First-line levetiracetam versus enzyme-inducing antiseizure medication in glioma patients with epilepsy

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RESEARCH ARTICLE

First-line levetiracetam versus enzyme-inducing antiseizure medication in glioma patients with epilepsy

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Abstract

Objective: This study aimed to directly compare the effectiveness of first-line monotherapy levetiracetam (LEV) versus enzyme-inducing antiseizure medications (EIASMs) in glioma patients.

Methods: In this nationwide retrospective observational cohort study, Grade 2–4 glioma patients were included, with a maximum duration of follow-up of 36 months. Primary outcome was antiseizure medication (ASM) treatment failure for any reason, and secondary outcomes were treatment failure due to uncontrolled seizures and due to adverse effects. For estimation of the association between ASM treatment and ASM treatment failure, multivariate cause-specific cox proportional hazard models were estimated, adjusting for potential confounders.

Results: In the original cohort, a total of 808 brain tumor patients with epilepsy were included, of whom 109 glioma patients were prescribed first-line LEV and 183 glioma patients first-line EIASMs. The EIASM group had a significantly higher risk of treatment failure for any reason compared to LEV (adjusted hazard ratio [aHR] = 1.82, 95% confidence interval [CI] = 1.20–2.75, $p = .005$). Treatment failure due to uncontrolled seizures did not differ significantly between EIASMs and LEV (aHR = 1.32, 95% CI = .78–2.25, $p = .300$), but treatment failure due to adverse effects differed significantly (aHR = 4.87, 95% CI = 1.89–12.55, $p = .001$).

Significance: In this study, it was demonstrated that LEV had a significantly better effectiveness (i.e., less ASM treatment failure for any reason or due to adverse effects) compared to EIASMs, supporting the current neuro-oncology guideline recommendations to avoid EIASMs in glioma patients.

KEYWORDS

antiepileptic drug, brain tumor, glioma, levetiracetam, retention rates, seizure, treatment failure

1 | INTRODUCTION

Clinical management of seizures is a vital aspect in the disease trajectory of many patients with a brain tumor, especially patients with glioma. Antiseizure medication (ASM) treatment is generally advised after a first seizure has occurred.[1] However, with about 30 different types of ASMs to choose from, ASM selection can be complicated.[2,3] There is a general lack of randomized controlled trials (RCTs) in brain tumor-related epilepsy to help guide clinicians in their choice. Only two small ASM RCTs have been conducted in brain tumor patients with epilepsy, comparing levetiracetam (LEV) with pregabalin and LEV with phenytoin (PHT).[4,5] In both studies, LEV showed good efficacy and tolerability,[4,5] but due to the small sample sizes, these RCTs cannot provide a definitive answer as to whether LEV is the preferred ASM in brain tumor patients. A recent large retrospective observational study compared first-line LEV with valproic acid (VPA) in glioma patients and showed LEV has a more favorable efficacy, whereas the two ASMs have a similar level of toxicity.[6] An extensive longitudinal cohort study in non-brain tumor-related epilepsy (BTRE) patients, spanning ASM treatment over 4 decades, could not establish an improved tolerability of second-generation (e.g., LEV and pregabalin [PGB]) compared to first-generation ASMs (e.g., VPA and carbamazepine [CBZ]).[7] Although expert opinion argues for the improved tolerability of newer ASMs,[8–10] this can be disputed.[6,7] Prescribing enzyme-inducing antiseizure medications (EIASMs), such as (older) agents like PHT, phenobarbital (PB), CBZ, and oxcarbazepine (OXC) in glioma patients is generally discouraged.[1,8] This is mainly due to their metabolization in the liver and induction of cytochrome P450-dependent hepatic enzymes, thereby increasing their own metabolism and that of systemic agents frequently prescribed in glioma patients.[8] The most commonly prescribed systemic antitumor therapies in glioma patients are PCV (combination of procarbazine, CCNU [lomustine], and vincristine), single-agent lomustine, and temozolomide.[1] Whereas EIASMs affect pharmacokinetics of lomustine and vincristine, this is not true for procarbazine, bevacizumab, and temozolomide.[8,11] Because only a minority of glioma patients treated with ASMs receive lomustine and/or vincristine, whereas the majority of glioma patients are prescribed temozolomide,[6,12,13] the conventional strategy that EIASMs should be discouraged in all glioma patients seems a bit extreme. Despite the possible interactions between EIASMs and antitumor treatment in glioma patients with epilepsy, there are currently limited data that discourage the use of EIASMs due to lack of effectiveness compared to non-EIASMs. Effectiveness encompasses both efficacy and tolerability of the treatment and is reflected in its retention rate or its inverse treatment failure rate for any reason (i.e., mainly inefficacy or intolerable adverse effects).[14] The International League Against Epilepsy recommends the retention rate (or its inverse) as primary outcome for clinical studies in epilepsy research.[15]

