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Epilepsy in the Elderly: Risk Factors and Management Approaches

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Abstract

Purpose of Review Epilepsy, particularly new onset, disproportionately affects the elderly at high rates. We summarize the literature on etiologic risk factors and the evidence behind medical and surgical treatments for geriatric epilepsy.

Recent Findings Incident epilepsy in the elderly is most commonly focal onset resulting from structural brain disease. Levetiracetam was well tolerated and as effective as older medications for new onset seizures. Small studies on epilepsy surgery show favorable outcomes in older patients; however, surgery may be associated with an increased risk of cognitive deficits and complications.

Summary Further studies are needed to examine the utility of newer antiepileptic medications in the elderly. In particular, the selection of a good surgical candidate in this age group requires more detailed investigation.

Keywords Epilepsy · Seizure · Elderly · Geriatric · Surgical care · Risk factors

Introduction

Epilepsy is the fourth most common neurological disorder in the U.S., surpassed only by migraine, stroke, and Alzheimer's disease [1]. Defined as at least two unprovoked seizures occurring more than 24 h apart or a single unprovoked seizure with a high risk of recurrence based on neuroimaging or EEG studies [2], epilepsy affects nearly 1% of the population with a prevalence estimated at 6–9 per 1000 people [1]. The incidence of new onset epilepsy, however, varies greatly by age. Epilepsy is well known to have a bimodal distribution, with peaks seen in both infancy/childhood and in old age [3]. In fact, incident epilepsy in the elderly, which we define as adults > age 65 years, occurs at over three times the rate observed in children [4]. The 65+ years age group is the most rapidly growing segment of the US population and is predicted to double from 43.1 million in 2012 to 83.7 million by 2050 [5•]. With the graying of the U.S., the number of older adults with epilepsy is expected to rise even further.

Despite the fact that incident epilepsy disproportionately affects the elderly, there are considerable research gaps in this area [1]. For example, although the proportion of patients with unknown etiologies for epilepsy was historically highest among children and young adults [3], advanced genetic testing methods have reported diagnostic yields of up to 17–58% in selected pediatric populations [6]. These numbers are expected to rise. By contrast, half of incident epilepsy in older adults continues to have no identified cause [3, 4, 7]. How as-yet unknown or unidentified risk factors contribute to the development of epilepsy in the elderly needs to be explored. Furthermore, there is a dearth of data on the comparative efficacy of antiepileptic medications and outcomes after epilepsy surgery in this age group. In this article, we will review research on risk factors and etiology for new onset epilepsy, as well as the current evidence behind pharmacologic and surgical treatments for epilepsy in older adults.

Risk Factors for New Onset Epilepsy in the Elderly

The International League Against Epilepsy (ILAE) classifies epilepsy types as focal or generalized in onset [8]. Correct classification of epilepsy type is crucial for prognosis and treatment. Focal epilepsies originate from a portion of one hemisphere, while generalized epilepsies are believed to have

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more widespread, bilateral onset [9]. Generalized epilepsies include specific syndromes such as childhood absence epilepsy or juvenile myoclonic epilepsy. These epilepsies have a common age of onset and typically first present in early childhood to young adulthood and thus would be unusual to manifest de novo in an elderly patient. Moreover, because older adults are more susceptible to structural brain disease, such as ischemic or hemorrhagic stroke, brain tumors, and neurodegenerative disorders, new onset epilepsy in this age group tends to be predominantly of focal onset [7, 10]. The recommended work-up after a single new-onset seizure in an elderly patient includes both a routine EEG and neuroimaging, preferably with a brain MRI [11]. Epileptiform abnormalities on EEG or abnormal neuroimaging findings predict seizure recurrence and warrant antiepileptic drug treatment [12]. The risk for further seizures rises dramatically after the second unprovoked seizure, and treatment is certainly required at that time [11, 12].

To investigate age-specific etiology further, Stefan and colleagues prospectively recruited 202 patients from five European epilepsy centers [13]. The investigators categorized the patients into three groups: (1) patients with late onset epilepsy occurring after age 65 years, (2) patients > age 65 years with the onset of epilepsy before age 50 years, and (3) younger patients between 18 and 50 years with epilepsy. Nearly all cases in the late onset epilepsy group had focal seizures, with just one patient out of 79 (1.2%) suspected to have generalized epilepsy. By contrast, generalized epilepsy patients comprised 14.9 and 21.9% of groups 2 and 3, respectively ($p = 0.001$). They also found that the late-onset patients most commonly had cerebrovascular disease (36.7%) and tumors (11.4%) as seizure foci, but roughly 40% of patients lacked an identifiable etiology for their epilepsy.

