Received: 12 May 2020 | Accepted: 5 June 2020

DOI: 10.1111/epi.16594

Epilepsia®

LETTER TO THE EDITOR

Misperceptions on the chance of seizure freedom with antiseizure medications after two failed trials

To the Editors:Kwan and Brodie's landmark article[1] was a significant step in our understanding of refractory epilepsy. The long-term data[2] and the work of others have helped to confirm that about one third of people with epilepsy will continue to have seizures despite the use of antiseizure medications (ASMs). However, the way the results were reported has led to persistent confusion over the implications for the care of individual patients. This article is commonly cited as demonstrating that the chance of seizure freedom after failing two ASMs is 5% or less; this is wrong. This misperception has become so common that it has even been included in the work of highly respected academics in prestigious journals.[3–6] A recent advertisement for a vagus nerve stimulator attached to the cover of *Epilepsy Currents*, the official journal of the American Epilepsy Society, stated that "after two medications have failed, the chance of a third medication failing is 95%." This error prompted us to write this letter to help dispel the myth.

The 5% number comes from the data that <5% *of the total study cohort* achieved at least 1 year of seizure freedom with additional drug trials after failing the first two ASMs. This is misleading when considering the impact on individual patients. As reported in the most recent follow-up study,[2] the percent of patients who became seizure-free when undergoing a third drug trial after failing two prior ones was *23.6%*. Even the sixth ASM trial led to seizure freedom in 14% (6 of 43). Other recent work has supported this conclusion. One study found that 31% of 403 patients ≥16 years of age having failed at least two ASMs due to inefficacy were in continuous seizure freedom for at least 1 year at the end of the observation period.[7] Similarly, a prospective trial of adults with focal epilepsy showed that 11.8% (per protocol) to 17.4% (intention to treat) became seizure-free with the third ASM trial.[8]

This should not diminish the importance of early referral to a comprehensive epilepsy center after failing two ASMs for definitive diagnosis and to begin evaluation for potentially curative epilepsy surgery, as early surgery in carefully selected patients has been proven to be dramatically more effective than continued medical treatment for obtaining seizure freedom.[9] Our concern is that the use of this misleading statistic when promoting alternatives to ASMs serves to discourage continued medication trials. The rates of long-term seizure freedom with neurostimulation therapies are <20%; thus in nonlesional, multifocal, or otherwise less-than-ideal surgical candidates, additional ASM trials may be advised before surgery. More concerning would be promoting a sense of nihilism, leading patients and clinicians to abandon further medication trials, even in patients for whom alternatives are limited. This would deny a small but significant proportion of people with epilepsy the opportunity for sustained seizure freedom, and the resulting benefits to survival[10] and quality of life.

CONFLICT OF INTEREST

Dr Blond and Dr Mattson have no conflicts of interest relevant to this letter to the editor. Dr Hirsch has received research support to Yale University for investigator-initiated studies from Eisai, Proximagen, and Sunovion; consultation fees for advising from Aquestive, Ceribell, Marinus, Medtronic, Monteris, Neuropace, and UCB; royalties for authoring chapters for *UpToDate-Neurology*, and from Wiley for co-authoring the book "Atlas of EEG in Critical Care," by Hirsch and Brenner; and honoraria for speaking from Neuropace. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
2. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
3. Miller JW, Hakimian S. Surgical treatment of epilepsy. Continuum (Minneap Minn). 2013; 19:730–42.
4. Englot DJ. Continued medical management of drug-resistant epilepsy: implications for surgical consideration. Epilepsia. 2016;57:1525–6.
5. McDonald TJW, Cervenka MC. Ketogenic diets for adults with highly refractory epilepsy. Epilepsy Curr. 2017;17:346–50.
6. Green SF, Nguyen P, Kaalund-Hansen K, Rajakulendran S, Murphy E. Effectiveness, retention, and safety of modified ketogenic diet in adults with epilepsy at a tertiary-care centre in the UK. J Neurol. 2020;267:1171–8.
7. Choi H, Hayat MJ, Zhang R, Hirsch LJ, Bazil CW, Mendiratta A, et al. Drug-resistant epilepsy in adults: outcome trajectories after failure of two medications. Epilepsia. 2016;57:1152–60.
8. Mula M, Zaccara G, Galimberti CA, Ferrò B, Canevini MP, Mascia A, et al. Validated outcome of treatment changes according to International League Against Epilepsy criteria in adults with drug-resistant focal epilepsy. Epilepsia. 2019;60:1114–23.
9. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307:922–30.
10. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10:961–8.

