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SPECIAL REPORT

Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly

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Abstract

Older adults represent a highly heterogeneous population, with multiple diverse subgroups. Therefore, an individualized approach to treatment is essential to meet the needs of each unique subgroup. Most comparative studies focusing on treatment of epilepsy in older adults have found that levetiracetam has the best chance of long-term seizure freedom. However, there is a lack of studies investigating other newer generation antiseizure medications (ASMs). Although a number of randomized clinical trials have been performed on older adults with epilepsy, the number of participants studied was generally small, and they only investigated short-term efficacy and tolerability. Quality of life as an outcome is often missing but is necessary to understand the effectiveness and possible side effects of treatment. Prognosis needs to move beyond the focus on seizure control to long-term patient-centered outcomes. Dosing studies with newer generation ASMs are needed to understand which treatments are the best in the older adults with different comorbidities. In particular, more high-level evidence is required

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for older adults with Alzheimer's disease with epilepsy and status epilepticus. Future treatment studies should use greater homogeneity in the inclusion criteria to allow for clearer findings that can be comparable with other studies to build the existing treatment evidence base.

KEYWORDS
antiseizure medications, older adults, treatment

1 | INTRODUCTION

Optimal management of epilepsy in older adults requires a specialized, patient-centered, and multidisciplinary approach that draws upon the expertise of the treating team of epileptologists, neurologists, gerontologists, pharmacists, primary care physicians, specialist nurses, and aged care staff. In addition, to deliver the best quality care, families may also provide informal and formal care as part of the team.[1] A number of factors associated with aging make older adults both a vulnerable and a unique population that requires special consideration in the use of antiseizure medications (ASMs) and other treatment modalities. These include factors that may affect medication tolerability and adherence, for instance, heightened sensitivity to neurocognitive adverse effects, drug–drug interactions, reduced drug metabolism, and deleterious effects on bone health and cholesterol homeostasis through enzyme induction. The impact of ASM adverse effects is magnified by the increased burden of comorbid medical conditions that are present at or emerge during treatment, including cognitive impairment, osteoporosis, and vascular and metabolic disorders. The cognitive effects of ASMs may lead to safety concerns, in terms of reduced mobility and associated increase in the risk of falls and motor vehicle accidents. There is an increased risk of medication dosing errors due to memory decline. These concerns are compounded by aged-related social changes, for instance, retirement and lower income, and reduced social interactions with family due to living alone, resulting in loneliness and/or depression.

In this article, we critically review the evidence pertinent to the management of epilepsy in older adults, focusing on studies that have assessed treatments, including pharmacological and nonpharmacological modalities, and/or prognosis. The purpose of this article is not to provide a prescriptive treatment algorithm that needs to be individualized and based on the specific health care setting. Rather, we aim to provide a map of the key studies, highlight the current gaps and pitfalls in research studies, and propose recommendations for the optimal care model in this age group, based on the limited data available.

Key Points

- The "ideal" antiseizure medication for older adults does not exist; a personalized approach to treatment based on an individual's circumstances is needed to provide an optimal care model
- There is a lack of published large randomized clinical trials and long-term studies of antiseizure medications and surgical intervention involving the older adult population
- Greater homogeneity of older adult participants in intervention studies will provide clearer outcomes for comparability across studies and a more accurate evidence base
- Use of nursing home and community-dwelling cohorts for clinical trials and studies with less rigorous screening criteria should be considered for future research

2 | MATERIALS AND METHODS

We were aware of two systematic reviews and multiple narrative literature reviews at the time we were due to conduct our search of the literature (June 2020). With this in mind, our approach for this critical review was to conduct a systematic literature review combined with the methodology of a rapid evidence review to provide a comprehensive overview of the most up to date studies.

We searched the electronic medical database PubMed, the gray literature (Google Scholar), and the clinical trial database (clinicaltrials.gov) for articles or trials within the last 5 years (to identify the most up to date studies), using the keywords "epilepsy" AND "elderly". We included the following study types: systematic reviews, reviews, and clinical trials (randomized and observational) that reported on treatment effectiveness (ASMs, surgery, dietary therapies, and nonpharmacological interventions) and/or prognosis, and limited studies to the English language. In terms of the eligibility criteria, we included elderly people diagnosed with epilepsy who were aged ≥55 years, as

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we are aware of the inconsistency in the age cutoff used in studies in the field. The search was further supplemented by studies identified by the authors as important for inclusion. We also did an update to the search in June 2021 using the same keywords due to the growing popularity and interest of this area. As we did not conduct a systematic review, we did not use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

We identified 6381 articles in PubMed, 19 700 results in Google Scholar, and 327 clinical trial registrations. Following screening of the titles and abstracts, and subsequently reading of relevant articles in full, 58 studies and two clinical trials were included that assessed the treatment and/or prognosis of epilepsy in older adults. These studies included systematic reviews and/or meta-analyses ($n = 6$), narrative reviews ($n = 21$), randomized clinical trials ($n = 3$), and other clinical studies ($n = 28$; Figure 1). A recent narrative review provided a broad overview of most aspects relating to epilepsy in older adults.[2] A plethora of general reviews were identified on treatment; however, there were few outcome studies in older adults of interest published in the past couple of decades.

3 | SUBGROUP CONSIDERATION

Older adults with epilepsy are not a homogeneous population, but consist of various subgroups (e.g., chronic vs. new onset, employed vs. retired, living at home independently vs. living in aged/residential care) that may require different models of care.[3] Hence, broad statements about people within this population may not be relevant to an individual patient. Just as medical issues involving persons up to 18 years of age cannot be properly interpreted without using subcategories (newborn, infant, child, and adolescent), older adults should also be subdivided into appropriate cohorts. Commonly, the division is based on age range. However, because health issues may develop at different ages, further subdivisions, such as healthy older adults, older adults with multiple medical problems, and the frail elderly, those usually found residing in nursing homes, have also been proposed.[4] We propose the following subgroups be used as a guide when assessing and treating this patient population (Box 1).

