First seizure management

I can see clearly now?

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In the era of evidence-based medicine the need for guidelines should be diminishing. After all, if the evidence is so clear, why would one expect clinicians to have trouble interpreting and applying it? In reality, the evidence is not so clear. Most evidence is acquired using imperfect tools from populations who have varying degrees of similarity to the specific patient sitting in front of each of us every day. Even the best clinical trials yield subtly flawed evidence, as each requires interpretation of inclusion and exclusion criteria at the time of enrollment and ascertainment of endpoints that are imperfectly reported (e.g., seizure number, adverse events, compliance). Trials are also subject to important population stratification driven by inclusion and exclusion criteria, proximity to centers conducting trials, persuasiveness of investigators in recruiting participants, and receptivity of specific patient subgroups to enrolling and completing trials. Important subgroups of patients are frequently excluded from trials, e.g., women not committed to avoiding pregnancy; patients with a history of suicidal ideation, cardiac disease, hepatic disease, renal disease, or progressive conditions that might occlude trial endpoints; and, perhaps most importantly, children and the elderly. Finally, clinical trialists build academic careers and may earn significant fractions of their income based on their success in meeting recruitment goals and completing trials, likely leading to subtle biases in the day-to-day decisions that ultimately produce evidence. While blinding and randomization reduce the effect of these issues, they may not eliminate them completely. Furthermore, most epidemiologic and natural history studies are neither blinded nor randomized, and many are not prospective.

Not only is evidence flawed, it is often complicated and sometimes contradictory. The neurology community has proactively designed thoughtful processes and standards for the development of guidelines by committees of vetted experts screened for major conflicts of interest and nominated (or self-appointed) on the basis of interest and availability. These panels typically spend tremendous effort sifting through literature and applying their own experience to develop consensus statements describing what they judge to be best practice, usually presented with a statement of strength of the evidence. Guidelines are promulgated with the assumption that they represent a rational reduction of the evidence into digestible bits that can be easily accessed by practicing physicians, and they are typically wrapped in disclaimers denying their generalizability, authority, timeliness, and inclusivity.

In a recently published article in *Neurology*[®], Krumholz et al.¹ present a guideline on management of an unprovoked first seizure in adults. This guideline specifically addresses questions regarding the risk of recurrence in patients who are treated or untreated after a first event; the likelihood of remission, defined as a prolonged period of seizure freedom regardless of treatment, in patients who are treated early vs late; and the occurrence of side effects of

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Table Number of studies and level of evidence supporting questions addressed

Questions	Evidence			
	Class I	Class II	Class III	Total
What are the risks for seizure recurrence after a first seizure?	2	8	0	10
Are specific clinical variables associated with risk for seizure recurrence?				
Prior brain lesion	2	2	0	4
Epileptiform EEG	2	4	0	6
Abnormal MRI	0	2	1	3
Nocturnal event	0	2	0	2
Does immediate treatment with an antiepileptic drug reduce or change risks for a seizure recurrence?				
Short-term risks for a seizure recurrence	1	4	0	5
Long-term prognosis for seizure freedom or remission	1	1	0	2
For those patients prescribed immediate antiepileptic drugs, what are the risks for adverse effects?	0	4	1	5
Total unique studies cited across all questions	2	9	2	13

treatment. The summary conclusion is that "... recommendations whether to initiate immediate AED [antiepileptic drug] treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the AEs [adverse events] of AED therapy, consider educated patient preferences, and advise that immediate treatment will not improve the long-term prognosis for seizure remission but will reduce seizure risk over the subsequent 2 years." Most neurologists will find these comments neither surprising nor unexpected. After all, these recommendations reflect standard practice, conform to common sense, offer respect for patient input into individual decision making in specific clinical contexts, and teach us little that is new. And herein lies the trouble with guidelines. Seldom do guidelines contradict standards of practice, likely because standards have evolved organically from educated and experience-based interpretation of available evidence applied in a practical clinical context. It is instructive to look at the number of publications on which the current guideline is based (table). The majority of the recommendations come from 1 or both of a single pair of Class I studies, and several of the recommendations are based on no Class I trial data.

Curiously, a statement that treatment that reduces seizure recurrence may not improve quality of life (QOL) in patients treated early manages to make it into the abstract and the recommendations, although the statement is based on a single Class II study² and is not the focus of any specific question defined prospectively in the analysis. The guideline quotes the authors of this study, who speculate that AED side effects may negate the likely QOL benefit of reduced recurrence risk in treated patients. It should be highlighted that the single study cited on this point² was based on patients followed from 2000 to 2002, arguably quite dated when it comes to weighing the risks of AED side effects against other QOL factors in current practice. The prominence of this recommendation is particularly troublesome, as it suggests that even guideline makers are likely to consider minimal evidence, potentially overinterpreted, in formulating and structuring their "official" recommendations to patients and colleagues. One

might wonder whether clinical experience and judgment are gently encouraging the experts to offer such a strong opinion in the face of such weak evidence in this situation.

So at the end of the day we have a document, the product of extensive labor and thought, that addresses important questions by applying findings reported in a limited number of studies. Most, if not all, of the recommendations comport with common clinical practice based on experience, judgment, and common sense, but it is reassuring to see that the available evidence is supportive of what we do. Whether the cost, broadly defined, of developing guidelines of this nature is worthwhile is a question worth contemplation, and input from the membership of the Academy in this regard would be welcome. In spite of the disclaimers, it is likely that these guidelines will be cited by payers, quality managers, and attorneys, so it is important that the limited database on which they are based be appreciated. While the concept of guidelines may be justified by the complexity of the evidence and welcomed by many busy practitioners, we should be careful what we wish for.

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