Received: 5 June 2020 | Accepted: 11 June 2020

DOI: 10.1111/epi.16604

Epilepsia®

LETTER

Cannabidiol antiseizure activity and its interactions with clobazam: "It's déjà vu all over again" Yogi Berra

To the Editor:

In "Arrowsmith,"[1] published in 1925, Sinclair Lewis writes about the corrupting influence of commercial interests on medicine and science. In 1980, in a commentary entitled "The New Medical-Industrial Complex" by Arnold S. Relman, the then editor of *The New England Journal of Medicine*, he asserted: "The private health care industry is primarily interested in selling services that are profitable."[2]

Bialer and Perucca[3] have published a meta-analysis to address an issue that was well known before the publication of the articles in the meta-analysis, begging the question: Why wasn't this issue properly addressed by the original articles? The authors point out that one of the studies relied on an assumption regarding the enzyme-inhibiting effects of stiripentol, which the US Food and Drug Administration (FDA) accepted. "Apart from limitations related to the small sample sizes, this conclusion does not appear to have been supported by actual information on changes in plasma norclobazam (N-desmethylclobazam) in the trial patients" (page 6). Why, on earth, not? The meta-analysis concludes: "Overall, these results, with special reference to the meta-analyses conducted in patients off clobazam (CLB), provide a strong indication that cannabidiol (CBD) does have an antiseizure effect independent of its interaction with CLB. At the same time, however, *they confirm that the effect size across CBD dose groups is considerably greater among patients receiving concomitant CLB therapy (treatment ratios of 0.46-0.70) than among those receiving antiseizure medications other than CLB (treatment ratios of 0.71-0.92"* (page 5; emphasis added). The authors add: *"there is no question that the effect size observed in patients not taking CLB was quite modest"* (page 5) Why wasn't this made clear in the original papers? Why obfuscate instead of clarify? The authors end the paper with the following disclaimer: "Ultimately, definitive data on the independent antiseizure effects of CBD will require conduction of well-designed, adequately powered randomized-controlled trials exploring its efficacy in a clearly defined population of patients not receiving CLB" (page 7). The authors refer to the studies included in their meta-analysis as "pivotal trials." Why didn't these ostensibly "pivotal trials" address that fundamental question from the outset?

I recognize these are rhetorical questions because we know the answers. The scientific method has been subverted into a marketing tool. And, no, revealing conflicts of interest does not solve the problem of conflicts of interest, as evidenced above. In fact, these industry-sponsored studies don't even answer questions we are really interested in; their sole purpose is to attain government approval for medications. When studies are funded by independent funding agencies, we get head-to-head comparisons of medications, which answer questions relevant to patient management, for example: The United Kingdom Infantile Spasm Study study on Infantile Spasms;[4] Ethosuximide, valproate or lamotrigine for Absence epilepsy;[5] Levetiracetam vs Phenobarbital for neonatal seizures.[6] The Children's Oncology Group is a prime example of clinical questions being objectively answered using proper scientific methods with no vested interests. Sadly, most studies of medications for the treatment of epilepsy have not made any headway in addressing the concerns of Sinclair Lewis or Dr Relman.

CONFLICT OF INTEREST

None are relevant to this research activity.

Scientific Advisory Board, Teva Pharmaceuticals: Stereotypy and Other Repetitive Behaviors May 2019.

Editorial Boards: Pediatric Neurology; Journal of Child Neurology; Interdisciplinary.

Neurosurgery: Advanced Techniques and Case Management.

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ABPN Neurodevelopmental Disabilities Article Assessment Continuing Certification Pilot Committee.