4 | ROLE OF COMORBIDITIES

The Charlson Comorbidity Index (CCI) is widely used to guide the clinician on how aggressively to treat an

BOX 1 Subgroups of older adults with epilepsy

Age
• Young-old (65–74 years of age)
• Mid-old or old (75–84 years of age)
• Old-old (≥85 years of age)
Health status with epilepsy
• Healthy
• Multiple medical problems
• Frail elderly
Residential setting
• Community
• Nursing home
Marital status
• Single/alone
• Married
• Widowed
• Family

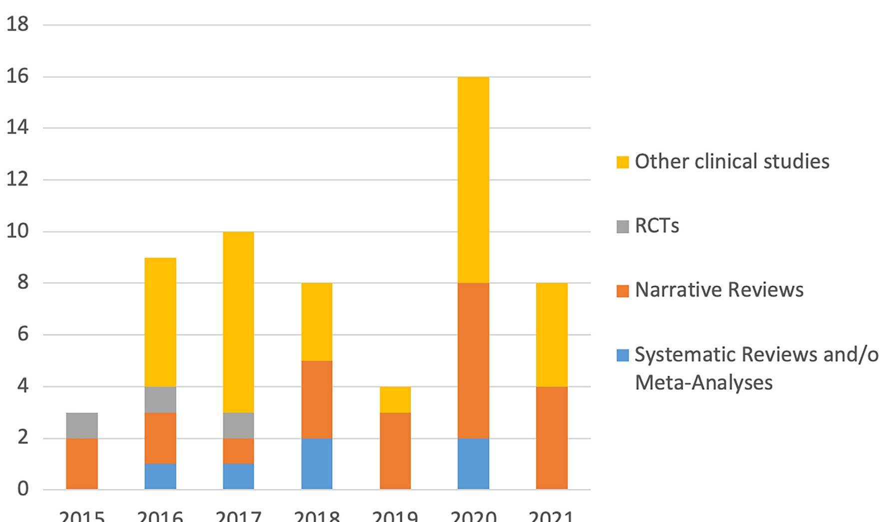

FIGURE 1 Types of studies included in this review. RCT, randomized controlled trial

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underlying condition.[5] The CCI has 10-year age categories that can be used for assessment and also takes into account comorbidities that are common in older adults. Previous studies have applied CCI to patients with newly diagnosed epilepsy,[6] and one study evaluated it in older residents in nursing homes.[7] In addition, there is growing awareness of the need to develop an epilepsy-specific comorbidity index to guide treatment, as there is often a bidirectional relationship between epilepsy and certain comorbidities.[8]

Worth highlighting are groups with specific medical diagnoses, such as individuals who have pre-existing mild cognitive impairment or dementia who develop epilepsy. The clinical evidence for the cognitive benefits of levetiracetam (LEV) is mixed; patients with amnestic mild cognitive impairment have shown both improved performance on memory testing[9] and yet no improvement with low-dose LEV. However, those patients with Alzheimer's disease (AD) and seizures have improved cognitive function with treatment with LEV.[10–12] Also, there is limited evidence in preclinical rodent models of AD that low-dose LEV improves performance in memory tasks, with reversed hippocampal remodeling.[13] It is unclear whether the cognitive benefit derives from improved seizure control or direct positive effects on memory through hippocampal remodeling, or a combination of both. New onset epilepsy is also associated with a higher incidence of objective executive deficits, whose possible causes are numerous and can alter possible outcomes.[14] We propose that routine cognitive–behavioral screening should be performed in all older adults with epilepsy. It allows for surveilling possible sedating adverse effects of common ASMs, a pathologic cognitive decline associated with an underlying neurodegenerative disorder, or increased seizure activity.

5 | STATUS EPILEPTICUS

The incidence of convulsive status epilepticus (SE) increases with age and is 15.5/100 000 in the 60–69-year age group, 21.5/100 000 in the 70–79-year age group, and 25.9/100 000 in those 80 years and older. In patients aged 60 years or older seen in the emergency department with confusion or altered mental status, approximately 16% have been found to have nonconvulsive SE.[15] At this time, due to a lack of evidence, treatment of SE in older adults is similar to that for younger adults. The recently reported ESETT study found no difference among fosphenytoin, LEV, and valproate in terms of efficacy and adverse events.[16] Unfortunately, only 13% of patients in the study were older adults (>65 years), and no subgroup analysis was performed. Given the potential difference in pharmacodynamic and pharmacokinetic response, a study of SE focused on the older age group is needed.

6 | TREATMENT OUTCOMES

Although the primary goal of treatment of epilepsy is the control of seizures, and ultimately seizure freedom, in older adults this must be carefully balanced against the potential adverse side effects that may significantly impact the quality of life (QoL) and care needs. Although Class I evidence is lacking, observational studies have suggested that treatment is more effective in older adults with new onset epilepsy compared with younger adults.[17] Monotherapy with an ASM is therefore generally an effective treatment approach in older adults who do not have complex issues or complications associated with their condition. Although many physicians would initiate treatment after a single seizure in older adults, studies are lacking as to the risk/benefit of preventing a second, recurrent seizure versus the chronic side effects of ASMs.

6.1 | Randomized controlled trials of ASMs

Table 1 summarizes the findings of published randomized controlled trials (RCTs) of ASMs that included older adults only, or performed subgroup analysis on older participants. Overall, the RCTs consistently showed that there was no significant difference in efficacy between the ASMs tested, although carbamazepine was found to be less tolerated than its comparators in several studies, leading to higher withdrawal rate.

6.2 | Systematic reviews of pharmacological treatments

We identified three systematic reviews relating to efficacy and tolerability of ASM treatment in older adults,[12,18–20] each of which had a specific research focus. One systematic review performed a meta-analysis on 10 of the 18 studies included.[20] Of the 12 ASMs studied, LEV was found to have a higher probability in achieving seizure freedom when compared to lamotrigine (risk ratio [RR] = .83, 95% confidence interval [CI] = .68–.97), and lamotrigine was better tolerated than carbamazepine (RR = 1.83, 95% CI = 1.23–2.43). LEV and carbamazepine were not found to have any significant differences in terms of efficacy and tolerability. The authors recommended that more research is required with newer generation ASMs, in particular regarding dosing. Of

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TABLE 1 Summary of published randomized controlled trials of antiseizure medications that included older adults only or performed subgroup analysis on older participants

