



# Progress Toward Obtaining Seizure Freedom With New Medications in Older Adults

## Characteristics and Treatment Outcomes of Newly Diagnosed Epilepsy in Older People: A 30-Year Longitudinal Cohort Study

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**Objectives:** To describe the clinical characteristics and evaluate the long-term treatment outcomes in older people with newly diagnosed epilepsy over the past 30 years. **Methods:** We included patients newly diagnosed with epilepsy and commenced on anti-seizure medications (ASMs) at age 65 years or older between July 1982 and October 2012 at the Western infirmary in Glasgow, Scotland. They were followed up until April 2016 or death. Seizure freedom was defined as no seizure for at least 1 year on unchanged medication at the last follow-up. **Results:** A total of 201 patients (median age 73 years, 59% male) were included. The median duration from initial seizure to starting treatment was 8 months (interquartile range: 3.0-24.0 months); 42.2% (85/201) patients had more than 5 seizures before commencing treatment. Brain imaging showed potentially epileptogenic lesions in 19.7% (38/193) of patients and other abnormalities in 56.5% (109/193); 78.6% patients (158/201) were seizure-free at the last follow-up, of whom 94.9% were taking monotherapy. Concomitant aspirin use ( $n = 80$ ) was associated with a lower probability of being seizure-free (relative risk 0.82, 95% confidence interval 0.70-0.97;  $P = .02$ ). The use of second-generation ASMs as the initial monotherapy increased from 31.5% (23/73) before 2000 to 70.3% (90/128,  $P < .001$ ) from 2000 onward. However, the seizure freedom rates (67.1% vs 55.5%;  $P = .35$ ) and intolerable adverse-effect rates (16.4% vs 19.5%;  $P = .45$ ) did not show any significant difference. **Significance:** There was often a long interval between seizure onset and the initiation of treatment in older people with new-onset epilepsy, although the majority responded well to ASM treatment. Brain imaging showed a high rate of abnormalities. Despite the increased use of second-generation ASMs, treatment outcomes in later-onset epilepsy have not improved over time. The possible effect of aspirin on treatment response warrants further investigation.

## Commentary

The incidence of epilepsy in older persons is high when compared to the general population, with annual incidence rates of 2.4 per 1000 being reported in Medicare beneficiaries in the United States.<sup>1</sup> Smaller regional studies have identified an increase in incidence after the age of 60 years.<sup>2</sup> As elderly patients typically have more comorbidities than younger adults, many of which require medications, clinical management can be more difficult when trying to maintain consistent drug therapy. Having information in this group of patients is important in order to determine how to best balance efficacy and tolerability of adverse effects, thus avoiding unnecessary toxicities that may appear at lower drug exposure than in younger populations.

The primary objective of the study by Als fouk et al was to assess efficacy and tolerability of anti-seizure medications (ASMs) over a 30-year period in elderly patients newly diagnosed with epilepsy.<sup>3</sup> The availability of 3 decades of data

allowed the group to identify changes in drug treatment and outcomes over a long period of time. Data consisted of records from the Epilepsy Unit of Western Infirmary in Glasgow, Scotland, between July 1, 1982, and October 31, 2012, and who began treatment for seizures when they were age 65 years or older. A prospective follow-up period was included to provide 3.5 years of potential subsequent follow-up for all patients. Details of the study are included in previous reports that explored treatment outcomes and tolerability in patients with newly diagnosed epilepsy regardless of age.<sup>4,5</sup> The earlier study included information on 1795 patients from the same unit with newly diagnosed and treated epilepsy from ages 9 to 93 years from the same time period as this study of 201 elderly patients (65 years or older). In general, an ASM was selected after a diagnosis of epilepsy and consideration of seizure type, adverse drug effects, and possible drug–drug interactions. Despite the age differences in the populations, both studies concluded that even with the availability of many newer ASMs,






outcomes and tolerability in newly diagnosed epilepsy have not improved substantially. This similar conclusion may be driven by a large overlap of individuals in each database as well as being from only one health care system where similar strategies for care are employed. However, it should be noted that in general there is still a substantial number of patients who are considered refractory to ASMs where seizure freedom does not seem possible based on current available therapy. Although seizure freedom is the ultimate goal for all patients, not all are able to obtain it. For this study, patients who had no evidence of seizures for at least the previous 12 months with no change in dose of ASM were considered to reach *seizure freedom*. Seizure type was classified according to the latest International League Against Epilepsy (ILAE) classification scheme.<sup>6,7</sup>