Key Points

- Levetiracetam had favorable tolerability compared to enzyme-inducing antiseizure medications.
- All different enzyme-inducing antiseizure medications had considerably worse tolerability than levetiracetam.
- Levetiracetam and enzyme-inducing antiseizure medications had similar efficacy.

A systemic review showed the EIASM PHT, together with LEV and PGB, had the highest efficacy in glioma patients. However, of all ASMs studied in the systematic review, PHT and PB had the highest treatment failure due to adverse effects.[16] Although some EIASMs may be effective in the treatment of brain tumor-related epilepsy, it is unclear whether these agents are more effective than the most commonly prescribed ASM in the glioma population, LEV. This retrospective observational study aimed to directly compare the effectiveness of first-line monotherapy LEV versus EIASMs in glioma patients.

2 | MATERIALS AND METHODS

2.1 | Study population and procedures

This study population is a subset of a previously published study by members of the Italian League Against Epilepsy Brain Tumor-Related Epilepsy Study Group. A more detailed description of the methodology has been described elsewhere.[17] In short, a nationwide, multicenter retrospective observational cohort study was conducted, and all 35 centers adhering to the study group were invited to participate on a voluntary basis. Consecutive patients with a histologically or radiologically diagnosed Grade 2–4 glioma ([anaplastic] astrocytoma, [anaplastic] oligoastrocytoma, [anaplastic] oligodendroglioma, or glioblastoma), seen by a physician and followed for at least 1 month between January 1, 2010 and December 31, 2011, with seizures in close temporal association with the tumor diagnosis, and first-line treatment with levetiracetam or an EIASM (CBZ,

OXC, PB, or PHT) were included. Patients with a history of non-BTRE were excluded. Medical charts of patients were examined to extract baseline sociodemographic data, tumor characteristics, antitumor treatment information, seizure characteristics, and ASM treatment information. The study was approved by the ethical committee of Regina Elena National Cancer Institute.

2.2 | Outcomes

Primary outcome was time to treatment failure, which was defined as the time from initiation of first-line ASM monotherapy until treatment failure, with a maximum follow-up duration of 36 months. ASM treatment failure was defined as discontinuation or the add-on of an additional ASM because of intolerable adverse effects, uncontrolled seizures, or other reasons. Secondary outcome was time to treatment failure with regard to specific reasons of treatment failure (i.e., uncontrolled seizures, adverse effects, and other reasons).

2.3 | Statistics

Multivariate Cox proportional hazard models were estimated to study the association between the risk factor ASM treatment and treatment failure, adjusted for potential confounders. In case of cause-specific reasons for treatment failure, these specific reasons should be handled as separate competing risks. Hence, a patient who experiences treatment failure due to uncontrolled seizures can no longer experience treatment failure due to adverse effects on their first-line ASM. Two competing risk models were estimated: (1) treatment failure due to uncontrolled seizures (event of interest) versus treatment failure due to adverse effects and other reasons; and (2) treatment failure due to adverse effects (event of interest) versus treatment failure due uncontrolled seizures and other reasons. The proportional hazards assumption was checked based on Schoenfeld residuals, nonlinearity by Martingale residuals, and influential observations by deviance residuals. The following baseline covariates, which were regarded as potential confounders, were selected based on pre-existing literature and included in the multivariate Cox proportional hazard models: age, sex, tumor grade, surgical resection, tumor involvement in the temporal and frontal lobe, Karnofsky performance status, size of epilepsy center, seizure type, and ASM started prophylactically. Data were analyzed using SPSS version 25.0. A p-value of $<.05$ was considered statistically significant.