Authors (publication year); country	Blinding	Number of older participants/mean age	Onset of epilepsy	Epilepsy syndrome/ seizure type	Intervention/outcomes	Findings/conclusions
Included older adults only						
Brodie et al. (1999); UK[65]	Double-blind	$n = 150$, aged ≥65 years, mean age 77 years	New onset	Mixed, all types	Monotherapy: • LTG ($n = 102$) • CBZ ($n = 48$) Duration: 24 weeks (after dose adjustment) Outcomes: Dropout due to AE, seizure freedom	More patients remained seizure-free after treatment with LTG (39%) compared to CBZ (21%) and continued on treatment for the study duration (71% vs. 42%)
Rowan et al. (2005); USA[24]	Double-blind	$n = 593$, aged ≥65 years, mean age 72 years	New onset	Mixed, all types	Monotherapy: • LTG • GBP • CBZ Duration: 12 months Outcomes: seizure freedom, rate of discontinuation	Seizure freedom rate: CBZ (71.4%), LTG (61.3%), GBP (60.0%) Rate of discontinuation due to adverse events: LTG (12.1%), GBP (21.6%), CBZ (31%)
Saetre et al. (2007); multiple (Croatia, Finland, France, Italy, Norway)[66]	Unblinded	$n = 184$, aged ≥65 years	New onset	$n = 70$ with idiopathic/ cryptogenic epilepsy and $n = 114$ with symptomatic epilepsy	Monotherapy: • LTG • Sustained-release CBZ Duration: 40 weeks Outcome: seizure freedom rate	No significant difference between LTG (52%) and CBZ (57%) for seizure freedom
Ramsay et al. (2008); USA[67]	Double-blind	$n = 77$, aged ≥60 years, mean age 69 years	Untreated or refractory	Focal	Monotherapy or adjunct to existing AED: • TPM 100 mg BID • TPM 25 mg BID + matched placebo Duration: 24 weeks Outcomes: time to first seizure, seizure reduction	With TPM as monotherapy, seizure freedom was "not substantially different between the two dosage groups," with "no substantial ... differences in the pattern of first seizure occurrence" With TPM as adjunctive therapy, seizure freedom was higher with 200 mg daily (50%) than 50 mg daily (21%)
Saetre et al. (2010); multiple (Croatia, Finland, France, Italy, and Norway)[68]	Double-blind	$n = 167$, aged ≥65 years, mean age 74 years	Untreated	Focal	Monotherapy: • LTG • Sustained-release CBZ Duration of follow-up: 40 weeks Outcomes: HRQoL (SEALS inventory), AEs	Effects on HRQoL and AEs "did not reach statistical significance either within or between groups"

(Continues)

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TABLE 1 (Continued)

Authors (publication year); country	Blinding	Number of older participants/mean age	Onset of epilepsy	Epilepsy syndrome/ seizure type	Intervention/outcomes	Findings/conclusions
Cumbo & Ligori (2010); Italy[10]	Unblinded	n = 95, with Alzheimer disease, aged 60–90 years, mean age 72 years	Untreated	Focal	Monotherapy: • LEV • PB • LTG Duration of follow-up: 12 months Outcomes: seizure frequency, cognitive function, mood, AEs	No significant difference in responder rate between LEV (71%), PB (64%), and LTG (59%); no significant difference in incidence of adverse events
Zhang et al. (2011); China[69]	Double-blind	n = 86, aged ≥65 years, mean age 73.4 years	Refractory	Focal	Adjunct therapy: • TPM • Placebo Duration of follow-up: 12 weeks Outcome: seizure reduction	Significantly more responders in the TPM group (47.8%) compared with placebo (7.5%); no significant differences in incidence of adverse events
Werhahn et al. (2015); Germany[25]	Unblinded	n = 359, aged ≥60 years	New onset	Focal	Monotherapy: • CBZ-CR • LEV • LTG Duration: 58 weeks Outcomes: seizure freedom, discontinuation	No difference in seizure freedom rate: CBZ-CR 33.3%, LTG 38.5%, LEV 42.6% Rate of discontinuation due to AEs: LEV (17.2%), LTG (26.3%), CBZ-CR (32.2%)
Subgroup analysis of older participants						
Nieto-Barrera et al. (2001); multiple countries[70]	Unblinded	n = 49, elderly subgroup aged 65+ years (total n = 417)	New onset or untreated	Focal	Monotherapy: • LTG (n = 35) • CBZ (n = 14) Duration: 16 weeks Outcomes: dropout due to AE, seizure freedom	No significant difference between LTG (65%) and CBZ (73%) in seizure freedom Fewer AEs with LTG (52%) than CBZ (60%); rates of discontinuation due to AEs: LTG (8%) < CBZ (13%)
Leppik et al. (2015); multiple countries[71]	Double-blind	n = 28, aged ≥65 years, mean age 68.5 years (total n = 1335)	Refractory	Focal	Monotherapy: • Perampanel 2, 4, 8, or 12 mg/day • Placebo Duration: 23 weeks Outcomes: seizure frequency, AEs	Elderly patients were "generally responsive" to perampanel (8 mg: 16.9%; 12 mg: 12.5%) vs. placebo (6.8%), similar to adult patients AEs were similar between elderly and adult patients

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TABLE 1 (Continued)

Authors (publication year); country	Blinding	Number of older participants/mean age	Onset of epilepsy	Epilepsy syndrome/ seizure type	Intervention/outcomes	Findings/conclusions
Pohlmann-Eden et al. (2016); Canada[23]	Unblinded	$n = 308$, aged ≥60 years (total $n = 1698$)	New onset	Mixed, all types	Monotherapy: • LEV ($n = 48$ vs. VPA; $n = 104$ vs. CBZ-CR) • VPA-ER ($n = 53$) • CBZ-CR ($n = 103$) Duration: 52 weeks Outcomes: treatment withdrawal, seizure freedom	Time to withdrawal was longer and treatment withdrawal less in LEV than standard AEDs and CBZ-CR; no difference in time to first seizure and seizure freedom
Baulac et al. (2017); multiple countries[21]	Double-blind	$n = 119$, elderly subgroup aged 65+ years (total $n = 185$)	New onset	Mixed: focal or GTCS	Monotherapy: • Lacosamide • CBZ-CR Duration: up to 121 weeks Outcomes: seizure freedom, AEs	Seizure freedom was similar between lacosamide and CBZ-CR in the elderly subgroup Fewer drug-related AEs with lacosamide (35%) than CBZ-CR (53%)
Brodie et al. (2016); multiple countries[72]	Double-blind	$n = 32$, aged ≥65 years, mean age 70 years	Refractory	Focal	Adjunctive treatment: • BRV 50, 100 or 200 mg/day • Placebo Duration: 12 weeks Outcomes: AEs, seizure reduction	Median reduction in seizure frequency on BRV 50/100/200 mg/day (25.5%/49.6%/74.9%) was greater than for placebo (14.0%)

Abbreviations: AE, adverse side effect; AED, antiepileptic drug; BID, twice daily; BRV, brivaracetam; CBZ, carbamazepine; CR, controlled release; ER, extended release; GBP, gabapentin; GTCS, generalized tonic–clonic seizures; Health-Related Quality of Life (HRQoL) LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; TPM, topiramate; VPA, valproic acid.