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Lewis S. Arrowsmith. Harcourt US, Jonathan Cape (UK), publisher; 1925.
2. Relman AS. The New Medical-Industrial Complex. N Engl J Med. 1980;303:963–70.
3. Bialer M, Perucca E. Does cannabidiol have antiseizure activity independent of its interactions with clobazam? An appraisal of the evidence from randomized controlled trials. Epilepsia. 2020;61:1082–9. https://doi.org/10.1111/epi.16542
4. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol. 2005;4:712–7.
5. Tracy A, Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010;362:790–9.
6. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics 2020;145:e20193182. http://pediatrics.aappublications.org/content/early/2020/05/12/peds.2019-3182

Received: 11 June 2020 | Accepted: 11 June 2020

DOI: 10.1111/epi.16601

Epilepsia®

LETTER

Response: Cannabidiol antiseizure activity and its interactions with clobazam: "It's déjà vu all over again" Yogi Berra

Dear Editor,

When referring to our analysis of efficacy data from the pivotal regulatory trials of cannabidiol,[1] Dr Mandelbaum asks repeatedly "*why wasn't this issue properly addressed by the original articles?*."[2] Although we are not among the authors of the original articles, the short answer is that those studies were not designed, and were not powered, to assess the contribution of the interactions with clobazam to the antiseizure response to cannabidiol. Our self-initiated commentary/critical review, not funded by pharma industry, addressed the question posed in the title, namely "*Does cannabidiol have antiseizure activity independent of its interactions with clobazam?*." Previous studies had highlighted the relevance of these interactions as a cause of greater risk of adverse effects in patients receiving cannabidiol, and their likely contribution to improvement in seizure control in these patients. However, any therapeutic benefit derived from cannabidiol per se has remained uncertain, and has even been questioned.[3] Resolving the uncertainty concerning the independent therapeutic action of cannabidiol in epilepsy was the primary goal of our commentary.

A meta-analysis was needed to address the issue, and we believe that the data shown in our article provide "*the best clinical evidence to date that cannabidiol exerts therapeutic effects in patients with epilepsy that are independent of its interactions with clobazam*," even though effect size in the absence of clobazam comedication was modest.[1] We agree with D. Mandelbaum that the original publications could have highlighted more explicitly the limitations that we discussed in our commentary. The key point, however, is that placebo-controlled regulatory trials are designed to obtain a marketing license, and not to inform on the relative value of a medicine in everyday clinical practice.[4] We agree that the comparative role of novel treatments should be assessed in independent, randomized, flexible-dose head-to-head trials in the population of interest. Governmental institutions and other funding agencies should do more to facilitate the implementation of these trials.

ACKNOWLEDGMENTS

This work was not supported by any funding source.

CONFLICTS OF INTEREST

MB received speaker's or consultancy fees from Alkaloid, Boehringer Ingelheim, Medison, and US WorldMeds. EP received speaker's or consultancy fees from Amicus Therapeutics, Arvelle, Biogen, Eisai, GW Pharma, Intas Pharmaceuticals, Laboratorios Bagò, Sanofi, Sun Pharma, UCB Pharma, and Xenon Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Bialer M, Perucca E. Does cannabidiol have antiseizure activity independent of its interactions with clobazam? An appraisal

of the evidence from randomized controlled trials. Epilepsia. 2020;61:1082–9.
2. Mandelbaum D. Cannabidiol antiseizure activity and its interactions with clobazam: Cannabidiol antiseizure activity and its interactions with clobazam: "It's déjà vu all over again" Yogi Berra. Epilepsia, this issue.
3. Groeneveld GJ, Martin JH. Parasitic pharmacology: a plausible mechanism of action for cannabidiol. Br J Clin Pharmacol. 2020;86:189–91.
4. Perucca E, Wiebe S. Not all that glitters is gold: A guide to the critical interpretation of drug trials in epilepsy. Epilepsia Open. 2016;1:9–21.

Received: 13 June 2020 | Accepted: 17 June 2020

DOI: 10.1111/epi.16607

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LETTER

Cannabidiol efficacy and clobazam coadministration: Where do we stand now?

To the Editor

In this issue of *Epilepsia*, two articles deal with the debated relationship between cannabidiol (CBD) efficacy and concomitant clobazam (CLB) use.[1,2] The differences and similarities of these studies deserve some comments to adequately appreciate their strengths and limits.

