Approximately 75,000 primary brain tumors and 170,000 cerebral metastases are diagnosed each year in the US. Many types of intracranial tumors predispose patients to seizures. By the time of diagnosis, 20%–40% of patients with brain tumors have already had seizures, and significantly more will develop them after diagnosis depending upon tumor location, pathology, and treatment. Neurosurgical biopsy or resection can, at least transiently, further increase that risk.

Prophylactic use of postoperative AEDs in seizure-naïve patients is controversial. Seizures in the immediate postoperative period impede clinical assessment and can result in hypoxemia, cardiovascular instability, and transient increases in intracranial pressure. Long-term consequences of postoperative seizures may include chronic AED therapy, cognitive decline, and death. Even in the absence of overt complications, a single seizure may have a profoundly negative impact on quality of life.
example, by precluding a patient’s ability to drive and thus limiting independence. Conversely, prophylactic AEDs can cause serious adverse effects, interfere with the metabolisms of chemotherapies and corticosteroids, and, if ineffective, are a wasted expenditure. Guidelines remain unclear. The American Association of Neurology (AAN) recommends against routine prophylaxis for newly diagnosed tumors in seizure-naïve patients but leaves prophylaxis in the first postoperative week up to surgeon discretion. The AANS recommends against routine prophylaxis in the case of cerebral metastases but is notably silent on prophylaxis for other tumors. Survey data suggest that between 63% and 81% of US neurosurgeons prescribe AEDs postoperatively to seizure-naïve patients with brain tumors.

Multiple trials and meta-analyses have evaluated AED prophylaxis for patients with brain tumors and found no benefit of prophylaxis over control in the prevention of seizures. However, these studies have typically failed to address the efficacy of perioperative AED prophylaxis due to the inclusion of both surgical and nonsurgical patients. Furthermore, most of these meta-analyses have combined data from widely different periods of treatment and follow up (from 3 days to 12 months), making it difficult to assess the true efficacy of common clinical practices.

The objective of this meta-analysis was to evaluate the impact of perioperative AED prophylaxis on short- and long-term seizure incidence among patients undergoing brain tumor surgery. It is the first meta-analysis to focus exclusively on AED prophylaxis among patients undergoing brain tumor surgery.

Methods

Study Design

In accordance with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) and AMSTAR (A Measurement Tool to Assess Systematic Reviews) guidelines, a protocol for this meta-analysis was developed and submitted to the PROSPERO international prospective registry of systematic reviews prior to implementation of the literature review. The defined goal of the meta-analysis was to pool data from randomized controlled trials (RCTs) to evaluate the efficacy of AED prophylaxis in the prevention of seizures among seizure-naïve brain tumor patients undergoing craniotomy. Prior meta-analyses pooled short- and long-term seizure outcomes. To address this methodological issue, the decision was made in the present study to pool data on short-term seizure incidence (within the first postoperative week) and long-term (total) seizure incidence separately.

Search Strategy

A systematic literature search of PubMed/MEDLINE, Embase, and Cochrane Central Register of Controlled Trials was conducted using the following terms: “brain tumor,” “brain tumour,” “craniotomy,” “craniotomies,” “neurosurgery,” “neurosurgeries,” “cerebral tumor,” “cerebral tumour,” “brain neoplasm,” “brain cancer,” “glioma,” “glioblastoma,” “GBM,” “cerebral metastasis,” “cerebral metastases,” “meningioma,” “prophylactic,” “antiepileptic,” “anticonvulsant,” “prophylaxis,” “AED,” “phenytoin,” “phenobarbital,” “divalproex,” “valproic acid,” “carbamazepine,” “levetiracetam,” “etiracetam,” “gabapentin,” “lamotrigine,” and “topiramate.” Terms were combined using appropriate Boolean operators. No limitations in language, publication type, or publication period were applied. Gray literature (print and electronic works not published by commercial publishers, including but not limited to doctoral dissertations, research reports, and conference proceedings) was further queried by performing similar searches in clinicaltrials.gov and the System for Information on Gray Literature in Europe (SIGLE).