Choi et al. assessed risk factors for the development of epilepsy in a large, population-based group, the Cardiovascular Health Study, a diverse cohort of 5888 adults in the U.S. ages > 65 years followed prospectively with annual in-person evaluations for more than 15 years [5•]. They identified 120 incident cases of epilepsy, with an overall incidence of 2.47 per 1000 person-years. Significant risk factors for new onset epilepsy after age 65 years included black race and a history of both prevalent and incident stroke. Of note, this study examined cardiovascular risk factors and did not include other etiologies such as brain tumor, traumatic brain injury, or dementia. Interestingly, the highest rates of incident epilepsy occurred in the age 75–79-year-old cohort (when divided into age categories of 65–69, 75–79, and > 80 years), even compared to the > 80-year-old group. This finding was reported in other studies [3, 7] and may be an effect of survivor bias.

Martin and colleagues examined psychiatric disorders as potential predictors of new onset epilepsy in older adults [14]. The authors found 3514 cases of new onset epilepsy from a randomly selected 5% sample of Medicare beneficiaries and compared them to over 1.1 million Medicare beneficiaries without epilepsy. They then identified psychiatric and neurologic co-morbidity ICD9 diagnosis claim codes in the 365 days preceding the first epilepsy diagnosis code. Similar to the findings observed by Choi et al., older age (specifically the 75–84 years age group), black race, as well as increased numbers of medical co-morbidities were associated with new onset epilepsy [5•, 14]. Not surprisingly, neurologic conditions were the strongest independent risk factors, in descending order: cerebrovascular disease (adjusted odds ratio [aOR] of 9.38), traumatic brain injury (aOR 6.32), brain tumor (aOR 4.06), and dementia (aOR 2.42). Among psychiatric risk factors, they found that substance abuse/dependence (aOR 2.50), a history of psychosis (aOR 2.30), and to a lesser extent, bipolar disorder (aOR 1.96), schizophrenia (aOR 1.65), and depression (aOR 1.45) were associated with new onset epilepsy.

Several notable characteristics emerged as common themes in these studies. New onset epilepsy in the elderly was most strongly associated with cerebrovascular disorders, with traumatic brain injury, brain tumors, and dementia also identified as contributing etiologies. Several studies established black race, older age (75–79 years in one study and 75–84 years in another), and medical co-morbidities as notable risk factors [5•, 14]. Although many of these conditions are non-modifiable (e.g., age or race), better primary prevention of diseases like stroke would likely improve the incidence of epilepsy in the elderly.

The relationship between psychiatric illness and the subsequent development of epilepsy is intriguing. Chronic epilepsy coincides with a high likelihood of developing depression, cited at between 8 and 48% in various studies, considerably higher than the general population [15]. Conversely, a large population based study by Josephson et al. of nearly 10.5 million patients in Canada found that incident depression was associated with an increased risk of epilepsy over all ages (hazard ratio 2.55). Higher rates corresponded with more severe cases of depression [16]. The bidirectional relationship between epilepsy and psychiatric disorders like depression represents a fascinating new area of research, generating many as-yet unanswered questions.

Antiepileptic Drug Treatment for New Onset Epilepsy in the Elderly

The fact that most new onset epilepsy in the elderly is focal onset [7, 10, 13, 14] is pertinent to formulating an appropriate treatment strategy. Many antiepileptic medications are indicated only for focal epilepsy and can in fact worsen generalized epilepsy (Table 1), an epilepsy type not typically seen in new onset elderly epilepsy. Thus, available medication options are more varied for older patients. Treating elderly patients with