3 | RESULTS

The original study population consisted of 808 patients.[17] Within this cohort, $n = 292$ (36%) glioma patients were recruited who used LEV or EIASMs as first-line ASM. Of these 292 patients, $n = 109$ (37%) patients used LEV, $n = 41$ (14%) CBZ, $n = 49$ (17%) OXC, $n = 74$ (25%) PB, and $n = 19$ (7%) PHT. Baseline cohort characteristics of patients on first-line monotherapy LEV or EIASMs are reported in Table 1. Patients in the LEV versus the EIASM group significantly more often had a high-grade glioma (83% [91/109] vs. 68% [124/183], $p = .013$) and were treated in large epilepsy centers (94% [103/109] vs. 84% [153/183], $p = .006$), but less often had surgical resection (40% [44/109] vs. 57% [104/183], $p = .005$) at baseline.

3.1 | Time to treatment failure for LEV versus EIASMs

Of the patients who were prescribed first-line monotherapy LEV, 30% (33/109) showed treatment failure for any reason in the 36-month follow-up period, whereas this was 68% (125/183) for patients prescribed EIASMs. At 6 and 12 months, treatment failure for any reason was 20% (22/109) and 26% (28/109) for LEV versus 34% (63/183) and 47% (86/183) for EIASMs, respectively. Patients prescribed EIASMs had a significantly higher risk of treatment failure for any reason compared to LEV (adjusted hazard ratio [aHR] = 1.82, 95% confidence interval [CI] = 1.20–2.75, $p = .005$; Table 2).

The main reason for treatment failure in the 36-month follow-up period for LEV and EIASMs was uncontrolled seizures (18% [20/109] vs. 36% [65/183] of patients), followed by adverse effects (6% [6/109] vs. 22% [41/183] of patients), and other reasons (6% [7/109] vs. 10% [19/183] of patients). Patients prescribed EIASMs did not have a significantly higher risk of treatment failure due to uncontrolled seizures compared to LEV (aHR = 1.32, 95% CI = .78–2.25, $p = .300$; Table S1), but had a higher risk of treatment failure due to adverse effects (aHR = 4.87, 95% CI = 1.89–12.55, $p = .001$; Table S2), whereas the number of events was too low to estimate the aHR for treatment failure due to other reasons. Percentages of treatment failure for any reason, due to adverse effects, due to uncontrolled seizures, and due to other reasons at 6, 12, and 36 months for LEV and the EIASMs separately (CBZ, OXC, PB, and PHT) are reported in Table 3. The number of events was too low to estimate the aHR of these different EIASMs compared to LEV for treatment failure.

TABLE 1 Demographic characteristics of the patients at baseline

Characteristics	Antiseizure medication treatment		
	LEV	EIASMs	*p*
Patients included, *n*	109	183	
Age, *n* (%)			.180
≤40 years	20 (18)	46 (25)	
>40 years	89 (82)	137 (75)	
Sex, *n* (%)			.100
Male	56 (51)	112 (61)	
Female	53 (49)	71 (39)	
Tumor grade and pathology, *n* (%)			.013
Grade 2 glioma	18 (17)	59 (32)	
Diffuse astrocytoma	8 (7)	27 (15)	
Oligodendroglioma	6 (6)	24 (13)	
Oligoastrocytoma	4 (4)	8 (4)	
Grade 3 glioma	34 (31)	46 (25)	
Anaplastic astrocytoma	17 (16)	19 (10)	
Anaplastic oligodendroglioma	6 (6)	16 (9)	
Anaplastic oligoastrocytoma NOS	11 (10)	11 (6)	
Grade 4 glioma			
Glioblastoma	57 (52)	78 (43)	
Surgical resection, *n* (%)			.005
Yes	44 (40)	104 (57)	
No, including biopsy	64 (59)	76 (42)	
Unknown	1 (1)	3 (2)	
Tumor located in the temporal lobe, *n* (%)			.339
Yes	33 (30)	46 (25)	
No	75 (69)	136 (74)	
Unknown	1 (1)	1 (1)	
Tumor located in the frontal lobe, *n* (%)			.908
Yes	49 (45)	81 (44)	
No	59 (54)	101 (55)	
Unknown	1 (1)	1 (1)	
Karnofsky performance status, *n* (%)			.256
≥70	81 (74)	139 (76)	
<70	25 (23)	32 (17)	
Unknown	3 (3)	12 (7)	
Size of epilepsy center, *n* (%)			.006
≥20	103 (94)	153 (84)	
<20	6 (6)	30 (16)	
Seizure type, *n* (%)			.483
Focal	57 (52)	92 (50)	
Focal to bilateral tonic–clonic[a]	42 (39)	81 (44)	
Unknown	10 (9)	10 (5)	
ASM started prophylactically, *n* (%)			.423
Yes	40 (37)	79 (43)	
No	59 (54)	95 (52)	
Unknown	10 (9)	9 (5)	