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note, the review included studies of patients diagnosed in their childhood (early onset) or middle age, and people with a diversity of comorbid health conditions, for example, dementia. Therefore, caution is needed when applying the conclusions to older adults with new onset epilepsy. The authors acknowledge that a subgroup analysis was intended for people with dementia and epilepsy and people without dementia and epilepsy, but due to the lack of studies, this was not performed. As it was a systematic review, the study types for inclusion were RCTs or quasirandomized studies only, and other study types were excluded.

Another systematic review and meta-analysis specifically studied monotherapy treatment of new onset epilepsy in older adults.[19] The authors were only able to identify five RCTs.[21–25] Overall, carbamazepine was not well tolerated and had the highest chance of discontinuation at 12 months. The newer generation ASMs—lacosamide, lamotrigine, and LEV—were the most effective treatments, in that order, to achieve 6- or 12-month seizure freedom, and no significant differences were found in efficacy across the three.

A third systematic review assessed treatment efficacy and tolerability of epilepsy in older adults with comorbid AD.[12] Only one RCT was identified that compared three treatments—two newer generation ASMs (LEV and lamotrigine) and one older generation ASM (phenobarbital).[10] It reported no differences for the proportion of persons becoming seizure-free among LEV, lamotrigine, and phenobarbital. However, LEV was able to improve cognition, whereas phenobarbital and lamotrigine worsened cognition, and in addition, phenobarbital made mood worse. Several other non-RCTs have looked at epilepsy patients with comorbid AD,[26] but there are limited studies that assess the newer generation ASMs in older adults with AD and epilepsy.

In summary, several reviews have concluded that there need to be more RCTs to assess the efficacy and tolerability of ASMs in older adults. However, such trials face unique challenges compared with those in the younger age groups. The design requires a more considered approach with less rigorous screening criteria. Ultimately, rapid titrations, strict inclusion and dosing criteria, and underrepresented populations all limit the external validity for real-life application.

6.3 | Ongoing trials

A search of the online clinical trials registries (e.g., clinicaltrials.gov) identified two clinical trials, both being conducted in France, that are currently recruiting elderly patients with epilepsy. The first trial (ZEBRE) is an observational study to evaluate the effect of eslicarbazepine acetate in patients with partial onset seizures as a first-line monotherapy or adjunctive treatment. The second study (BIOMALEPSIE) is analyzing the biological profile of cerebrospinal fluid for the predicative value of biomarkers of AD in older adults with new onset epilepsy.

6.4 | Practical considerations in drug selection

In selecting an ASM for older adults, there are four main practical considerations. First is the efficacy of the ASM to prevent seizures. Second is the potential of the ASM to cause adverse effects involving memory, cognition, mood, coordination and balance, sedation, and other QoL issues. The third consideration is drug–drug interactions, not only with other ASMs, but also with the many other drugs and "natural products" commonly used by many elderly people. Fourth, one must consider additional economic and practical factors. For instance, cost and availability may be an issue in some "rich" countries or in underdeveloped countries, dose sizes and colors that resemble other drugs may lead to confusion, and difficulty with swallowing large doses may also be an impediment.

Given that studies have found few differences in the ability of the ASMs to control seizures, selection is largely driven by the other factors. Adverse side effects from ASMs negatively impact QoL in older adults and can lead to noncompliance.[27] Studies involving younger adults have shown most ASMs can affect memory, cognition, mood, somnolence, and other issues. Older adults would likely experience these ASM-specific effects, but the degree may be different and more severe. One must thus listen carefully to a person started on an ASM, and ask questions regarding memory, cognition, mood, and behavioral effects on caregivers, sleep, and other issues. Titration schedules for dosing should be slow, as often a lower therapeutic dose than in younger adults is effective.[28]

When choosing an ASM in this population, particular attention should be paid to the possible side effects, for both their negative and positive features. Improved cognitive performance was noted in a population of patients with comorbid AD and new onset seizures when treated with LEV in comparison to phenobarbital.[10] Likewise, the mood-stabilizing effects of lamotrigine can be advantageous in this age group; those treated with lamotrigine at 12-month follow-up show significant improvement in measures of depression, when compared with those

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treated with phenobarbital or LEV.[10] Tremor at low doses is not uncommon in older individuals treated with valproic acid, and a minority can develop parkinsonism.[29] With increased awareness of the prevalence of seizures in neurodegenerative disorders, including Parkinson's disease, an advantageous ASM to use it zonisamide, as it is also an effective adjunctive treatment for motor symptoms in Parkinson's disease.[30]

Because older adults ingest many drugs and natural products for the treatment of various symptoms or diagnoses, the propensity of an ASM to interact with these must be a major consideration. These factors must be made at initiation of an ASM. One needs to approach an elderly person as one would a woman of childbearing potential. Although the person may be healthy at the time of initiation of an ASM, just as a woman may become pregnant before the next visit, older adults may develop a condition requiring an antihypertensive, anticoagulant, or other agent with interactions before the next visit. Fortunately, a great deal is known about the elimination pathways of ASMs, and this information can be put to good use without the need for further studies.

Other factors include those that may affect adherence. Ability to afford an ASM or have access to it can vary from country to country. A complicated dose regimen may make it difficult for a person with cognition issues to take an ASM as prescribed. Many elderly subjects may have difficulty with swallowing, and a formulation too large or "sticky" may cause difficulties. Many drugs, especially generic drugs, have few features such as color or shape that distinguish them from other drugs and may cause significant problems, especially if there is a pharmacy error in dispensing.

The ideal ASM for an elderly population would be one that has a long half-life to permit once per day dosing, stable serum drug level with a low peak but long absorption, no drug interactions, and very good antiseizure properties with minimal side effects on other functions. Although many of the available ASMs have some of these properties, none of them has all of them. In developing new ASMs, work should be directed at finding those with most or all of the ideal properties.

To have the best treatments for older adults, future studies should focus on specific comorbidities to identify which ASMs are best given the additional underlying issues. For example, persons with poststroke epilepsy are concerned with motor and speech function, and ASMs should be studied for their ability to avoid ataxia and speech production. ASMs for persons with epilepsy and dementia need to be evaluated for cognition. Studies should thus focus on specific groups of elderly subjects with similar medical conditions, rather than a population of elderly subjects with multiple types of disorders.