The first review[1] is a critical appraisal of publicly available analyses of seizure outcomes on CBD treatment as presented by the applicant and provided by the European Medicines Agency (EMA) Assessment Report.[3] Data from the four pivotal randomized-controlled trials (RCTs) were first analyzed independently using negative binomial regression for the primary efficacy outcome of change in baseline seizure frequency, and then combined using a stratified fixed-effects meta-analysis. Results were presented as treatment ratios (placebo/CBD) rather than absolute changes or relative reductions in seizure frequency. Only the meta-analysis for patients not on CLB co-medication was considered, preventing any comparison with CLB-On cohort. The treatment ratio for combined CBD dose (10 + 20 mg/kg/day) vs placebo was 0.85 (P = .023). The difference over placebo did not reach statistical significance in the individual dose groups.[1]

The second work is a systematic review with aggregate data meta-analysis of the four RCTs, accompanied by subgroups analyses according to CLB status.[2] The percentages of patients who had at least 50% reduction in seizure frequency during the treatment period were 29.1% in the CBD arm and 15.7% in the placebo group among patients not taking CLB, with a risk ratio of 1.80 (95% confidence interval 1.12-2.90; P = .015). The effect size of CBD treatment over placebo in CLB-On patients was similar to that observed in CLB-Off patients and reached statistical significance at both the 10 and 20 mg/kg/day doses. This methodology allowed evaluation of weight or contribution of each study toward the overall summary results and quantification of the degree of heterogeneity between trials and across subgroups.[2] Although the responder rate was a key secondary outcome for all trials considered, its use is recommended as primary end point by the EMA's guidelines for clinical investigations of medicines in epileptic disorders.[4] Seizure response might be more appropriate than seizure reduction in evaluating the potential overall impact of CLB. Of interest, the paradoxical increases in seizure frequency observed in a subset of CLB-Off patients with Lennox-Gastaut syndrome attenuated the response in change in the seizure count analysis, without affecting or having little impact on the ≥50% responder rate.[3]

Both studies pooled together data from trials performed in two different epileptic conditions.[1,2] The RCTs overall met the criteria for meta-analytic combination due to sufficient similarity in designs, treatment protocols, method of seizure frequency assessment, and outcomes. Structured meta-analytic approach increases the statistical power to detect treatment effects within subgroups.[5] Nonetheless, the lack of randomization for CLB status represents one main pitfall and may have introduced potential confounders like the degree of baseline severity and refractoriness of the subgroups.

So far, this is the best available clinical evidence that CBD has antiseizure activity independent of its interaction with CLB. The open question remains whether and, mainly, to what extent CBD efficacy is enhanced by concomitant CLB administration.[6,7]

CONFLICTS OF INTEREST

This study was not funded. SL has no conflict of interest. FB acted as a consultant for Eisai. ET received speaker's honoraria from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals Inc, LivaNova, and Novartis; consultancy funds from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, GW Pharmaceuticals, Sunovion Pharmaceuticals Inc, and Novartis; and directorship funds from Neuroconsult GmbH. ET's Institution received grants from Biogen, Red Bull, Merck, UCB, European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung outside the submitted work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Bialer M, Perucca E. Does cannabidiol have antiseizure activity independent of its interactions with clobazam? An appraisal of the evidence from randomized controlled trials. Epilepsia. 2020; 61(6):1082–9.
2. Lattanzi S, Trinka E, Striano P, Zaccara G, Del Giovane C, Nardone R, et al. Cannabidiol efficacy and clobazam status: a systematic review and meta-analysis. Epilepsia. 2020;61:1090–8.
3. European Medicines Agency. Assessment Report: Epidiolex. International non-proprietary name: Cannabidiol. Available from https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf. Accessed June 2020.
4. European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-epileptic-disorders-revision-2_en.pdf Accessed June 2020.
5. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet. 2005;365:176–86.
6. Lattanzi S, Brigo F, Trinka E, Zaccara G, Striano P, Del Giovane C, et al. Adjunctive cannabidiol in patients with dravet syndrome: a systematic review and meta-analysis of efficacy and safety. CNS Drugs. 2020;34:229–41.
7. Lattanzi S, Brigo F, Cagnetti C, Trinka E, Silvestrini M, et al. Efficacy and safety of adjunctive cannabidiol in patients with Lennox-Gastaut Syndrome: a systematic review and meta-analysis. CNS Drugs. 2018;32:905–16.

Received: 15 June 2020 | Accepted: 17 June 2020

DOI: 10.1111/epi.16606

Epilepsia®

LETTER

Epilepsy gene panel yield and impact on outcomes for adults with unexplained seizures

To the Editors:We read with great interest the article entitled "Utility of Genetic Testing for Therapeutic Decision-Making in Adults With Epilepsy" by Johannesen and colleagues, investigating 200 patients with gene panels over 6 years.[1] Their work achieved the same diagnostic yield as a smaller cohort published by us last year.[2] Both studies had similar study populations, consisting of adults with epilepsy, mostly accompanied by intellectual disability and medically refractory seizures.