Selection Criteria

Following elimination of duplicates, records were screened using titles and abstracts to identify publications that potentially addressed the subject of AED prophylaxis for patients with brain tumors undergoing craniotomy. Successfully screened studies were subsequently evaluated on the basis of prespecified inclusion and exclusion criteria. Only RCTs (with a control group consisting of either a placebo or no treatment arm) were included. At least a portion of patients had to have undergone craniotomy, at least a portion had to have been seizure-naïve prior to surgery (no preoperative seizure history), and seizure incidence had to be an outcome. Studies were excluded if craniotomy patient data were not extractable (in studies with patients who underwent craniotomy and patients who did not undergo craniotomy), if tumor patient data were not extractable (in studies with patients undergoing craniotomy for a wide range of indications), or if seizure-naïve patient data were not extractable (in studies with a combination of seizure-naïve and nonseizure-naïve patients). Two reviewers (E.F.J. and T.S.H.) independently performed literature searches and decided which records were eligible for inclusion. A third reviewer (B.E.Y.) mediated any disagreements.

Data Extraction

Two reviewers (E.F.J. and T.S.H.) independently extracted previously specified study data (study setting, patient population demographics, participant demographics and characteristics, dose/frequency and duration of AED prophylaxis, conditions of control arm, duration of follow up, seizure incidence within the first postoperative week, seizure incidence following first postoperative week, incidence of adverse effects) and evaluated the quality of each study using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials.

Statistical Analysis

Relative risk (risk ratios, RR) for early seizures and total seizures associated with AED prophylaxis compared with control were calculated with 95% confidence intervals (CIs) for each included RCT. Data from included trials were combined using the Mantel-Haenszel random-effects model to assess the pooled relative risk of seizures within the first postoperative week (short-term) and overall (short- and long-term). For each outcome, 95% CIs and
2-sided p values were calculated. A prespecified p value < 0.05 was considered statistically significant. Heterogeneity was evaluated using the I² statistic. An I² value > 40% was prespecified to be indicative of substantial heterogeneity. Publication bias was evaluated using funnel plots and Egger’s test. All analyses were conducted using Stata (version 14.0 SE). Forest plots and funnel plots were reformatted using Cochrane Review Manager.

Results

Search Results

Four thousand eight hundred thirty-three nonduplicate records were identified by an electronic search of PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, SIGLE, and clinicaltrials.gov, as well as a manual reference search (Fig. 1). Four thousand five hundred eighty-six records were excluded on the basis of title and abstract because they were not relevant to the subject of AED prophylaxis for brain tumor surgery (see Appendix A for a full list of negatively screened records). The 247 remaining full-text articles were reviewed according to inclusion/exclusion criteria. Two hundred twenty-four records were excluded because they were not RCTs, 7 because they reported preliminary data that were subsequently published in another included study, 1 because data on patients with brain tumors could not be extracted, 1 because data on seizure-naïve patients could not be extracted, 2 because data on patients who underwent craniotomy could not be extracted, and 8 because full-text articles were not available (an attempt was made to contact each corresponding author; see Appendix B for the full list of excluded articles and rationale for exclusion). Four studies ultimately met criteria for qualitative and quantitative synthesis (Table 1).

Description of Included Studies

Two studies (North et al. and Lee et al.) included patients undergoing supratentorial craniotomy for a range of indications from which the data on patients with brain tumors could be extracted. One study (Franceschetti et al.) included patients with and without prior seizures, but data on seizure-naïve patients were readily extractable because these patients had been randomized separately. The final study (Wu et al.) included only seizure-naïve patients with brain tumors.
Two of the studies (Lee et al. and Franceschetti et al.) included patients with gliomas, meningiomas, and metastases, while one study (North et al.) also included patients with sellar tumors, and the last (Wu et al.) included only patients with gliomas and metastases. Two of the studies (North et al. and Lee et al.) were placebo controlled, while the control group in the other two (Franceschetti et al. and Wu et al.) received no treatment. The AED arm in three of the studies (North et al., Lee et al., and Wu et al.) received comparable doses of phenytoin; in the fourth study (Franceschetti et al.), a portion of the AED arm received phenobarbital. The duration of treatment and follow up varied considerably: 1) 3 days of prophylaxis and 3 days follow up (Lee et al.); 2) 7 days of prophylaxis plus AED taper and 12 months of follow up (Wu et al.); 3) 12 months of prophylaxis and 12 months of follow up (North et al.); and 4) variable duration of prophylaxis and follow up from approximately 6 to 18 months (Franceschetti et al.). Patient characteristics were roughly equivalent across studies and between both arms of each study (detailed patient characteristics of both arms were available for all studies except Franceschetti et al.; Table 2).

