A Comparison of Clinical Practice Guidelines in the Initial Pharmacological Management of New-Onset Epilepsy in Adults

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ABSTRACT

OBJECTIVE: Clinical practice guidelines (CPGs) are intended not only to provide supportive information for health care providers but also to act as a guide for health care policy decisions. However, extant CPGs do not always reach the same conclusions. The objective of this study was to compare recommendations for the initial pharmacological treatment of new-onset epilepsy in adults as stated within published CPGs.

METHODS: We performed a systematic review of CPGs, which were published by prominent national organizations between January 2000 and June 2005, regarding the initial pharmacological treatment of epilepsy in adults.

RESULTS: Five CPGs and 1 evidence report were identified that focus on pharmacological management in epilepsy. The 3 guidelines most relevant to the question of new-onset epilepsy treatment in adults were developed by the American Academy of Neurology (AAN), Scottish Intercollegiate Guidelines Network (SIGN), and National Institute for Health and Clinical Excellence (NICE). AAN recommends the use of both recently introduced antiepileptic drugs (AEDs: gabapentin, lamotrigine, topiramate, and oxcarbazepine) and standard agents (carbamazepine, phenytoin, valproic acid/divalproex, and phenobarbital) in newly diagnosed epilepsy, i.e., a non-tiered approach. Alternatively, NICE recommends using newer AEDs (lamotrigine, topiramate, and oxcarbazepine) only in patients who derive no benefit from older agents—a tiered approach. SIGN notes that all AEDs licensed for monotherapy have similar efficacy in newly diagnosed epilepsy—a recommendation for a non-tiered approach. The newer AEDs (lamotrigine and oxcarbazepine) are recommended as first-line initial treatment as are standard agents (carbamazepine and valproic acid/divalproex). The NICE guideline includes economic and quality-of-life evidence in their recommendations while AAN and SIGN do not. In these regards, current data fails to show superiority for newer agents.

CONCLUSION: In the past 5 years, several CPGs have been published in epilepsy management. Only 3 guidelines have explicit recommendations for the initial pharmacological treatment of adults with epilepsy. With some variation regarding which medications are recommended from each group, all CPGs promote standard and newer AEDs as having similar clinical efficacy. Until efficacy, quality of life, or cost data for the newer agents demonstrates a superior outcome, older AEDs remain viable options as first-line for monotherapy in newly diagnosed patients and may provide cost benefits over newer agents.

KEYWORDS: CPGs, Systematic review, Epilepsy, Initial treatment, Policymakers, Policy

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Epilepsy is a life-altering chronic condition that affects approximately 2.3 million people in the United States, with 150,000 to 200,000 new cases diagnosed each year. The annual cost of epilepsy is approximately $12.5 billion, with 85% of expenditures attributable to nonmedical costs such as lost productivity both at work and at home. Patients with newly diagnosed epilepsy have approximately a 50% chance of seizure remission after initial treatment with moderate doses of antiepileptic drugs (AEDs).

The number of available AEDs has increased recently. Prior to 1990, carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, and ethosuximide were used to treat all forms of epilepsy. Although these older AEDs are generally effective in newly diagnosed epilepsy and are much less expensive than newer agents, some undesirable characteristics such as complex pharmacokinetics and adverse-effect profiles make them less appealing to clinicians and patients. The newer U.S. Food and Drug Administration (FDA)-approved AEDs include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. It has been argued that the advantages of the newer agents compared with the older agents are fewer side effects and drug interactions. With the large number of AEDs available, physicians are presented with difficult drug selection decisions. While the most critical aspect of AED product selection is safety, tolerability, and efficacy, cost is an additional and increasingly important consideration.

Concern about health care quality has contributed to policymakers’ need for the development of uniform and systematic guidelines to aid physicians in making better-informed decisions. Clinical practice guidelines (CPGs) are systematically developed statements of clinical recommendations to assist practitioner and patient decisions regarding appropriate health care. Consistent use of CPGs promotes the concept of “best practices” in order to improve treatment outcomes. CPGs rely on 2 basic assumptions: (1) outcomes identified in clinical trials are reproducible in normal practice and (2) adoption of effective treatment guidelines leads to improved treatment for the whole population. Guidelines developed by an evidence-based approach are founded upon conclusions supported by scientific evidence as well as expert opinion. Efforts are made to link the strength of recommendations to the quality of evidence.