Table 1 Common antiepileptic medications used in elderly patients

Drug name	Type of epilepsy	Recommended in the elderly	Common side effects	Major medication interactions	Metabolism
Levetiracetam	Focal or generalized	Yes	• Irritability • Anxiety/depression	No	• Renal metabolism
Gabapentin	Focal	Yes	• Somnolence	No	• Renal metabolism
Lamotrigine	Focal or generalized	Yes	• Dizziness, tremor • Can worsen myoclonus • Drug rash, Stevens-Johnson Syndrome	No	• Hepatic metabolism • Concurrent use of enzyme inducing drugs affects metabolism of lamotrigine
Carbamazepine	Focal	No	• Dizziness, diplopia, nausea • Rash • Hyponatremia	Yes	• Hepatic metabolism • CYP enzyme inducer • HLA-B*1502 allele testing recommended in Asian patients
Oxcarbazepine	Focal	No	• Dizziness, diplopia, nausea • Hyponatremia	Yes	• Hepatic metabolism • Weak CYP enzyme inducer
Valproate	Focal or generalized	Yes, second line	• Weight gain • Hair loss • Tremor	Yes	• Hepatic metabolism • CYP enzyme inhibitor
Phenytoin	Focal	No	• Nausea, dizziness, ataxia • Gingival hypertrophy • Rash	Yes	• Hepatic metabolism • CYP enzyme inducer
Phenobarbital	Focal or generalized	No	• Sedation, lethargy	Yes	• Hepatic metabolism • CYP enzyme inducer
Topiramate	Focal or generalized	Little data	• Weight loss • Paresthesias • Slowed cognition	No	• Renal and hepatic metabolism • Low potential for CYP enzyme induction
Zonisamide	Focal or generalized	Little data	• Weight loss • Paresthesias	No	• Hepatic metabolism
Clobazam	Focal or generalized	Little data	• Sedation, lethargy	No	• Hepatic metabolism
Lacosamide	Focal	Little data	• Dizziness, nausea • Prolonged PR interval	No	• Hepatic metabolism

Sources: [17•, 18–23]

epilepsy, however, is complicated by multiple age-related changes limiting their ability to metabolize medications [17•,18,19]. Older adults tend to suffer from polypharmacy for chronic medical conditions, and many antiepileptic medications induce or inhibit metabolism by the CYP450 pathway, thereby causing significant drug-drug interactions [17•, 18, 19]. Elderly patients are often also more sensitive to side effects, particularly by medications that act on the central nervous system [18, 19]. Older or first-generation antiepileptic medications like phenytoin, phenobarbital, and carbamazepine typically have more side effects and drug interactions making them less ideal for use in this population.

Two recent randomized clinical trials compared the efficacy and tolerability of older versus newer antiepileptic medications for elderly patients with new onset epilepsy. Werhahn et al. conducted a randomized, double-blind multicenter clinical trial at 47 sites in Austria, Germany, and Switzerland, recruiting 361 patients ages > 60 years with new onset focal epilepsy [17•]. At the time of the study, carbamazepine was the standard choice for elderly patients in Europe, but the investigators hypothesized that lamotrigine and levetiracetam could be better options. Patients were randomized 1:1:1 to controlled release carbamazepine, lamotrigine, and levetiracetam, which were uptitrated over 6 weeks to initial target doses (400 mg/day of CR-carbamazepine, 100 mg/day of lamotrigine, and 1000 mg/day of levetiracetam). They then continued on the study drug for a 52-week maintenance period, during which time dose adjustments up or down were allowed for tolerability and seizure control, mimicking usual clinical practice. The primary outcome measure was the retention rate at week 56, which was significantly higher for patients treated with levetiracetam (61.5%) compared to controlled-release carbamazepine (45.8%; $p = 0.02$). With lamotrigine, 55.6% of patients remained on treatment at the end of week 56, which was not statistically different from either of the other groups. Carbamazepine had the highest rate of discontinuation specifically due to adverse events (32.2% of the carbamazepine group), which occurred nearly two times more frequently than with levetiracetam (17.2%; $p < 0.01$). There were no differences in the secondary outcome measures of seizure freedom rates at week 30 or 58 or the time to first seizure after randomization for any of the medications. The latter results are unsurprising and reflect the greater antiepileptic drug literature, which has not shown major differences in efficacy between medications. The authors concluded that levetiracetam was better tolerated as initial monotherapy for older adults than carbamazepine.