6.5 | Surgery

There is an ever-growing body of case series that suggest advanced age should not be a contraindication for epilepsy surgery[31–34]; however, this is not without controversy.[35–37] Table 2 summarizes the studies of outcomes of surgery that included the older adults only, or performed subgroup analysis on older participants. Studies reporting newer minimally invasive techniques, such as laser interstitial thermal therapy (LITT), do not address the particular outcomes of older patients; however, this population is not excluded from these studies.[38] In the oncology literature, where often the population is older, LITT is a promising technique; however, a direct comparison in morbidity has not been reported. Theoretically, the risk should be lower and clinically the recovery faster.[39] Larger studies tend to report on slightly younger surgical populations (>45 years),[33,37] whereas studies reporting on older populations (>60 years) tend to be smaller.[31,32] When comparing outcomes, the homogeneity of the reported population needs also to be taken into consideration. Homogeneous studies of resective surgery for mesial temporal sclerosis in older adults have shown excellent seizure freedom, comparable to the younger population,[40] whereas in studies that included more heterogeneous etiologies, temporal lobectomy was less successful in older patients.[37,41] Increased risk of surgical complications is both a perceived and a reported risk in this population.[42] It should be noted, however, that most patients who underwent surgery in these studies were relatively healthy, a bias that likely influenced the rate of surgical complications and perhaps seizure outcome. Due to the perceived higher risk, it is possible that the older patients are subject to more rigorous screening than their younger counterparts. Those with a visible lesion on magnetic resonance imaging that corresponded to an epileptogenic focus, as expected,[43] had better seizure outcomes.

An oft-cited reason to withhold surgery from this age group is the longer duration of disease,[35,41] due to the proposed effects of secondary epileptogenesis.[44,45] This has not been uniformly confirmed, with patients with the youngest age at onset of seizures having better outcomes in one case series.[34] Likewise, the effects of "age and epilepsy duration" are proposed to affect long-term outcomes at 3–5 years[35]; however, this has not been uniformly confirmed. Secondary epileptogenesis cannot be ignored; those with bilateral interictal activity had worse outcomes, again performing in a similar manner to younger patients.[46] The importance of this finding is that the time to which kindling and secondary epileptogenesis exerts an effect may be longer in some patients than others, and although it is prudent to perform surgery as soon as necessary, if an older patient with longstanding epilepsy presents with unilateral electrographic disease,

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TABLE 2 Studies reporting outcomes of surgery that included older adults only or performed subgroup analysis on older participants

Authors (publication year); country	Study design	Number of older participants/mean age	Onset of epilepsy	Epilepsy syndrome/ seizure type
Included older adults only				
Dewar et al. (2016); USA[31]	Retrospective case series	$n = 12$, aged ≥60 years, mean age 65 years (range = 60–74)	Mean epilepsy duration: 26.9 years Mean age at onset: 38.2 years	Focal
Punia et al. (2017); USA[73]	Retrospective case series	$n = 7$, aged ≥70 years (range = 70–77)	Median epilepsy duration: 23 years Median age at onset: 48 years	Not reported
Delev et al. (2020); Germany[74]	Prospective case series	$n = 114$, aged >50 years, mean age 56.1 years (range = 50–71)	Drug-resistant epilepsy Mean age at surgery: 56.1 years Mean epilepsy duration: 31.3 years	Not reported
Ichikawa et al. (2020); Japan[75]	Retrospective cohort study	$n = 32$, aged ≥50 years, mean age 56.1 years (SD = 21.4)	Refractory epilepsy Mean age at onset: 34 years Mean epilepsy duration: 23.4 years	Not reported
Hebel et al. (2021); Germany[76]	Retrospective cohort study	$n = 51$, aged ≥50 years	Drug-resistant epilepsy	Temporal lobe epilepsy
Gomez-Ibanez et al. (2020); Spain[77]	Retrospective cohort study	$n = 38$, aged ≥50 years	Refractory epilepsy Median age: 56 years Median epilepsy duration: 42 years	Focal epilepsy (mainly mesial temporal sclerosis)
Delev et al. (2020); Germany[78]	Cohort study	$n = 94$, aged ≥50 years	Refractory epilepsy Median age: 56 years Median duration of epilepsy: 31 years	Temporal lobe epilepsy
He et al. (2020); China[79]	Retrospective cohort study	$n = 45$, aged >45 years	Drug-resistant epilepsy Mean age at surgery: 52 years Mean epilepsy duration: 18 years	Temporal lobe epilepsy
Subgroup analysis of older participants				
Punia et al. (2020); USA[80]	Registry-based retrospective cohort study	$n = 100$, aged ≥50 years (total $n = 416$)	Refractory epilepsy	Focal epilepsy

Abbreviations: HRQoL, health-related QoL; ILAE, International League Against Epilepsy; LLF, Liverpool Life Fulfillment tool; MRI, magnetic resonance imaging; QoL, quality of life; QoLIE, Quality of Life in Epilepsy.

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Intervention/outcomes	Findings/conclusions
Resective epilepsy surgery, temporal lobe $n = 11$, frontal lobe $n = 1$ Duration of follow-up: mean 3.1 ± 2.1 years Outcomes: • Surgical outcome (Engel classification) • Life satisfaction (LLF)	At final follow-up, 11/12 (91.7%) had good surgical outcomes (Engel Class I/II); 75% had no post-op complication; 6/12 (50%) were completely seizure-free LLF was available for 11 patients; mean score 26.7 ± 6 8/11 noted excellent satisfaction; 5 noted post-op improvements in overall health
Anterior temporal lobectomy Duration of follow-up: median 1.9 years Outcomes • Surgical and medical complications • Seizure outcome • Neuropsychological and mood outcome (Beck depression score) • QoL (QoLIE-10)	6/7 patients had good surgical outcomes (Engel Class I/II); 4 were completely free of disabling seizures after a median follow-up of 1.9 years However, 3/4 patients who underwent pre- and postsurgery neuropsychological testing showed post-op decline in memory QoL index (QoLIE-10) was available for 3 patients; 2/3 showed minimal improvement; 1/3 showed no change Mood outcomes showed decline in the 2 patients not achieving Engel I seizure outcome
Resective epilepsy surgery Outcomes: HRQoL	Resective surgery for drug-resistant epilepsy in elderly patients improved HRQoL; anxiety and patients' subjective perception of postsurgical consequences showed the highest impact on HRQoL
Epilepsy surgery Duration of follow-up: median 2.7 years Outcomes • Seizure outcome • Surgical complications	• 56.3% completely seizure-free (ILAE Class I) • Surgery complications in 11.5% • Permanent deficits in 3.8% • Transient in 7.7%
Resective epilepsy surgery ($n = 5$ with reoperations) Outcomes: seizure outcome, memory performance, psychopathology	• 65% with 1st time surgeries were seizure-free after 1 year; 91% had a favorable outcome • 49% were seizure-free at last follow-up • 3/5 reoperated patients had Engel I outcome • Seizure outcome not dependent on age at surgery, duration of epilepsy • No significant decline in memory after surgery
Resective surgery Outcomes: • Seizure outcomes • Cognitive outcomes	• 86.8% achieved good outcome (Engel I/II) • None had post-op permanent neurological complications • Of $n = 22$ with neuropsychological information, 73% scored lower than in presurgical test, mainly in memory
Temporomesial resections ($n = 85$) Outcomes • Seizure freedom • Morbidity • Neurocognitive changes • Changes in HRQoL	• 60.6% seizure-free • 10% morbidity • 5 surgical complications • 5 permanent neurological deficit • 25%–45% showed losses in different domains on neuropsychological testing • 25% showed gains • Significant increase in post-op HRQoL in all domains for those who have HRQoL data available ($n = 75$)
Resective surgery Follow-up duration: median 4.53 years Outcomes • Seizure outcome • Surgical complications	• 73.3% were seizure-free • Surgical complications in 13.3% MRI-negative finding only independent predictor of unfavorable seizure outcome
Epilepsy surgery Outcomes: • QoL (QoLIE-10) • QoL difference between age groups	Age not related to pre-op, post-op or change in QoLIE-10 scores