In the past 5 years, several epilepsy management CPGs have been published that refer to efficacy and safety of both older and newer AEDs. This paper is intended to provide policymakers with a comparison of conclusions reached in the extant CPGs that deal with pharmacological choices for initial management.
of epilepsy in adults. Specifically, we sought to answer the question “How do current, prominent guidelines compare in regard to recommendations for treatment of new-onset epilepsy in adults?” Thus, it does not address AED selection when treating refractory epilepsy, management of children, or any AED treatment patterns. It is intended to facilitate the practice of pharmacy benefit managers by providing information for policy-makers and to compare clinical treatment guidelines.

**Methods**

**Search Strategy**

A systematic review process was applied to obtain relevant CPGs that were published by prominent national organizations between January 2000 and June 2005 in the United States and other countries (published in English only). We did not include the guidelines that were published before the year 2000 because we considered them to be outdated. The research question in this review was “What are the differences among guideline recommendations of new-onset seizure in adults?” National CPGs were identified by a computerized search from various sources, including electronic databases, (e.g., MEDLINE, PsycINFO, Cochrane Library, Current Contents, and Proquest Research Library), guideline Web sites (e.g., the U.S. National Guideline Clearinghouse [NGC], National Institute for Health and Clinical Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN], Agency for Healthcare Research and Quality [AHRQ]), and hand searches of relevant journals. MeSH terms used were “epilepsy or seizure” with limits of “all adult: 19+ years,” “publication date from 2000/1/1 to 2005/6/31,” “English, practice guideline/ review,” “humans.” Other key search terms were “clinical practice guideline and epilepsy,” “anti-epileptic drug and epilepsy,” “initial treatment and epilepsy,” “review and drug treatment of new-onset epilepsy in adult,” “monotherapy and newly diagnosed epilepsy,” “drug management and newly diagnosed epilepsy,” “first seizure,” “new-onset epilepsy,” and “first diagnosis.”

**Inclusion and Exclusion Criteria**

Inclusion criteria regarding selection of CPGs were: (1) guidelines that are sponsored by governmental and prominent professional organizations, (2) publication in the English language, and (3) CPGs that address the role of AEDs in the initial management of epilepsy in adults (age >18 years). Exclusion criteria were: (1) CPGs in refractory epilepsy only, (2) CPGs of epilepsy treatment in childhood only, (3) any other examples of complex presentations of epilepsy that may be referred for specialist care, and (4) CPG does not address the research question “How do current prominent guidelines compare in regard to recommendations for treatment of new-onset epilepsy in adults?” Searches of the reference lists and bibliographies of all papers for additional studies were performed as a part of the review.

**Comparison of Clinical Practice Guidelines**

Similarities and differences of the guidelines were evaluated and addressed to provide policymakers with information to support the use of CPGs in rational policymaking in the United States, focusing on the initial pharmacological treatment of new-onset epilepsy in adults.

**Results**

Five national CPGs and 1 evidence report were identified from a systematic search according to the inclusion criteria. These CPGs included 3 from the United Kingdom (NICE, National Collaborating Centre for Primary Care [NCCP], and Joint Epilepsy Council [JEC]), 1 from Scotland (SIGN) and 1 from the United States (American Academy of Neurology [AAN]).

The evidence report was from AHRQ. Characteristics of each are summarized in Table 1.