Pohlmann-Eden and colleagues performed a subgroup analysis on elderly patients enrolled in the Keppra versus Older Monotherapy in Epilepsy Trial (KOMET study), a multicenter, unblinded, randomized superiority trial comparing the efficacy of levetiracetam with both extended-release valproic acid and controlled-release carbamazepine for monotherapy in patients ages 16 years and over with new onset epilepsy [18]. The investigators separated patients into two groups based on expected standard first-line treatment (valproic acid being favored in generalized epilepsy and carbamazepine in focal epilepsy; Table 1). Patients in the valproic acid group were then randomized in a 1:1 fashion to levetiracetam or valproic acid, and similarly, the carbamazepine group was assigned to levetiracetam or carbamazepine. Like the previous trial, dose adjustments were made in accordance with best clinical judgment. The primary outcome was time to withdrawal from the study drug, with secondary outcomes consisting of overall treatment withdrawal rates, time to first seizure after randomization, and seizure-freedom rates at 6 and 12 months.

Of the 1698 patients randomized, the authors conducted a post-hoc subgroup analysis for patients ages > 60 years, which included 206 patients in the carbamazepine group and 101 in the valproic acid group [18]. Notably, more of the older adults were randomized to carbamazepine, consistent with focal epilepsy being more common in this age group, as previously discussed. In the carbamazepine subgroup, the majority of epilepsy was caused by cerebrovascular disease. The time to treatment withdrawal was longer in patients treated with levetiracetam compared to carbamazepine, with a treatment effect hazard ratio (HR) of 0.45 (with a HR of < 1 favoring levetiracetam and > 1 favoring carbamazepine; 95% confidence interval [CI] 0.28–0.67). In the valproic acid arm, there was a trend towards longer time to treatment withdrawal from levetiracetam compared to valproic acid (HR 0.46, again favoring levetiracetam), but this did not reach statistical significance (95% CI 0.16–1.33). Finally, as previously noted by other studies, there was no difference in seizure efficacy for any of these medications.

Earlier studies previously established that gabapentin and lamotrigine, which have few drug-drug interactions and low overall side effect profiles, were well tolerated in older patients with focal epilepsy [19, 20]. Likewise, the randomized clinical trials performed by Werhahn et al. and the KOMET study investigators demonstrated better tolerability and equivalent efficacy of levetiracetam in the elderly population compared to carbamazepine. Therefore, levetiracetam could also be considered as an initial option for new onset seizures in older adults and may additionally be an appropriate choice for adjunctive therapy. Several other newer antiepileptic medications such as lacosamide, zonisamide, or clobazam are frequently prescribed for older patients but have not yet been examined in this age group for tolerability and efficacy.

Surgical Treatment of Epilepsy in the Elderly

Despite the development of many new anticonvulsant medications since the 1990s, the overall proportion of patients with medically refractory epilepsy (ongoing seizures

despite trialing at least two medications) remains high. Approximately one third of all epileptic patients will continue to be drug resistant despite multiple trials of medications. A seminal article by Kwan and Brodie noted that after failing two antiepileptic drugs, the likelihood of seizure freedom with additional medications was only 4% [24]. Epilepsy surgery in medically refractory patients results in improved seizure outcomes. In fact, up to 60–70% of temporal lobe epilepsy patients attain seizure freedom after resection [25]. However, there is often a long delay in consideration of surgery even among younger patients, with an average duration of epilepsy of 22 years prior to surgery [26]. Older adults may be even more hesitant given concerns of increased surgical risks due to age and the presence of comorbidities common in the elderly.

To explore this issue further, two recent single-center retrospective studies in Italy and the UK described cohorts of patients > 50 years of age who underwent epilepsy surgery. d'Orio and colleagues identified 50 surgical patients at their center age > 50 years, with a mean age of 53.8 years (range 50–62) and predominantly long-standing epilepsy (mean duration 32.5 years) [27]. They compared outcomes with a younger cohort ($n = 1369$) less than 50 years of age who also received epilepsy surgery. Most of the surgeries performed (80%) in the older group were temporal lobe resection or lesionectomy, a removal of lesions such as cavernous malformation thought to be causing epilepsy. After follow-up for at least 2 years, 78% of the older patients ($n = 39$) achieved seizure-freedom (Engel class I), 16% ($n = 8$) had notable improvement in seizure frequency, though they were not seizure-free (Engel class II-III), and 6% ($n = 3$) were not improved after surgery (Engel class IV) (Table 2). These seizure outcomes were similar when compared to the younger cohort ($p = 1$). The older patients notably had a statistically higher rate of surgical complications (10%, 5/50 patients, in the older group versus 4%, 50/1369 patients, in the younger group; $p < 0.0001$). Five older patients suffered a stroke or intracerebral hemorrhage, though four of them had only transient neurologic deficits and made full recoveries. The authors also analyzed pre- and post-operative neuropsychological testing to determine the effects of epilepsy surgery on cognition. They did not find a significant decline in language function, verbal or visuospatial memory, executive function, visual perception, abstract reasoning, or depression scores. They concluded that epilepsy surgery is effective in patients 50 years and older, though this population may have a slightly higher risk of surgical complications than younger patients.

