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Stay, Hit, or Fold? What Do You Do If the Treatment May Be as Bad as the Problem—Results of a Q-PULSE Survey

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Understandably, a great deal of attention in clinical epileptology is focused on the management of patients with treatment-resistant epilepsy. However, the potential impact of epilepsy and treatment on the other two-thirds of patients with epilepsy who are well controlled is not necessarily trivial. For patients who have been seizure free for extended periods of time, adverse drug effects can pose a significant clinical conundrum for both the patient and the physician. The situation largely boils down to a blackjack scenario: 1) do you “stay” on the current anti-epileptic drug(s) (AEDs) and manage the adverse effects as well as possible; 2) do you take a “hit” and switch to an alternative AED to try and maintain seizure freedom without the adverse effects; or 3) do you “fold” on AEDs altogether and taper off the medication to see if seizure freedom is maintained without further treatment.

Complications from longstanding treatment with some AEDs are well described, but relatively few studies exist to establish the risks of tapering AEDs in medically managed seizure-free adults (1–5). A systematic meta-analysis has identified a relapse rate of 29% (5), whereas the prospective studies have identified relapse rates of 27 to 52 percent (1–4).

Literature reviews on this topic have occurred in the past (6–8), and the relative safety of withdrawal of AEDs in the setting of 2 or more years of seizure freedom has been reported. The Italian League Against Epilepsy published guidelines recommending “antiepileptic treatment might be discontinued after a minimum of two years of seizure freedom” (8).

The Q-PULSE panel comprising 146 epilepsy experts from level-4 epilepsy centers in the United States (9) was asked to answer a series of questions about this topic based on the following clinical scenario. “A 50-year-old gentleman presents with a history of focal epilepsy with seizure onset in his 20s, has been on phenytoin monotherapy for over 2 decades, and has been seizure free for the past 12 years. His recent bone density testing shows him to be more than 2 SD below the age- and sex-adjusted normative results. His most recent MRI and EEG (from within the last year) studies are normal”. Assume, for

purposes of answering this question that you have counseled him on the risks and benefits of all approaches, and he wishes to follow your recommendation.

A total of 99 panelists responded. Given the scenario above, 49 (50%) said other factors would have to be considered before a decision could be made, 2 (2%) would continue the patient on phenytoin, 18 (18%) would transition to an alternative medication, and 30 (30%) would discontinue medications. The other factors to be considered are summarized in Figure 1. The 18 physicians who said they would transition to an alternative medication were asked to choose up to three medications they would consider. The top three choices were levetiracetam (33%), lamotrigine (16%), and lacosamide (17%).

The scenario was modified for the next question, which asked if the approach would be the same if the patient had an abnormal EEG with focal slowing but no epileptiform abnormalities. The majority (80%) would not change their original response; but 20 changed their response, with 1 choosing to discontinue medications altogether, and 18 (a total of 36 of the 99 respondents including those that kept the same response) choosing to transition to a new medication (one respondent abstained).

The next questions asked respondents whether they had ever experienced negative consequences (a catastrophic result) following discontinuation of a medication. The majority of respondents reported that they had

FIGURE 1. On what factor(s) does it depend? Note that respondents could choose more than one answer. Total respondents: 47/49.

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FIGURE 2. In your experience, have you had a catastrophic result (e.g., recurrent uncontrolled seizures or severe sequelae of a seizure) in the setting of removing or switching a patient (with a history of more than 2 years of seizure freedom) from anti-epileptic therapy? Total respondents: 99.

FIGURE 3. If you have had a catastrophic response, did this change your management approach to subsequent patients with similar clinical situations. Total respondents: 62/62.

FIGURE 4. If you have had a catastrophic response, please describe. Responses reviewed and categorized; many responses referenced more than one patient experience and had more than one category. Treatment-resistant epilepsy refers to patients becoming treatment resistant when seizures recurred. Seizure recurrence was noted by 10 respondents without specific mention that they resulted in injuries or that they remained resistant to treatment. Total respondents: 56/62.

TABLE. Responses to the Original Case Scenario Based Upon Whether a Catastrophic Occurrence Had Been Reported in the Past*

	Discontinue PHT	Continue PHT or New AED	It Depends
Catastrophic occurrence	13	14	35
No catastrophic occurrence	17	6	14

Abbreviations: PHT, phenytoin.

*Total respondents: 99.

witnessed a significant bad outcome following withdrawal of anti-epileptic treatment (Figure 2). The majority of those with a catastrophic outcome (69%) reported that it had “a little” impact on how they managed later patients with similar circumstances (Figure 3). Respondents were asked to comment on the nature of the catastrophic response (through free text), and the response categories are shown in Figure 4. Using the anonymous individualized response data, the responses to the initial question were analyzed based upon whether or not a catastrophic occurrence had been reported in the past (Table). Utilizing the χ^2 statistic, a significant difference was seen between those with, versus those without, a previous catastrophic occurrence ($p = 0.03$), with a higher percentage of respondents with a history of a negative outcome choosing either “it depends” or to transition to an alternative AED.

In the fairly common scenario presented here, the initial action for the near majority of Q-PULSE respondents was to evaluate additional information before making a decision. In the Italian guidelines, EEG abnormalities, a known etiology, older age at onset, and focal seizures were identified as potential predictors of a higher likelihood of relapse (8). Among those who would act without additional information, very few respondents (2%) chose to remain on the AED to which the adverse reaction was attributed, and nearly twice as many elected to do a trial off of the AED versus immediately transitioning to an alternative medication. The variability in clinical approach and the large number of clinicians that required additional information in the decision-making process highlight the need for a multi-center study aimed at assessing if and when (as well as how) to taper patients with extended periods of seizure freedom off of medications.

This Q-PULSE panel is meant to stir discussion—what would you do in this scenario? We hope to continue this discussion as part of the new American Epilepsy Society (AES) Web site.

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