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they should not be excluded from surgical consideration. Advanced age should not be a deterrent against epilepsy surgery, unless the predicted morbidity from anesthesia would preclude undergoing surgery. The clinical factors that predict a reduction in seizure frequency for younger adults hold also for older adults.

6.6 | Dietary approaches

Restrictive diets are in general discouraged in older adults due to the risk of malnutrition. However, there may be circumstances where older patients with epilepsy do not tolerate medications due to side effects and drug–drug interactions. No specific clinical trials have studied a ketogenic diet in older adults with epilepsy. Beyond epilepsy, few studies have investigated dietary interventions in patients with neurodegenerative diseases, finding some effectiveness but also concerning side effects such as weight loss.[47,48] Although older patients are likely to have comorbidities that require dietary adjustment, this should not constitute an absolute contraindication to offer diet therapy for epilepsy. A less restrictive diet such as low glycemic index or medium-chain triglyceride diet may be considered; however, with no studies having been done in the elderly with epilepsy, no recommendations can be made.

6.7 | Clinical practice guidelines for treatment

As awareness of the prevalence of epilepsy in older adults grows, more frequently clinical practice guidelines are including specific recommendations for this population. These recommendations are drawn from a very small number of randomized controlled trials, yielding most frequently Level B/II evidence. We were unable to identify guidelines other than drug treatment in the past 5 years.

Compared to the younger adult and pediatric populations, guidelines for older patients tend to rely on smaller studies that have investigated older ASMs more frequently than newer ASMs. The International League Against Epilepsy (ILAE) guidelines for initial monotherapy (from 2013) report comparable efficacy of gabapentin and lamotrigine and both as more efficacious than carbamazepine, topiramate, or valproic acid.[49] Joint practice guidelines from the American Academy of Neurology and American Epilepsy Society recommend that lamotrigine be considered to decrease seizure frequency.[50] Gabapentin was concluded to be possibly as effective as lamotrigine and better tolerated than carbamazepine-immediate release. Zonisamide and LEV were also concluded to decrease seizure frequency, although with less efficacy than lamotrigine.[50] In the past 10 years, there has been a trend to preferentially prescribe newer generation ASMs that is borne out of many recommendations and expert opinions made throughout the literature[51–53]; however, it should be noted that these studies have not been put through the same experimental rigor as the abovementioned guidelines. A more recent meta-analysis that included a broader range of randomized and quasirandomized trials deserves mention with regard to its findings, due to the rigorous methodology employed.[20] Lamotrigine is better tolerated than carbamazepine; however, there is a higher probability (with borderline importance) of seizure freedom when comparing LEV to lamotrigine.

7 | OUTCOMES BEYOND SEIZURE CONTROL

Risk of falls

A systematic review analyzed the risk of falls among the older adults taking ASMs. The review concluded that there is an overall association between the use of ASMs and the risk of falls and recurrent falls, although it did not necessarily imply causation.[18] Although the review was able to provide evidence for an association between ASMs and risk of falls in older adults, of the 13 studies identified, the authors did not include epilepsy in their search, choosing to keep it broad. ASMs are used for indications other than epilepsy, including mood disorders and neuropathic pain. Therefore, the findings of this review may not be generalizable to elderly subjects with epilepsy. The review is limited by having only one author reviewing studies for inclusion, thus risking assessor bias. The authors also included studies that looked at multiple ASMs within the study, except for one study that used ASM monotherapy. Future research based on the review should therefore include the addition of a standard outcome measure for falls and fractures in clinical trials, to examine the indication for use of ASMs in older adults and falls with a linkage study or prospective cohort study, and to develop ASMs that reduce the risk or number of falls.

Quality of life

The psychosocial effects of new onset epilepsy in older adults are critical for understanding the effectiveness of treatment and long-term outcomes (prognosis). A previous review identified five studies in a review specific to new onset epilepsy in older adults.[54] Following this review, we have identified a recent systematic review that assessed QoL in older adults with epilepsy.[55] The author included 10

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studies to look at the overall QoL in elderly in comparison to younger age groups, to identify which specific QoL factors were most and least negatively impacted by epilepsy and being elderly, and further which factors would be predictive of QoL. The quality of the studies was found to be moderate to high; however, only one author rated the quality of the studies included, thus no interrater reliability was performed and a potential for assessor bias may exist.

The author found that from the studies, elderly subjects with epilepsy had a poorer overall QoL compared to the general population, with energy/fatigue levels as the most affected factor. No clear differences were found between older adults and younger age groups in terms of overall QoL. However, these findings are limited by the small number of studies included, as acknowledged by the author. Although six of the 10 studies used the Quality of Life in Epilepsy-31 (QoLIE-31), they all employed additional measures. This suggests that the QoLIE-31 alone may not adequately cover the characteristics of the older adult population, as this tool was originally developed and targeted for younger age groups. It would also be more appropriate for the author to compare studies of older adults with epilepsy with similar aged peers rather than younger age groups as a control for analysis. Only three of the included studies were RCTs, with all others being observational studies, therefore reflecting a need for future research studies.