It is not unusual for adverse events to appear when ASMs are being introduced. Chronic therapy with medications can also lead to side effects which may have more of an impact on older adults. Intolerable adverse events were defined as those given as the main reason for discontinuation within 180 days initiation of an ASM. The cutoff year for first generation ASMs was before 1980 so included mostly phenytoin, carbamazepine, and valproate. In order to compare ASM treatment and outcomes over time, 2 epochs were created based on ASM start dates (July 1, 1982, to December 31, 1999, for epoch 1 and January 1, 2000, to April 30, 2016, for epoch 2). More patients in the second epoch started with a newer ASM, however, adverse events and seizure freedom rates were noted to be similar in both groups as with younger patients.<sup>4</sup> These observations do not take into account other factors such as how many ASMs were tried and what order they were presented. A newer ASM, lamotrigine, was the most commonly prescribed drug. Lamotrigine was more tolerated over gabapentin and carbamazepine in a randomized, double-blind, parallel study of newly diagnosed elderly patients (>60 years) from 18 Veterans Affairs Medical Centers (VA)<sup>8</sup> that occurred during the middle of the time frame of the Alsfook study (January 1998 to April 2002 with 1 year of follow-up). The VA study found no significant differences in seizure freedom rates, but tolerability favored lamotrigine. Similarly, cardiovascular disease including hypertension, stroke, and cardiac disease was a frequent comorbidity in the VA study. In the VA study, fewer patients receiving lamotrigine discontinued treatment due to adverse events compared to gabapentin or carbamazepine. It is important to note that the choice of drugs chosen for the VA study reflected the newer approved drugs at the time—those approved around 1998—and many medications have been approved since then which would be reflected in the Alsfook study. Interestingly, the second and third most frequently prescribed ASMs were older generation ASMs and with significant enzyme inhibitor (valproate) and inducer (carbamazepine) properties that lead to known drug interactions. This can be of even more significance in populations who are on multiple drugs for other conditions such as elderly patients. As not all medical systems are centralized, and patients may have more than one clinic that is prescribing medications it can be especially important to assess the full complement of medications

including supplements and over-the-counter medications that are being ingested. Although most patients (91.5%) were on ASM monotherapy, a majority had comorbid conditions (72.1%) in addition to their epilepsy and were receiving at least one and up to 16 other medications (67%). Possible complications such as unanticipated adverse events or drug interactions can arise with the addition or withdrawal of interacting drugs by another prescriber especially *after* scheduled visits with a patient's epilepsy provider. Prompting patients to inform clinicians of medication changes when reporting adverse events or changes in function (eg, cognition, gait) that are more common in the elderly is beneficial for a thorough assessment. One unusual finding is the inverse association of aspirin use to seizure freedom. Aspirin was included as a possible inducer in the current analysis; however, it is not typically thought of as a potential inducer of cytochrome P450 enzymes. Aspirin is highly protein bound and can interact with highly protein bound ASMs such as phenytoin causing decreases in total drug<sup>9</sup>; but protein displacement on its own does not necessitate dose changes. Interestingly, aspirin has been reported to interact with valproic acid in respect to both protein binding and enzyme inhibition resulting in increases in unbound valproic acid concentrations which can lead to toxicity.<sup>10</sup> Based on the pharmacokinetics of ASMs and aspirin, it is probable that the aspirin finding is confounded by comorbidities or a spurious result.

Although observational data has several limitations, the ability to examine characteristics of a population over multiple decades of time adds valuable information. Indicators of efficacy and tolerability can be detected in clinical data; however, other factors such as overall health or changes in individual baseline are also important when assessing older adults and may be key factors in how treatment is tolerated or when determining the initial ASM. Already accumulated comorbidities that come with medications add to the overall cognitive burden and increase the chances of drug–drug interactions. This can make drugs with fewer known pharmacokinetic interactions such as levetiracetam desirable from a pharmacokinetic perspective, although side effect profile and changes due to age must also be considered as these can affect the overall tolerability of a particular treatment. An overall assessment of the patient's baseline functioning, drug pharmacokinetic profile, and additional negative impact from side effects must be considered when treating older individuals.

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