to both SV2A and the $GABA_A$ benzodiazepine receptor, performed very well in the models expected to differentiate a drug that would be effective in treatment-resistant epilepsy, including intrahippocampal kainate, the amygdala kindled mouse, and the 6 Hz model, in some cases outperforming all existing compounds.[12] Sadly, it had only a modest effect in a randomized placebo-controlled add-on study in treatment-resistant focal epilepsy and did not separate from placebo in its primary end points, which optimistically included a 75% responder rate.[13] In contrast to padsevonil, the new drug cenobamate which was recently approved for adjunctive therapy of treatment-resistant focal epilepsy by the Food and Drug Administration has demonstrated in several randomized controlled trials that its ability to render treatment-resistant focal epilepsy patients seizure free far surpasses any other of the novel drugs (21% of treatment-resistant patients remained free of seizures during the 12 week maintenance phase).[14] Yet, cenobamate was discovered purely through "standard" blind screening. When put into development, the mechanism of action was completely unknown (subsequently evidence supports a dual mechanism of GABA enhancement and preferential inhibition of the persistent sodium channel).[15,16]

Because of cenobamate, and hopefully more drugs like it, there is indeed hope that we can change the proportion of people with epilepsy who become, and stay, free of seizures by treatment with medication alone. At this point, we need to be humble enough to conclude that the best way to find the next magic bullet is still unknown, and we need to keep our minds open to all avenues.

*By Jacqueline A. French*
*NYU, USA*

## ORCID iD

Jacqueline A. French https://orcid.org/0000-0003-2242-8027

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