Abbreviations: ASM, antiseizure medication; EIASM, enzyme-inducing antiseizure medication; LEV, levetiracetam; *n*, number of patients; NOS, not otherwise specified.

[a]Patients had either solely focal to bilateral tonic–clonic seizures or both focal and focal to bilateral tonic–clonic seizures.

4 | DISCUSSION

In this retrospective observational cohort study, the effectiveness of first-line monotherapy LEV was compared to EIASMs as a group in glioma patients with epilepsy. We demonstrated that LEV had a significantly lower treatment failure for any reason versus EIASMs, meaning a more favorable effectiveness. This difference in effectiveness was (mainly) attributable to a better tolerability, whereas no significant differences were found between the two groups with regard to efficacy (i.e., treatment failure due to uncontrolled seizures). Treatment failure due to adverse effects at 36 months ranged from 11% to 26% between the different EIASMs, but all were considerably higher than LEV (6%). LEV has thus shown improved tolerability over EIASMs in glioma patients in our study. Our findings are in line with current guidelines in which LEV is considered one of the preferred first-line ASMs in glioma patients with epilepsy without a history of psychiatric disease (e.g., anxiety disorder).

Treatment failure (due to adverse effects) of EIASMs tended to be similarly high in other studies examining EIASMs in glioma patients. In a systematic review evaluating ASMs in glioma patients, the two ASMs with the highest treatment failure for any reason (64%, with unknown duration of follow-up) were CBZ and PB, which was similar in our study. The 12-month treatment failure due to adverse effects for CBZ was 26% versus 22% in our study, but remarkable is the high 12-month treatment failure due to adverse effects for PHT of 34% versus 5% in our study.[16] This might be explained by the relatively high treatment failure due to other reasons for PHT in our study, possibly reflecting

TABLE 2 Cause-specific HRs of time to treatment failure for any reason

	Treatment failure for any reason			
Parameter	**uHR (95% CI)**	***p***	**aHR (95% CI)**	***p***
ASM treatment				
LEV [ref]				
EIASMs	2.30 (1.57–3.38)	<.001	1.82 (1.20–2.75)	.005
Age	1.00 (.99–1.01)	.873	1.00 (.98–1.01)	.842
Sex				
Male [ref]				
Female	1.00 (.73–1.38)	.979	1.17 (.81–1.67)	.404
Tumor grade				
2 [ref]				
3	.62 (.41–.93)	.020	.84 (.53–1.33)	.453
4	.71 (.49–1.03)	.068	.81 (.51–1.27)	.355
Surgical resection				
No [including biopsy, ref]				
Yes	1.46 (1.06–2.01)	.021	1.21 (.84–1.74)	.317
Tumor involvement in the temporal lobe				
No [ref]				
Yes	.67 (.46–.99)	.042	.65 (.41–1.02)	.062
Tumor involvement in the frontal lobe				
No [ref]				
Yes	.90 (.66–1.23)	.502	.76 (.52–1.11)	.159
Karnofsky performance status				
≥70 [ref]				
<70	.83 (.53–1.29)	.403	.91 (.54–1.51)	.706
Size of epilepsy center				
≥20 [ref]				
<20	1.86 (1.22–2.83)	.004	1.94 (1.08–3.47)	.026
Seizure type				
Focal [ref]				
Focal to bilateral tonic–clonic[a]	.91 (.66–1.26)	.580	1.10 (.77–1.58)	.594
ASM started prophylactically				
No [ref]				
Yes	.97 (.70–1.34)	.866	.96 (.66–1.37)	.805

Abbreviations: aHR, adjusted HR; ASM, antiseizure medication; CI, confidence interval; EIASM, enzyme-inducing antiseizure medication; HR, hazard ratio; LEV, levetiracetam; ref, reference; uHR, unadjusted HR.