Assessment of Study Quality

Study quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Fig. 2).14

In the allocation category (randomization and allocation concealment), all four studies were at unclear risk of bias because methods of randomization and allocation concealment were not reported in detail.

For blinding, two studies (North et al. and Lee et al.) were at low risk of bias because satisfactory methods of blinding were reported. One study (Wu et al.) was at high risk of performance bias because participants and personnel were unblinded but at low risk of detection bias because seizure assessors were blinded. One study (Franceschetti et al.) was at unclear risk of bias because methods of blinding were not reported in detail.

Regarding incomplete outcome data, two studies (North et al. and Wu et al.) were at low risk of bias because of no missing data. Two studies (Lee et al. and Franceschetti et al.) were at unclear risk of bias because they provided limited information on the analysis of 26 excluded patients who died during randomization and 24 patients lost to follow up, respectively.

In the selective reporting category, all four studies were at unclear risk of bias because no study protocol was available for comparison.

Finally, regarding other potential sources of bias, three studies were at low risk of bias (North et al., Lee et al., and Franceschetti et al.), whereas one study (Wu et al.) was at unclear risk of bias because of early termination after futility analysis showing no effect.

### Table 1. Summary of 4 studies that met inclusion criteria

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Comparison, Tx Duration, &amp; FU</th>
<th>Total No. of Patients</th>
<th>Study Setting</th>
<th>Method of Seizure Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>North et al., 1983</td>
<td>Randomized to phenytoin (250 mg IV b.i.d. started in recovery room, then 100 mg p.o. t.i.d.) vs identical placebo; Tx &amp; FU 12 mos</td>
<td>281 seizure-naïve patients undergoing supratentorial op for trauma, aneurysm, tumor, or VA shunt</td>
<td>1 tertiary care hospital</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lee et al., 1989</td>
<td>Randomized to phenytoin (15 mg/kg IV started 15–20 min before wound closure, then 5–6 mg/kg/day IV) vs identical normal saline placebo; FU 3 days; Tx &amp; FU 3 days</td>
<td>374 seizure-naïve patients undergoing intracranial, supratentorial op for trauma, aneurysm, hemorrhage, tumor, etc.</td>
<td>1 tertiary care hospital</td>
<td>Not specified</td>
</tr>
<tr>
<td>Franceschetti et al., 1990</td>
<td>Randomized to phenytoin (10 mg/kg p.o. q.d. for 5 days, then 5 mg/kg q.d. p.o. thereafter) or phenobarbital (4 mg/kg q.d. p.o. for 5 days, then 2 mg/kg q.d. p.o. thereafter) vs no Tx; AEDs were started perioperatively, &amp; plasma levels were monitored prior to op; prophylaxis duration &amp; FU period were variable (up to &gt;1 yr)</td>
<td>128 patients (w/ &amp; w/o history of prior seizures) undergoing craniotomy for supratentorial tumor resection</td>
<td>1 tertiary care neurological institute</td>
<td>Not specified</td>
</tr>
<tr>
<td>Wu et al., 2013</td>
<td>Randomized to phenytoin (15 mg/kg IV in OR, then 100 mg IV or p.o. t.i.d. for 7 days postoperatively for goal phenytoin level 10–20 mg/L, then taper starting postop day 8 w/ 100-mg dosage decrease every 2 days until discontinuation) vs no Tx; Tx 7 days followed by taper, FU 12 mos</td>
<td>123 seizure-naïve patients undergoing craniotomy for glioma or metastasis</td>
<td>1 tertiary care hospital</td>
<td>Clinical or EEG diagnosis by independent, blinded neurologist</td>
</tr>
</tbody>
</table>

b.i.d. = twice a day; EEG = electroencephalography; FU = follow-up; IV = intravenous; OR = operating room; p.o. = orally; q.d. = every day; t.i.d. = three times a day; Tx = treatment; VA = ventriculostomy.
Effectiveness of AED Prophylaxis in the Prevention of Early Postoperative Seizures