Although some guidelines included some exclusionary criteria such as recommendations for refractory symptoms or children, they were included because they addressed the primary research question. AAN, in conjunction with the American Epilepsy Society, addressed specific initial drug agent selection in the first part of its guideline. SIGN provided complete recommendations for epilepsy management for both adults and children. The NICE guideline reviewed all aspects of newer drugs for epilepsy in adults. The NCCP guideline regarding newly diagnosed patients mirrors the NICE guideline; therefore, it was excluded to prevent redundancy. We also excluded the JEC guideline and AHRQ report because they do not have specific therapeutic recommendations for initial treatment of epilepsy. After excluding the guidelines from NCCP, JEC, and AHRQ according to our established criteria, the CPGs from AAN, NICE, and SIGN were included in the final comparison chart (see Table 2).

**Discussion**

After comparing the guidelines, we found valid evidence that older, less-expensive AEDs still have an important role as first-line drugs of choice in adults with new-onset epilepsy; the role of newer AEDs is still controversial. SIGN and NICE guidelines contain recommendations to use AEDs as first-line treatment only under their licensed indications, while AAN recommendations include the use of AEDs that fall outside labeled FDA indications. AAN and SIGN also recommend the use of newer agents as first-line treatment in newly diagnosed patients. SIGN states, “Comparative, randomized, double-blind trials in patients with newly diagnosed partial and generalized tonic-clonic seizures suggest similar efficacy for phenytoin, carbamazepine, sodium valproate, lamotrigine, and oxcarbazepine” and “The new AEDs, lamotrigine and oxcarbazepine, seem to be better tolerated and may produce fewer long-term side effects and adverse interactions.” These recommendations are consistent with other scientific literature. NICE supports the
# TABLE 1
Summary of National Practice Guidelines and Evidence Reports for Epilepsy Management
(Published January 2000-June 2005)

<table>
<thead>
<tr>
<th>Title</th>
<th>AHRO12*</th>
<th>AAN12†</th>
<th>NICE6†</th>
<th>NCCP9*</th>
<th>JEC10*</th>
<th>SIGN11†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHRO12</strong>*</td>
<td>Management of Newly Diagnosed Patients with Epilepsy: A Systematic Review of the Literature</td>
<td>Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy</td>
<td>Newer drugs for epilepsy in adults</td>
<td>The diagnosis and management of the epilepsies in adults and children in primary and secondary care</td>
<td>The JEC National Statement of Good Practice for the Treatment and Care of People Who Have Epilepsy</td>
<td>Diagnosis and Management of Epilepsy in Adults—A national clinical guideline</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To systematically review the best available evidence in the published literature regarding health care services pertinent to the diagnosis, treatment, and monitoring of patients with a first diagnosis of epilepsy</td>
<td>To assess the evidence demonstrating efficacy, tolerability, and safety of 7 new AEDs (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide) in the treatment of children and adults with newly diagnosed partial and generalized epilepsies</td>
<td>To examine the clinical effectiveness, tolerability, and cost-effectiveness of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and vigabatrin for epilepsy in adults</td>
<td>To offer best-practice advice on the diagnosis, treatment, and management of the epilepsies in children and adults</td>
<td>To provide a series of recommendations for attaining high-quality National Health Service care for people with epilepsy in England</td>
<td>To provide evidence-based recommendations on the diagnosis and treatment of epilepsy, including recommendations on AED treatment, management of drug-resistant epilepsy, management of status epilepticus, management of provoked seizures, management of people with learning disability and epilepsy, and contraception, pregnancy, and meno-pause</td>
</tr>
<tr>
<td><strong>Type of document</strong></td>
<td>Systematic review</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
<td>Clinical guideline</td>
</tr>
<tr>
<td><strong>Intended users</strong></td>
<td>Developers of clinical practice guidelines and other quality-enhancement tools, those involved with reimbursement and coverage policies</td>
<td>Physicians</td>
<td>Patients, physicians, health care providers, caregivers, those involved in public policy</td>
<td>Individual health care professionals, people with epilepsy and their caregivers, health care commissioning organizations, provider organizations</td>
<td>Advanced-practice nurses, nurses, occupational therapists, physician assistants, physicians, psychologists/nonphysician, behavioral health clinicians, social workers</td>
<td>Advanced practice nurses, patients, pharmacists, physician assistants, physicians, public health department social workers</td>
</tr>
<tr>
<td><strong>Type of patients</strong></td>
<td>Newly diagnosed (not specific in any age group)</td>
<td>Children and adults with newly diagnosed partial and generalized epilepsies</td>
<td>Adults with newly diagnosed or refractory epilepsy</td>
<td>Children, adolescents, adults, older people, women who are pregnant, women of childbearing potential, and people with learning disabilities</td>
<td>Individuals with epilepsy</td>
<td>Adult patients with epilepsy or status epilepticus</td>
</tr>
<tr>
<td><strong>Major outcomes considered</strong></td>
<td>Health outcomes: clinical, HrQoL, and cost-effectiveness</td>
<td>Efficacy, tolerability, and safety of newer AEDs</td>
<td>Clinical effectiveness, serious, rare, and long-term adverse events, cost-effectiveness</td>
<td>All issues important in the diagnosis, treatment, and management of epilepsy in children and adults</td>
<td>Rate of epilepsy misdiagnosis and efficacy of AEDs and their adverse-event profiles</td>
<td>Clinical outcomes</td>
</tr>
<tr>
<td><strong>Method used</strong></td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Systematic review</td>
</tr>
</tbody>
</table>