[a]Included either solely focal to bilateral tonic–clonic seizures or both focal and focal to bilateral tonic–clonic seizures.

discontinuation of the ASM due to interactions with systemic treatment.

In a previous large Dutch observational cohort study, first-line monotherapy LEV showed superior effectiveness compared to VPA in the glioma population. The difference in effectiveness between these two agents was attributable due to a difference in efficacy, whereas tolerability was similar, with treatment failure due to adverse effects at

TABLE 3 Percentages of treatment failure for the enzyme-inducing antiseizure medications at 6, 12, and 36 months

Reason for treatment failure	Antiseizure medications				
	LEV, $n = 109$	CBZ, $n = 41$	OXC, $n = 49$	PB, $n = 74$	PHT, $n = 19$
Treatment failure for any reason					
6 months, *n* (%)	22 (20)	10 (24)	13 (27)	28 (38)	12 (63)
12 months, *n* (%)	28 (26)	19 (46)	18 (37)	37 (50)	12 (63)
36 months, *n* (%)	33 (30)	32 (78)	26 (53)	51 (69)	16 (84)
Treatment failure due to uncontrolled seizures					
6 months, *n* (%)	13 (12)	1 (2)	6 (12)	10 (14)	6 (32)
12 months, *n* (%)	18 (17)	6 (15)	11 (22)	17 (23)	6 (32)
36 months, *n* (%)	20 (18)	15 (37)	17 (35)	25 (34)	8 (42)
Treatment failure due to adverse effects					
6 months, *n* (%)	5 (5)	7 (17)	6 (12)	15 (20)	1 (5)
12 months, *n* (%)	6 (6)	9 (22)	6 (12)	17 (23)	1 (5)
36 months, *n* (%)	6 (6)	10 (24)	8 (16)	21 (28)	2 (11)
Treatment failure due to other reasons					
6 months, *n* (%)	4 (4)	2 (5)	1 (2)	3 (4)	5 (26)
12 months, *n* (%)	4 (4)	4 (10)	1 (2)	3 (4)	5 (26)
36 months, *n* (%)	7 (6)	7 (17)	1 (2)	5 (7)	6 (32)

Abbreviations: CBZ, carbamazepine; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin.

12 months of 14% for LEV versus 15% for VPA.[6] Despite the Italian cohort from this study appearing to be relatively similar to the Dutch cohort, with newly diagnosed glioma patients prescribed first-line monotherapy ASM treatment, treatment failure due to adverse effects of LEV at 12 months differs considerably between the Dutch and Italian cohorts (14% vs. 6%, respectively).[6] This difference in tolerability of LEV between the cohorts is not entirely clear. There is a certain degree of subjectivity in attributing experienced adverse effects by patients to LEV, especially in glioma patients undergoing antitumor treatment. It might be that Dutch neuro-oncology professionals attribute more frequently experienced adverse effects to LEV (e.g., fatigue and somnolence) instead of the disease and antitumor treatment. If the suspicion arises that a medicine caused an adverse effect, the Naranjo scale can be used to assess the probability of the causality. The Naranjo scale is a 10-item questionnaire to assess causality for adverse drug reactions and can assist in whether changing the ASM treatment regimen is justified.[18]

Currently, guidelines in neuro-oncology discourage prescribing EIASMs in BTRE patients, because of their drug–drug interaction with certain chemotherapeutic agents and their supposed worse tolerability compared to newer ASMs such as LEV.[1,19] In a recent international survey, it was found that only approximately 5% of neuro-oncology clinicians view an EIASM as the first-choice ASM in brain tumor patients with mainly focal seizures, mainly bilateral tonic–clonic seizures, or most effective in reducing seizure frequency, and none of the clinicians viewed an EIASM as the best tolerated ASM.[20] Our data confirm that EIASMs significantly more often cause treatment failure due to adverse effects compared to LEV, whereas efficacy seems similar. The worse tolerability, drug–drug interactions, and high number of potential alternative ASMs make EIASMs in glioma patients less attractive treatment candidates that should be avoided. A commonly chosen equivalent first-choice ASM to LEV is lamotrigine (LTG) in BTRE patients.[20] The recent SANAD II study including $n = 990$ non-BTRE patients demonstrated inferiority of LEV compared to LTG and concluded that LTG should remain the first-line treatment for patients with focal epilepsy. Among other worse outcomes, LEV had significantly higher treatment failure for any reason and treatment failure due to adverse effects, but not treatment failure due to uncontrolled seizures.[21] Findings from non-BTRE studies are not necessarily directly applicable to BTRE patients, but these favorable results with regard to LTG warrant evaluating LTG in BTRE patients, especially given the lack of studies evaluating the efficacy of LTG in BTRE patients.[16]