Two hundred seventy-one patients were evaluated for the outcome of early postoperative seizures, including 147 who received AED prophylaxis and 124 who did not (Fig. 3). In pooled meta-analysis, AED prophylaxis with phenytoin or phenobarbital provided a statistically significant reduction in risk of early seizure compared with control (Mantel-Haenszel random-effects model: RR 0.352, 95% CI 0.130–0.949, p = 0.039). There was minimal heterogeneity (I² = 0%, p value for heterogeneity = 0.782).

Effectiveness of AED Prophylaxis in Prevention of Early or Late (Total) Postoperative Seizures

Two hundred sixty-seven patients were evaluated for the outcome of early or late (total) postoperative seizures (Mantel-Haenszel random-effects model: RR 1.033, 95% CI 0.498–2.141, p = 0.931). There was moderate heterogeneity (I² = 51.8%, p value for heterogeneity = 0.125).

Adverse Effects From AED Prophylaxis

It was not possible to pool adverse effects data (Table 3) because one study did not report them (Lee et al.), two studies reported them at markedly different time points (Franceschetti et al. at 1 week and Wu et al. at 1 month), and data from tumor patients could not be extracted from the fourth study (North et al.). The study of Wu et al. provided the clearest account of adverse events, noting 20 adverse effects of phenytoin among 62 patients in the AED prophylaxis arm within 30 days of surgery. Adverse effects included rash, dry skin, elevated liver function test values, thrombocytopenia, confusion, aphasia, altered consciousness, nausea, vomiting, and ataxia. There were 5 major adverse events (National Cancer Institute Common Toxicity Criteria grades 3, 4, or 5), including 2 gastrointestinal and 3 neurological events. There were no adverse events in the control arm.

### TABLE 2. Patient characteristics of 4 included studies

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Total N</th>
<th>Sex Ratio (M:F)</th>
<th>Age (yrs)</th>
<th>Seizure-Naive Tumor Patients</th>
<th>Glioma</th>
<th>Metastasis</th>
<th>Meningioma</th>
<th>Sellar Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>North et al., 1983</td>
<td>AED 140</td>
<td>1.37:1</td>
<td>Mean 46.7 ± 17.7 (SD)</td>
<td>42</td>
<td>16</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Control 141</td>
<td>1.47:1</td>
<td>Mean 50.1 ± 17.5 (SD)</td>
<td>39</td>
<td>16</td>
<td>7</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Lee et al., 1989</td>
<td>AED 189</td>
<td>1.9:1</td>
<td>Mean 39.86 ± 2.92 (SE)</td>
<td>44</td>
<td>15</td>
<td>3</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control 185</td>
<td>2.1:1</td>
<td>Mean 37.49 ± 2.67 (SE)</td>
<td>41</td>
<td>15</td>
<td>2</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Franceschetti et al., 1990</td>
<td>AED 106</td>
<td>1.2:1</td>
<td>Mean 55 ± 11 (SE) (entire study)</td>
<td>41</td>
<td>23</td>
<td>13</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control 22</td>
<td></td>
<td></td>
<td>22</td>
<td>(entire study)</td>
<td>(entire study)</td>
<td>(entire study)</td>
<td></td>
</tr>
<tr>
<td>Wu et al., 2013</td>
<td>AED 62</td>
<td>1.5:1</td>
<td>Median 56 (range 16–80)</td>
<td>62</td>
<td>23</td>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control 61</td>
<td>1.0:1</td>
<td>Median 61 (range 35–84)</td>
<td>61</td>
<td>23</td>
<td>38</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SD = standard deviation; SE = standard error.