* CPGs that were excluded from the final comparison.
† CPGs that were included in the final comparison (See Results section in article).
AAN = American Academy of Neurology; AED = antiepileptic drug; AHRO = Agency for Healthcare Research and Quality; CPG = clinical practice guideline; HrQoL = health-related quality of life; JEC = Joint Epilepsy Council; NCCP = National Collaborating Centre for Primary Care; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network.
The use of the older AEDs and clearly states that newer AEDs should be second-line in initial treatment, based upon a lack of good-quality evidence from clinical trials to support the preferential use of newer AED monotherapy over the older drugs. They state, "Almost all studies comparing newer drugs with older drugs have found no statistically significant differences in terms of seizure-related outcomes... However, it cannot be concluded that the drugs have been shown to be equivalent in terms of efficacy..." The one important clinical question for the treatment of newly diagnosed patients is whether lamotrigine, oxcarbazepine, and topiramate are more effective than older AEDs. This review found insufficient evidence from good-quality clinical trials to answer this question. NICE suggests that a review of the adverse events and tolerability from clinical trials does not provide sufficiently consistent results necessary to draw conclusions to support a preference for the newer AEDs compared with the older ones. Important information uniquely found in NICE is the health-related quality-of-life (HrQoL) evidence review. Quality of life is an important advantage proposed for the newer AEDs.
NICE states, “However, only nine of the 19 studies comparing monotherapy using newer drugs versus older drugs assessed quality-of-life” and “These studies do not provide strong evidence of improved quality of life with the newer drugs.”

Based on a broader review of the literature, NICE concludes that there is insufficient evidence to confirm an advantage for the newer AEDs over the older agents related to their ability to improve patients’ HrQoL. AAN did mention in its guideline that “…the burden is on the treating physician to select the AED that is the most tolerable, has the lowest potential for harm, and has the least likelihood of negatively impacting quality of life”; however, AAN did not included this parameter in its review.

The NICE guideline declares that the evidence on cost-effectiveness considered by the reviewing committee indicates that none of the published economic evaluations satisfied the criteria for a robust economic evaluation, but monotherapy with the older AEDs is considerably less expensive, considering only drug cost. They state, “Even when the most optimistic treatment scenario for the newer drugs was compared with the worst-case treatment scenario for the older drugs, monotherapy with the older drugs was considerably less costly.” Finally, they conclude that “the older monotherapies appeared to be cost effective when compared to newer AEDs for the treatment of newly diagnosed patients experiencing generalised seizures.”