Table 2 Engel class surgical outcomes (adapted from [28])

Engel class	Definition
Class I	Free of disabling seizures
Class II	Rare disabling seizures ("almost seizure free")
Class III	Worthwhile improvement
Class IV	No worthwhile improvement

Similarly, Thompson and colleagues published data from their cohort > 50 years of age ($n = 55$) who underwent temporal lobe epilepsy surgery, a procedure known to carry potential risks of noticeable memory and language decline, particularly when performed on the dominant hemisphere with language function (most frequently located in the left hemisphere) [29]. They analyzed pre- and post-operative neuropsychological testing at 3 and 12 months after surgery and compared the results to two younger cohorts (ages 18–30 years, $n = 185$ and 31–49 years, $n = 220$). The neuropsychological domains assessed included visual and verbal memory, naming, and anxiety/depression. Post-operative testing did not reveal a significant difference compared to pre-operative baseline testing for any of the groups. However, when classified with a bivariate measure of scores having "improved" or "declined," the older 50+-year-old group had a significantly greater proportion of patients who experienced verbal memory or naming decline ($p < 0.05$). This was most prominent in the patients who underwent left temporal resections. The older patients were furthermore less likely to report subjective memory improvement after surgery. Thompson et al. concluded that temporal lobe surgery in older patients carries an increased risk of cognitive deterioration, particularly after left/dominant temporal resection [29].

Dewar and colleagues likewise detailed their surgical experiences at UCLA; they reported on outcomes for patients over 60 years of age [30]. Twelve patients with a mean age of 65 years (range 60–74 years) underwent resective surgery, nine of whom had standard temporal lobe resections (eight right and one left temporal). The other cases included two temporal lesionectomies and one right frontal lesionectomy. None of the patients included had intracranial monitoring. Six patients achieved seizure freedom (Engel class I). Five had nondisabling or rare disabling seizures (Engel class I-II outcomes), and one patient experienced a significant reduction in seizures, though continued to have them (Engel class III) (Table 2). Two patients suffered major neurologic complications but made a full recovery without lasting deficits. This study was limited by a lack of post-operative neuropsychological outcomes, but included life fulfillment scores. The majority of the patients (8 out of 12) reported excellent satisfaction with surgery. Although this was a small case series, the surgical outcomes were comparable to those of other studies [25, 26], without significant medical or permanent neurologic complications. The authors concluded that epilepsy surgery can be safe and effective in this population and should not be ruled out based on age alone.

Current studies on epilepsy surgery outcomes in older adults are somewhat limited as data stem from single-center

surgical case series. Additionally, much of the literature includes patients as young as age 50 years, not a particularly "geriatric" population by most definitions. Epilepsy surgery outcome studies also report mostly on temporal lobe procedures. There is less information available on extratemporal epilepsy cases, which tend to have lower rates of seizure freedom [31]. More research will facilitate the decision-making process and counseling of older adults considering epilepsy surgery.

Conclusion

New onset epilepsy disproportionately affects older patients compared with other age groups. With the elderly population growing in the U.S., geriatric specialists and neurologists will need to collaborate effectively in order to provide quality epilepsy care. New onset geriatric epilepsy is typically of focal onset, commonly associated with cerebrovascular disease. While brain tumors, traumatic brain injury, and dementia represent other causes, about half of all new onset epilepsy cases have no identifiable etiology in the elderly. Emerging evidence suggests that older adults with psychiatric disorders may be at increased risk. Regarding antiepileptic medication selection, levetiracetam, lamotrigine, and gabapentin all have relatively good tolerability in this age group. For those who continue to have seizures refractory to medications, several case series showed that epilepsy surgery can be effective. More studies are needed in elderly patients for (1) identification of risk factors in those patients with no clear etiology, (2) comparative effectiveness of newer antiepileptic medications, and (3) better clarification of complication rates of epilepsy surgery through multicenter trial design.

Compliance with Ethical Standards

Conflict of Interest Brad Kamitaki and Hyunmi Choi declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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