It is also important to note that QoL is a multifaceted concept, composed of numerous factors relating to physical health, social relationships, level of independence, personal beliefs, psychological well-being, and environment.[56] Hence, focusing on the overall QoL alone does not provide a comprehensive or accurate picture of the individual factors that may be affected and is potentially misleading. This is an issue identified in a previous review,[54] and places a lower value on QoL outcomes for epilepsy and older adults in regard to treatment.

We propose that future research on QoL in older adults should also include qualitative studies to provide a deeper insight into the experience of epilepsy itself from the perspective of people living with the condition. This may reflect people's values, needs, and preferences, which is important for patient-centered outcomes and care. Providing treatment that takes this into account facilitates trust and a better care provider to patient relationship, resulting in greater treatment adherence.

8 | MANAGEMENT IN THE COMMUNITY—EXTENDING THE TREATMENT PARADIGM

The community setting is of high importance in the treatment of epilepsy in older adults, most of whom have retired or have part-time/voluntary roles, instead of working full time. This stage of life is akin to the transition period we similarly observe in adolescents becoming adults that necessitates careful planning for optimal health care and management. Given the popularity of "aging in place" and "independent living," coupled with the large older adult population, there is a strong view that treatment requires an approach that focuses on a continuum of care with multidisciplinary experts working together. Closer integration of primary and secondary care has been recommended as a way of improving care,[1,2] requiring greater collaboration among epilepsy specialists, primary care physicians, nurse practitioners, residential care nurse managers, and family caregivers in the community (Figure 2). Care in the community is also highly diverse between developed countries and cultures. In some countries, the quality of care in settings like nursing homes is fairly poor and generalized to a "one size fits all" model. Low financial incentives and high physical labor are not attractive for maintaining sufficient staffing within nursing homes and assisted/supported residential living.

Once care patterns have been established, a further decline in health may necessitate a change in residential location, perhaps to an assisted living facility or shared living with a relative. Few epileptologists practice in these

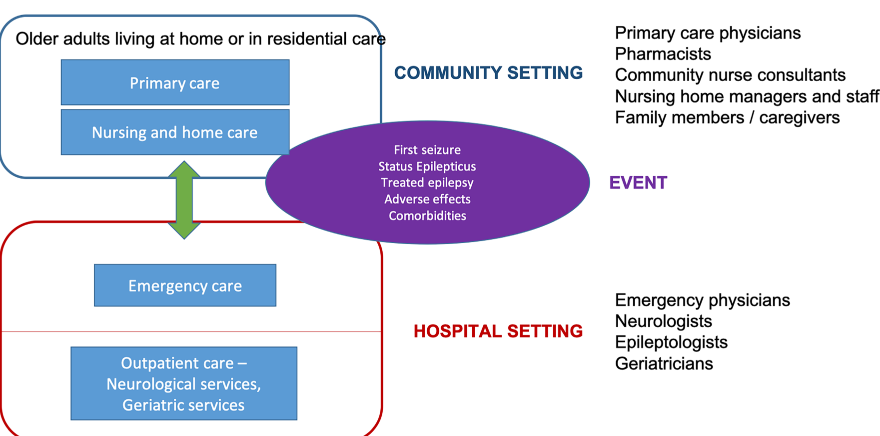

FIGURE 2 Proposed integrated model of primary and secondary care for management of epilepsy in older adults

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facilities. For the physicians providing care in nursing homes, epilepsy is often not a major focus, and their level of knowledge may be limited. Appropriate referrals to a neurologist for specialized diagnosis and management do not occur as easily as compared with younger people. Other barriers within nursing homes include rapid staff turnover, a shortage of primary care physicians, and untrained staff, leading to untimely treatment of epilepsy and inadequate service provision,[57,58] putting older adults at risk of dangerous complications and safety concerns.

A significant number of persons do not have epilepsy on admission to nursing homes, but have their first seizure with no warning and thus there is no preparation by the staff. Often this leads to emergency transportation to a hospital, and the seizure is over by the time the person arrives. In persons with a condition known to have a high incidence of new onset epilepsy, such as stroke, AD, and other conditions, the seizure resolves and the person returns to baseline within a short period of time. Nursing homes that have a protocol with trained staff in place can administer a rescue medicine to stop the seizure, and then develop a treatment plan, often including an ASM. However, there is little evidence regarding the rate of occurrence of a second seizure with various comorbidities. Because ASMs have effects on balance, cognition, and behavior, the initiation of an ASM may worsen a person's condition. This may be especially true with advanced AD. Unfortunately, there is little research on this, but personal experience has revealed this.

For community dwelling older adults with new onset epilepsy, integrated and consistent care networks of physicians and other health care providers need to be developed, and the many barriers to access deriving from social issues should be eliminated. Community providers should develop relationships with chronic care facilities so that if a person with epilepsy is admitted to one, the transition is accompanied by a full care plan. Nursing homes need to develop protocols to treat someone with a first seizure to avoid the chaos that often results when the staff does not have clear protocols. Although it is common to initiate ASM treatment after the first seizure in older adults, there is very little evidence for the efficacy and safety of this practice. Activities of daily living, comorbidity burden, and cognition scores were worse in persons with than without epilepsy or seizures.[7] It is not known how much of this is from the ASMs. Therefore, although difficult to do, controlled studies need to be done. These are not unethical in this cohort, because it is not known whether treatment to prevent a second seizure in the remaining lifetime may be worse than treating with ASMs with their side effects to prevent a seizure that may not occur.

A lack of knowledge, misunderstanding about epilepsy, and negative attitudes or stigma toward persons with epilepsy by older adults, their support networks, and community health professionals affect its management. A study in Australia found that elderly people had a poor level of knowledge about epilepsy and its management.[59] Furthermore, in the same study, elderly people living with epilepsy, although they had more knowledge of the condition compared with those without, still did not have adequate knowledge. Providing clear information has been suggested to assist people living with epilepsy to cope and manage their condition better.[60] Fortunately, educational programs greatly improve the knowledge of epilepsy and persons with epilepsy, and these programs are found to lead to a better experience of living with the condition, including more positive psychosocial states.[61] However, at present, educational programs in older adults with epilepsy are scant.