---

**FIG. 2.** Risk of bias assessment (adapted from the Cochrane Handbook for Systematic Reviews of Interventions). Figure is available in color online only.
Assessment of Publication Bias

Studies included in the early seizure analysis and studies included in the total seizure analysis were evaluated in separate funnel plots (Figs. 5). The absence of obvious asymmetry in either funnel plot suggests an absence of publication bias. For early seizure data, Egger’s test revealed a coefficient for bias of $-1.540$, a standard error of $0.227$, and $p$ value of $0.093$, suggesting little evidence of small-study effects. For total seizure data, Egger’s test revealed a coefficient for bias of $-3.678$, a standard error of $6.136$, and a $p$ value of $0.656$, again suggesting little evidence of small-study effects. However, it should be noted that funnel plots and Egger’s test have limited power to detect publication bias when fewer than 10 studies are evaluated.15

Discussion

Our meta-analysis demonstrates that AED prophylaxis provides a statistically and clinically significant reduction in early seizures (within the first week) following brain tumor surgery in seizure-naive patients. It is the first meta-analysis to evaluate exclusively perioperative AED prophylaxis for brain tumors and the first meta-analysis to demonstrate a statistically significant benefit of AED prophylaxis in patients with brain tumors. Our meta-analysis showed no statistically significant effect of AED prophylaxis on total (combined short- and long-term) incidence of seizures.

Prior meta-analyses have sought to evaluate the efficacy of AED prophylaxis for patients with brain tumors by pooling operative and nonoperative patients. In this manner, Glantz et al. 200011 and Perry et al. 200613 concluded that AED prophylaxis had no effect on incidence of seizures among patients with brain tumors. Additional meta-analyses have pooled RCTs that reported exclusively short- or long-term postoperative seizure incidence. Sirven et al. 200418 and Tremont-Lukats et al. 2008,19 a Cochrane Review, thus combined short- and long-term outcome data from surgical and nonsurgical patients to conclude that AED prophylaxis provided no benefit.

Separate evaluation of the effect of AED prophylaxis on short-term seizure rates has important implications for current postoperative management. First, according to neurosurgeon survey data, a week of postoperative AED prophylaxis is the most common duration of prophylaxis prescribed.6 Second, for seizure-naive patients with brain tumors, AAN guidelines recommend tapering and discontinuing perioperative AED prophylaxis after the first week.11 Thus, it is reasonable to evaluate whether this common practice, supported by AAN guidelines, is effective. Third, the highest risk of postoperative seizures occurs within the first week of surgery.9,10,29,40 Early postoperative seizure reduction should therefore be a priority, but there was previously no clear evidence that AEDs mitigate the risk.

Our study suggests that postoperative AED prophylaxis has benefit for short-term seizure outcomes but not for long-term outcomes. There are several potential mechanisms to explain the different effect of AED prophylaxis on short- and long-term seizure rates. First, AED prophylaxis may be effective in reducing seizure incidence in the immediate perioperative period when seizure risk is acutely elevated due to surgical manipulation. The effect of AED prophylaxis may subside as this acutely elevated
risk passes. Second, long-term postoperative seizures are more likely to be associated with radiographic evidence of tumor progression.\textsuperscript{10,40} Given that seizures related to tumor progression are not effectively prevented by AEDs,\textsuperscript{11} it is thus possible that tumor growth gradually dilutes any difference in seizure incidence between AED prophylaxis arms and control arms over time. Furthermore, the results of the long-term analysis do not support the so-called “kindling hypothesis,” the notion that prevention of early seizures can reduce the formation of a scarred epileptogenic focus and thus reduce the risk of later seizures. Indeed, the lack of long-term benefit of AED prophylaxis seen in our meta-analysis argues against this hypothesis.\textsuperscript{29,34}