Altogether, these two studies have found a genetic cause in 60 of 264 patients tested (22.7%). One-third of these adult patients were diagnosed with *SCN1A*-related seizures.

Further analysis of the data from both studies allows us to speculate whether other clinical findings may have influenced the diagnostic yield for these patients. Although neither study required early onset of seizures for molecular investigation, 49 of 60 (81.7%) had seizures starting before or at 36 months. Thus, seizure onset before or at 36 months is likely a turning point for caregivers and clinicians seeking to end their diagnostic odyssey.

The annual incidence of monogenic epilepsies starting before 3 years of age is one per 2120 live births. Data extrapolation indicates that 10-50 per 100 000 individuals will need an adult neurologist due to childhood onset monogenic epilepsies remaining active throughout their lives.[3,4] Considering that most grownups seen in adult epilepsy clinics were not investigated in childhood with the genomic technology available today, the work from Johannesen and colleagues demonstrates the utility of molecular analysis of adults with unexplained seizures.

It has become clear that Dravet patients will benefit from a molecular diagnosis at any stage. However, there are other forms of genetic epilepsies whose late diagnosis can have therapeutic implications, such as GLUT1 deficiency, as beautifully demonstrated by Johannesen et al.[1]

Furthermore, molecular diagnosis may improve outcomes by the screening of gene-specific potential comorbidities. For instance, a diagnosis of *PURA*-related neurodevelopmental disorder (found in three of 60 adult patients from those two cohorts) should prompt an evaluation of cardiac, urogenital defects, and endocrine disorders.[5] Ultimately, these additional investigations could prevent morbidity related to *PURA*-related neurodevelopmental disorder.

It should be pointed out that even after being tested with most commercially available epilepsy gene panels, >75% of adult patients will not have a diagnosis. It is also worthwhile to mention that interpretation of variants of unknown significance in institutionalized adults can be challenging, as first-degree relatives are often not available for these patients.

Given that the genetic basis for many adults with unexplained seizures is still unsolved, it would be interesting to learn whether these patients could benefit more from distinct diagnostic approaches. Copy number variants and coding exon analysis are not enough to narrow the current diagnostic gap.[1,2,6] Whole-genome sequencing is one strategy, despite the variant-interpretation challenges. Target sequencing panels with single molecule molecular inversion probes (smMIPs) and finally brain tissue transcriptome analysis with total RNA sequencing are emerging technologies that are providing answers to a number of previously unsolved cases.[7,8]

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Johannesen KM, Nikanorova N, Marjanovic D, et al. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. Epilepsia. 2020;61(6):1234–9.
2. Borlot F, de Almeida BI, Combe SL, Andrade DM, Filloux FM, Myers KA. Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability. Epilepsia. 2019;60:1661–9.
3. Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142:2303–18.
4. Lewis-Smith D, Ellis CA, Helbig I, Thomas RH. Early-onset genetic epilepsies reaching adult clinics. Brain. 2020;143:1–6.
5. Reijnders MRF, Leventer RJ, Lee BH, et al. PURA-related neurodevelopmental disorders. In: Adam MP, Ardinger HH, Pagon RA, eds. GeneReviews. Seattle (WA): University of Washington; 1993–2020.
6. Borlot F, Regan BM, Bassett AS, Stavropoulos DJ, Andrade DM. Prevalence of pathogenic copy number variation in adults with pediatric-onset epilepsy and intellectual disability. JAMA Neurol. 2017;74:1301–11.
7. Ye Z, McQuillan L, Poduri A, et al. Somatic mutation: the hidden genetics of brain malformations and focal epilepsies. Epilepsy Res. 2019;155:160161.
8. Gonorazky HD, Naumenko S, Ramani AK, et al. Expanding the boundaries of RNA sequencing as a diagnostic tool for rare mendelian disease. Am J Hum Genet. 2019;104:466–83 [published correction appears in Am J Hum Genet. 2019;104:1007].

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1. Blümcke, Ingmar, et al. "Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy." *Epileptic Disorders* 21.2 (2019): 129-140.

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