International peak bodies have an important role to play in providing education and information to health professionals in the hospital and community settings, and to older adults and family caregivers. Epilepsy Scotland has produced guides for health professionals in primary care and the community about the management of epilepsy in later life.[62] Similarly, the Epilepsy Foundation in Australia in partnership with other key community organizations has developed a suite of resources for older adults, families, and aged care staff.[63] Although these guides are evidence-based, their effectiveness in clinical practice and the community is yet unknown, as no evaluation studies have been published. Given the differences in the older adult population compared to younger age groups, it would be of particular benefit to clinicians in all settings to have specific evidence-based guidelines for assisting with treatment. Sauro and colleagues found that there is a gap for clinical practice guidelines specifically for older adults with epilepsy.[64] However, without suitable, high-level quality evidence of treatment interventions in older adults, this will remain a gap.

9 | RECOMMENDATIONS FOR AN OPTIMAL CARE MODEL AND FUTURE RESEARCH

No randomized clinical trials have been conducted within the past 5 years. Based on the available evidence, we propose the following recommendations for health professionals and researchers in the field for the treatment of epilepsy in older adults. We propose a more innovative treatment approach than what is currently provided that

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is specialized, holistic, and patient-centered, with a focus on long-term care.

Treatment

- Older adults diagnosed with new onset epilepsy should be prescribed with ASMs that account for their comorbidities. If they have cardiac disease, ASMs that may prolong QTc intervals should be used cautiously. Doses of ASMs that are primarily renally eliminated may need to be reduced in persons with compromised kidney functioning. Persons receiving medications metabolized by the liver, or who have liver disease, should avoid ASMs that are metabolized by the liver or have a potential for drug–drug interactions. Enzyme-inducing ASMs may also increase the risk of osteoporosis and should therefore be avoided in this age group.
- ASM blood levels should be measured when the therapeutic goal is reached to determine the individual's therapeutic range and whenever a breakthrough seizure occurs, toxicity develops, or a change in health condition happens.
- Treatment should be commenced as early as possible to facilitate better long-term outcomes.
- When prescribing ASMs for older adults, the dosage may need to be lower than those used for the general population. Titration should be slow, but this needs more evidence.
- Monitor cognitive decline with routine cognitive behavioral screening.
- A geriatrician, primary care physician, or neurologist with specialized expertise should conduct regular reviews (at least monthly).
- Regular psychological assessments should be performed for early detection of negative consequences or side effects such as depression, social isolation, loss of control, and feeling dependent on others.

Care provision and outcomes

- Neurologists, geriatricians, general practitioners, and aged care providers need to work together to best manage this patient group, with a focus on multidisciplinary (including family and friends) management.

- Risk management and long-term monitoring of ASMs by physicians in both primary care/community and the outpatient setting should be done for:
    - Falls (to prevent nursing home admissions) and subsequent fractures;
    - Cognitive decline using screening tools;
    - Well-being/QoL (in particular for fatigue or mental health issues).
- Unified standard provision of care is recommended, with a particular focus in transitioning from community to residual pathway with different levels of assisted living within one roof to provide a consistent team of support workers and continuity of care.

Community

- Integrated and consistent care networks of physicians and other health care providers need to be developed.
- Community providers should develop relationships with chronic care facilities so that if a person with epilepsy is admitted to one, the transition is accompanied by a full care plan.
- Nursing homes need to develop protocols to appropriately manage a resident who experiences a first seizure, in terms of both acute management/monitoring and referral pathway.
- Formal education programs for public and primary health care providers should be developed for the community to raise awareness. For example, the field peak bodies —the ILAE and the International Bureau for Epilepsy—need to arrange in partnership with community organizations specialist educational and training programs for community health professionals (pharmacists, primary care physicians, nurses, aged care managers, and personal care assistants), individuals, and families, and evaluate their effectiveness.

Future research and clinical trials

- A standardized and accepted age definition or classification of epilepsy in older adults should be agreed on by the field to allow for more consistency and pooling of studies with smaller sample sizes.
- Studies should confirm the effect of age and duration of epilepsy on long-term outcomes of surgery, and to evaluate the risks and benefits of surgery in older adults.
- Studies need to ensure that the patient groups included are not mixed in terms of their time from diagnosis (i.e., newly diagnosed vs. chronic epilepsy).
- More granular data about epilepsy in the nursing home is required; there is a case for a prospective long-term study of people who enter nursing homes and develop epilepsy subsequently compared with those who develop epilepsy in the community setting.
- We recommend the development of clinical practice guidelines specific for the treatment of epilepsy in older adults.
- A roadmap or research strategy should be developed, with a call to funding bodies to make epilepsy research in the older population a priority.
- Larger and longer-term RCTs that study the efficacy, tolerability, and pharmacokinetics of ASMs are needed.

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- An epilepsy-specific scale for assessing QoL in older adults is needed.
- Changes in QoL should be monitored over the long term, examining the difference between older adults who are community dwelling and those living in nursing homes.

10 | CONCLUSIONS

It is clear upon critical review of research evidence that the management of older patients with epilepsy requires a more nuanced approach that is specific to this particular age group. This group defines itself biologically, clinically, and socially as a population distinct from younger adults, and we should not be averse to treating them as such. Children are not therapeutically managed as "young, small adults" but are named a separate pediatric population and treated according to pediatric principles; the same should hold true for the older adult population. However, there are no current guidelines from leading professional organizations specific to the management of epilepsy in this age group. Existing measures for QoL and psychiatric comorbidities often address difficulties specific to the life of a working adult, not that of an individual who is retired and wishes to live independently as long as possible. The needs of caregivers, who are often vital partners in management, have been poorly addressed.

It is our view that another review or meta-analysis will not generate new evidence that can adequately address the needs of this ever-growing population. Subgroup analysis will not be able to directly answer key therapeutic questions, such as whether a new ASM is effective and tolerated in older adults. Rather, it is time to perform research that is tailored to the older adults living with epilepsy. The optimization of their management and treatment cannot come to fruition until we recognize and acknowledge, bereft of any notion of ageism, that older adults with epilepsy are a unique population whose needs should be met with the principles of geriatric medicine. We advocate the acknowledgment of geriatric epilepsy as an entity. This will help focus the community's effort in addressing the clinical challenges it poses with original research specific to older adults. Concerted effort across disciplines is needed to yield meaningful findings and guidelines to improve the outcomes of older adults living with epilepsy.

AUTHOR CONTRIBUTIONS

All authors were involved in the planning and design of this report. Loretta Piccenna, Rebecca O'Dwyer, Ilo Leppik, and Patrick Kwan drafted the manuscript. All authors participated in meetings and discussions of the Task Force, and in critical revision of the draft, and approved the final submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST

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