There are several limitations to this study. First, because there are relatively few RCTs of AED prophylaxis with extractable data from brain tumor patients undergoing craniotomy, the sample sizes for our pooled analyses are somewhat small. In particular, sample sizes were not large enough to stratify seizure risk or AED benefit by type of tumor, which may be an important variable. Second, although the interventions in the selected short-term analysis were fairly comparable, there was greater variation in interventions included in the analysis of long-term outcomes. Among the studies that reported long-term follow up, Wu et al. provided 7 days of AED prophylaxis plus a taper, while North et al. provided 12 months of prophylaxis; in the study of Franceschetti et al., prophylaxis duration ranged from approximately 6–18 months. Given the differences between these interventions, our conclusions about the long-term effect of AED prophylaxis are more limited. At most, these data suggest that prevention of early postoperative seizures with AED prophylaxis does not appear to affect the incidence of late postoperative seizures. A third limitation of this meta-analysis was our inability to pool adverse effects data from the included studies. The lack of adverse effects data makes it difficult to assess the extent to which the observed benefit from AED prophylaxis outweighs the associated risk of side effects. Furthermore, because the included studies used older AEDs (phenytoin and phenobarbital) for prophylaxis instead of newer AEDs such as levetiracetam (which are known to be more tolerable), a risk-benefit analysis from the included studies would have been largely obsolete even if pooling of adverse effects had been possible.\textsuperscript{26} Finally, the studies included in this meta-analysis are at uncertain risk of bias because of certain limitations in the details published about each study design. Particularly because such norms of design reporting have evolved over time, the results of these older studies should not be discarded because of this uncertainty. However, the uncertain quality of these studies nonetheless must be factored into the confidence with which the conclusions of this meta-analysis are made.

**FIG. 5.** Funnel plots for early seizure incidence (**left**) and total seizure incidence (**right**). Each **dashed vertical line** indicates the point estimate of pooled relative risk. Ninety-five percent of studies would be expected to fall within the **diagonal dashed lines** in the absence of heterogeneity or biases. Figure is available in color online only.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Incidence of Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>North et al., 1983</td>
<td>Tumor patient data not extractable</td>
</tr>
<tr>
<td>Lee et al., 1989</td>
<td>Not reported</td>
</tr>
<tr>
<td>Franceschetti et al., 1990</td>
<td>4/41 “adverse effects” in first wk 0/22 in first 1 wk</td>
</tr>
<tr>
<td>Wu et al., 2013</td>
<td>5 major (grade 3, 4, or 5) &amp; 15 minor (grade 1 or 2) adverse events among 62 patients w/in 30 days of op* 0 adverse events among 61 patients w/in 30 days of op</td>
</tr>
</tbody>
</table>

* According to the National Cancer Institute Common Toxicity Criteria: 1) mild, 2) moderate, 3) severe, 4) life-threatening, and 5) death.
Conclusions

This meta-analysis demonstrates for the first time that perioperative AED prophylaxis for brain tumor surgery provides a statistically significant reduction in early postoperative seizure risk within the first week. While this analysis supports the use of AED prophylaxis for the first postoperative week, we are unable to make any conclusions about the maximally effective duration of AED prophylaxis. A well-powered RCT may help to determine the ideal duration of prophylaxis and to evaluate the benefit-to-risk profile of newer AEDs. However, given the contemporary practice of AED prophylaxis as well as the findings of this meta-analysis, the question of equipoise deserves careful consideration.

Acknowledgments

We would like to thank Jimmy Duong, MPH, and Walter Palmas, MD, MS, for additional statistical consultation, and Vivien Wong, PhD, for translation of a study published in Chinese.

References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Bruce, Joiner, Youngerman. Acquisition of data: Joiner, Hudson. Analysis and interpretation of data: Joiner, Youngerman. Drafting the article: Joiner. Critically revising the article: Bruce, Joiner, Youngerman. Reviewed submitted version of manuscript: Bruce, Joiner, Youngerman, Hudson, Welch, McKhann, Neugut. Approved the final version of the manuscript on behalf of all authors: Bruce. Statistical analysis: Joiner, Yang. Administrative/technical/material support: Joiner, Yang. Study supervision: Bruce, Joiner, Youngerman.

Supplemental Information
Online-Only Content
Supplemental material is available with the online version of the article.

Correspondence
Jeffrey Bruce: The Neurological Institute of New York, New York, NY. jnb2@cumc.columbia.edu.