When comparing U.S. and European studies, a limiting factor is the insufficient cost-effectiveness and HrQoL information for AEDs used as initial treatment of epilepsy in the United States. AAN states, “The older AEDs have an advantage of broad familiarity, lower cost, known efficacy, wide availability via coverage by third-party payers, and long-term experience” and “The new drugs are all substantially more expensive than the old. There is no literature that addresses the cost-benefit related to these issues.” In the United Kingdom, NICE asks pharmaceutical companies to submit both published and unpublished information to incorporate into the CPG. This provides a broader foundation for the examination of cost-effectiveness and HrQoL assessments. Although the AHRQ guideline includes costs and HrQoL in its review, it does not have recommendations regarding these issues for newer AEDs.

The AAN guideline recommends 11 newer AEDs (oxcarbazepine, gabapentin, lamotrigine, and topiramate) as first-line drugs along with the older agents. Notable is that 3 of these AEDs (except for oxcarbazepine) are not approved in the United States for monotherapy of newly diagnosed patients. AAN states, “The FDA does not accept such a finding as proof of efficacy, due to the possibility that two ineffective drugs might also exhibit no difference in effect when compared against one another. For the purpose of this parameter, we accepted the demonstration of equivalence between an established AED such as carbamazepine or phenytoin and a new drug as confirmation of effectiveness.” The FDA uses placebo-controlled clinical trials to evaluate the use of new AEDs as monotherapy in initial treatment of newly diagnosed epilepsy. This type of trial can present an ethical dilemma to investigators who must randomize newly diagnosed patients to the placebo arm. In the recommendation for future research, AAN states “There is no doubt that the ideal methodology for detecting drug effect in most cases is to use a placebo/control comparison. However, because trials in patients with newly diagnosed epilepsy must be performed, by definition, in the monotherapy condition, there are ethical concerns regarding a placebo or substandard control in this population. Therefore, comparative trials remain the preferred tactic. Clinicians favor these trial designs” and “…these trials are not acceptable for registration purposes in the United States, as the FDA has required demonstration of superiority.”

Kingdom and some countries in Europe accept active-control studies to approve monotherapy indication of new AEDs. This may contribute to an explanation as to why AAN recommendations of newer AEDs differ from licensed indications in the United States.

Beghi, in 2004, published a comparison of AAN and NICE guidelines. His review included the use of newer AEDs in the treatment of epilepsy for both adults and children as well as in special populations (children and patients with learning disabilities and intellectual deficits, women of childbearing age, the elderly). Yet, the paper mainly focused on the place in therapy of newer agents according to these recent guidelines. He concluded that “Both guidelines offer a clear picture of the efficacy, safety, and tolerability of the new antiepileptic drugs and agree on their use as add-on treatment in patients who do not respond to conventional drugs. The guidelines differ in the type and strength of recommendation.” And “The U.K. guidelines are more conservative when compared to the U.S. guidelines.”

When evaluating specific recommendations from CPGs, it is crucial to understand the rationale for excluding CPGs whose recommendations are not considered. This permits a more transparent understanding of the potential for bias in the recommendations used in managed care. In this paper, we attempted to model this as a practice that should be employed when using CPG recommendations to inform drug policy decisions. Policymakers tend to utilize the findings or recommendations from research evidence sources that are clear in content, valid, and up-to-date. The differences among CPGs recommendations present a dilemma to those trying to make drug policy decisions with an evidence-based approach and limit utilization of newer AEDs for maximum patient benefit. The variation among these CPGs might be a result of the process of guideline development. An evidence review to assess the treatment pattern of epilepsy management might be of interest, but it is beyond the scope of this paper. However, we could find no literature review regarding managed care in the U.S. practice. Since pharmacoconomics and HrQoL are obvious
Concerns of policymakers, future research should evaluate the cost-effectiveness and HrQoL of the initial AEDs treatment in adult patients with new-onset epilepsy in the United States to support drug policy decisions.

Conclusion

From our review of current CPGs for AEDs in the initial pharmacological management of epilepsy in adults published in the past 5 years, we found that the older AEDs, including carbamazepine, phenytoin, and valproic acid, still play an important role as first-line monotherapy for management of new-onset epilepsy in adults. Until cost-effectiveness data or quality-of-life studies show a convincing benefit for newer agents, they should remain second-line.

Disclosures

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References