# The place of generic modified-release formulations for epilepsy

## Slow and steady

Jacqueline A. French, MD
Michel J. Berg, MD

Correspondence to
Dr. French:
Jacqueline.French@nyumc.org

*Neurology*® 2016;86:1572–1573

In recent years, antiepileptic drug (AED) modified-release (MR) or extended-release formulations have become increasingly available. Once-daily formulations can ease the burden of the need to take AEDs every day for years, if not a lifetime. These formulations may also improve adherence and reduce fluctuations in serum concentrations that can lead to adverse effects (at maximum concentrations [Cmax]) or seizure breakthroughs (at minimum concentrations [Cmin]). The most commonly prescribed AEDs are now available in MR formulations, and many patients have come to expect that they will be able to use a once-daily pill to treat their epilepsy. In the United States, all the AEDs that are available as MR are also available as generic equivalents. Many patients and their physicians have expressed concerns about generic substitution, fearing that the generics could differ from the brand just enough to cause a breakthrough seizure. While concerns still exist, 3 recent randomized clinical trials suggest that, at least for immediate-release (IR) AEDs, the differences between brand and generic are minimal, and should not cause substantial concern.[1–3] Is this also true for MR generics?

The analysis, by Johnson et al.[4] in this issue of *Neurology*®, of the data submitted to the Food and Drug Administration (FDA) in the Abbreviated New Drug Applications for the generic MR-AEDs is reassuring in some ways, and yet raises some concerns. Area under the curve (AUC) and Cmax values of generics were close to the brand for most products, but not all. Values of time to achieve Cmax over the course of the day (Tmax) varied more considerably and, in some cases, this led to substantial differences in serum concentrations at various time points across the day while still resulting in AUC and Cmax confidence intervals within the approval limits. The variations for MR-AEDs were greater than seen in a similar analysis performed on the Abbreviated New Drug Application data of the IR-AED formulations, suggesting that the IR-AED studies should not be extrapolated to MR-AEDs.[5]

These generic studies were performed in healthy young adults given a single dose of the AED. The recent IR studies suggest generic single-dose studies in healthy controls are consistent with both single and chronic dosing studies in people with epilepsy, but it is not certain that these findings extend to MR products, especially since generic MR formulations commonly use different release methods. This uncertainty leaves the clinician and the patient in an awkward situation: Do MR generics provide the same efficacy and safety as the brand AEDs, or not?

For many patients, brand-name drugs are either not reimbursed at all by their health care plan or require substantially higher copays (often hundreds of dollars per month). Is such a financial outlay worth the price? What difference would a fluctuation across the day really make, if the "same amount of drug" (as represented by AUC) eventually gets in, and the main differences are in timing of drug concentrations across the day?

Of note, the FDA has suggested by its actions that fluctuations over time are of substantial interest and concern. When companies develop MR products, they are required to perform additional placebo-controlled studies of efficacy, even when the amount of drug, as demonstrated by AUC, is substantially similar.[6] Such placebo-controlled studies have been performed for MR formulations of carbamazepine, lamotrigine, levetiracetam, topiramate, oxcarbazepine, and others.[7] The FDA has argued that the differences between a drug that fluctuates between Cmin and Cmax, vs one that has levels that are more consistently maintained at some middle value between the two, could be substantial enough to cause a major change in the ability of the drug to demonstrate an effect. If this is the case, should we also be worried about the differences found by Johnson et al.? And if so, what should a clinician do?

As with many such questions, the available data are insufficient to provide certainty with MR-AEDs, and each patient's situation and the drug in question must be considered and taken into account. Not all drugs are created equal, in relation to the clinical consequences of variation in fluctuations. For example, patients taking IR-levetiracetam twice a day will

See page 1597

From the NYU Comprehensive Epilepsy Center (J.A.F.), New York, NY; and Strong Epilepsy Center (M.J.B.), University of Rochester Medical Center, Rochester, NY.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

typically have 3-fold fluctuations between minimum and maximum serum concentrations over the course of the day.[7] These data might suggest that drug-level fluctuations may be of less concern for levetiracetam. However, carbamazepine and oxcarbazepine fluctuations (when the IR formulation is used) can reduce tolerability at peak-dose times, suggesting that the clinical meaningfulness of any differences in formulation may be greater.[8]

There are differences in patients as well. Patients who have easily become seizure-free, and for whom once-daily dosing is likely to lead to improved adherence, will probably benefit from MR formulations and will be less disadvantaged by small differences between formulations.

Despite the potential concerns raised by this study, poor medication hygiene, including poor adherence, probably is a larger factor for efficacy and tolerability of AEDs than brand-to-generic switches. Also, a switch from IR formulations to MR, whether brand or generic, may cause substantial changes in Cmax and AUC that could destabilize a seizure-free patient. Clinicians should advise their patients to take their medications on the same schedule consistently, and in the same relation to food. Splitting pills that have not been designed to be cut will typically result in much greater differences than even the greatest generic–brand variations.

The old adage not to mess with success has a role. If a patient is seizure-free on a specific AED regimen, then it behooves the treating provider not to change that regimen unless there is a compelling reason to do so. If an MR-AED has a substantial likelihood of improving adherence or if there is a reasonable expectation that it will improve tolerability or efficacy, then the MR-AED should be tried. In most cases, the benefits of these improvements outweigh any concern over the variations in switching formulations.


## STUDY FUNDING

No targeted funding reported.


## DISCLOSURE

The Epilepsy Study Consortium pays Dr. French's university employer for her consultant time related to Acorda, Alexza, Anavex, BioPharm Solutions, Concert Pharmaceuticals, Eisai, GW Pharma, Marinus, Monteris, Nestle-Health Science, Neurelis, Novartis, Pfizer, Pfizer-Neusentis, Pronutria, Roivant, Sage, SciFluor, SK Life Sciences, Sunovion, Takeda, UCB Inc., Upsher Smith, Xenon Pharmaceuticals, and Zogenix. Dr. French has received grants and research funding from Acorda, Alexza, LCGH, Eisai Medical Research, Lundbeck, Pfizer, SK Life Sciences, UCB, Upsher-Smith, and Vertex. Dr. Berg reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

## REFERENCES


1. Ting TY, Jiang W, Lionberger R, et al. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: a field test of the FDA bioequivalence standard. Epilepsia 2015;56:1415–1424.
2. Privitera MD, Welty TE, Gidal BE, et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol Epub 2016 Feb 11.
3. Berg MJ, Diaz F, Bolger P, et al. Equivalence among generic AEDs (EQUIGEN): single-dose study. Presented at the 2014 Annual Meeting of the American Epilepsy Society; December 7, 2014; Seattle.
4. Johnson EL, Chang YT, Davit B, Gidal BE, Krauss GL. Assessing bioequivalence of generic modified-release antiepileptic drugs. Neurology 2016;86:1597–1604.
5. Krauss GL, Caffo B, Chang YT, Hendrix CW, Chuang K. Assessing bioequivalence of generic antiepilepsy drugs. Ann Neurol 2011;70:221–228.
6. Chen ML, Shah VP, Ganes D, et al. Challenges and opportunities in establishing scientific and regulatory standards for determining therapeutic equivalence of modified-release products: workshop summary report. Clin Ther 2010;32:1704–1712.
7. Leppik IE, Hovinga CA. Extended-release antiepileptic drugs: a comparison of pharmacokinetic parameters relative to original immediate-release formulations. Epilepsia 2013;54:28–35.
8. Steinhoff BJ, Wendling AS. Short-term impact of the switch from immediate-release to extended-release oxcarbazepine in epilepsy patients on high dosages. Epilepsy Res 2009;87:256–259.