4.1 | Limitations

Not all relevant data could be collected, hampering certain important analyses. For example, the date of chemotherapy and radiotherapy were missing, and therefore the estimates could not be adjusted for these relevant confounders in the Cox regression analyses. This also applies to date of death, hampering taking death into account as a competing event in a competing risk model. In addition, no detailed information was collected with regard to the specific adverse effects, so nothing can be said of what type of intolerable adverse effects seem to occur in glioma patients prescribed EIASMs. The type of intolerable adverse effects and data on whether the intolerable adverse effects improved after discontinuation of the ASM could have given more insight into the causality of the ASM and/or the interaction with other medication (e.g., chemotherapy) and the intolerable adverse effects. In addition, no data on titration and dosage at the time of treatment failure were collected. Titration rate can have a meaningful relationship with tolerability, which might have affected results. Despite the reasonable size of the entire cohort, several types of EIASMs had to be combined to perform meaningful analyses, given the small number of patients per different EIASM. Therefore, results largely apply to EIASMs as a group, although there are certainly differences between the individual EIASMs (e.g., OXC is only a weak enzyme-inducer). Primary prophylaxis of ASM in glioma patients is discouraged by international and national Italian neuro-oncology guidelines, including Glantz et al.,[22] Maschio et al.,[23] and Walbert et al.[24] Nonetheless, ASM primary prophylaxis was initiated in ~40% of patients in our study. This is in line with the findings from an international survey in which 50% of Italian neuro-oncology professionals reported prescribing ASMs solely as primary prophylaxis.[20] Unfortunately, due to the retrospective design of our study, the reasons behind the prescription of primary prophylaxis contrary to the guidelines are unclear; however, it is likely the tradeoff between the risk of adverse effects (nonmaleficence) and the benefit of preventing seizures (beneficence) was perceived by the treating physician as in favor of ASM primary prophylaxis. We do acknowledge current evidence for primary prophylaxis is minimal and faulty, and hopefully the ongoing SPRING (Prophylactic Levetiracetam Versus No Prophylactic ASM in Seizure-Naïve Glioma Patients) trial might elucidate this matter.[25] A relatively high number of patients were prescribed the barbiturate PB, which has been used for seizure control for >100 years, but is nowadays rarely prescribed as a first-line ASM in glioma patients in most countries.[6,16,20] PB was among the most frequently used ASMs during the early 2000s. Factors contributing to its widespread use were its low cost, its well-known safety profile, and ample experience among treating physicians in prescribing PB.[26–28]

5 | CONCLUSIONS

Our study supports the recommendation to avoid prescribing EIASMs in glioma patients. LEV is the most frequently prescribed (first-line) ASM in the glioma population, and given the available evidence, this seems justified. However, comparative efficacy RCTs in glioma patients are currently lacking, and trials comparing first-line LEV with other non-EIASMs (e.g., lacosamide or LTG) are warranted.

AUTHOR CONTRIBUTIONS

The study was designed by Pim B. van der Meer, Marta Maschio, Linda Dirven, Martin J. B. Taphoorn, and Johan A. F. Koekkoek. Data were curated by Pim B. van der Meer and Marta Maschio. Data-analyses were performed by Pim B. van der Meer. The original draft and subsequent versions of the manuscript were written by Pim B. van der Meer. All authors contributed to the interpretation of the results and critical revisions of the first and successive versions of the manuscript, and approved the final version of the manuscript. Pim B. van der Meer takes final responsibility for submitting the manuscript for publication and having full access to all data.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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