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Review

Epilepsy in the elderly: Unique challenges in an increasingly prevalent population

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ABSTRACT

Elderly individuals (aged at least 60 or 65 years) represent a rapidly growing segment of the population. The incidence and prevalence of epilepsy is higher in this age group than in any other. Diagnosing epilepsy in the elderly can be challenging because the causes and clinical manifestations of seizures often differ as compared with younger individuals. Particular differential diagnoses, such as syncope and amyloid spells, are commonly encountered in the elderly population. A diagnosis of epilepsy has important implications in the older adult, many of which already present a variety of concomitant complex medical problems, such as cognitive impairment, comorbid cerebrovascular disease, and frailty. The treatment of epilepsy in the elderly is complicated by a variety of factors related to aging, including physiological changes, medical comorbidities, and polypharmacy. In this narrative review, we will address the descriptive epidemiology, clinical presentation, differential diagnosis, diagnostic evaluation, treatment, and prognosis of epilepsy in the elderly individual.

1. Introduction

The most rapidly growing segment of the US population, individuals aged over 65 years, is projected to nearly double from 49.2 million in 2016 to 94.7 million by 2060 [1]. New-onset epilepsy has a higher incidence in the elderly than in any other age group. Epilepsy is costly and has a significant effect on elderly patients' quality of life, health status, and level of functional independence [2]. The diagnosis and treatment of epilepsy in the elderly are challenging, owing to atypical seizure presentations, the broad differential diagnosis, the frequent use of numerous comedications, the high prevalence of comorbidities, and the pharmacological changes associated with aging. Clinicians need expertise to minimize morbidity and maximize quality of life in this increasingly complex population.

2. The definition of an elderly individual: a heterogeneous population

The elderly are commonly defined as individuals aged 60 to 65 years or older. The origins of these age cutoffs are arbitrary and date back to the end of the nineteenth century when European countries legislated the age at which a person became eligible to receive pension benefits. The United Nations uses 60 years as a cutoff to refer to elderly people, while most high-income countries use 65 years [3].

2.1. Defining late-onset epilepsy

It has been proposed that new-onset epilepsy in the elderly exists as a different entity than in younger adults because of differences in the underlying etiology, seizure characteristics, and comorbidities. One recent study used machine learning to arrive at an empirical definition of the threshold age that best characterizes “elderly-onset epilepsy” [4]. Fourteen clinical variables were associated with age-specific new-onset epilepsy in adults. Stroke and a current chronic medical condition predicted age at onset above 65 years. A transition to “elderly-onset

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epilepsy" begins as young as age 35 years in some individuals and accelerates at age 45 years. Based on these data-driven analyses, the authors suggested a threshold cutoff for elderly-onset epilepsy of 65–70 years when a dichotomous definition is necessary, while emphasizing that features of late-onset epilepsy exist across a spectrum of ages.

2.2. The frail elderly

The differences in health status in the elderly population are not explained by chronological age alone. A concept of particular interest is the "frail elderly". Frailty is a physiological state of high vulnerability to adverse health outcomes in the face of stressors such as acute illness, surgery, or trauma. Frailty is associated with an increased risk of falls, fractures, procedural complications, hospitalization, institutionalization, physical disability, delirium, cognitive decline, and mortality [5]. Numerous causes and contributing factors include medical comorbidities, unexplained progressive age-related functional decline as well as genetic, environmental, educational, and psychological factors [5]. The combined effect of these contributing factors results in an accelerated biological decline in various physiological systems and decreased physiological reserve. Compared with chronological age, frailty relates more strongly to a decline in functional independence and explains varying levels of disability among elderly individuals with similar comorbidities [5].

An international group of delegates has recommended that all individuals over age 70 years be screened for frailty [6]. There is a lack of consensus, however, over what constitutes the "frailty" criteria. The most commonly used measurement tool, the Fried Frailty Phenotype (Table e-1), is purely based on physical deficits [7]. Other screening tools, such as the Reported Edmonton Frail Scale, also include cognitive, social, psychological, and functional declines in their operationalization of frailty [8]. At least 65 other different frailty screening tools have been used in the literature [9].

Because of the lack of a consensus on the measurements of frailty, its reported prevalence in the elderly varies from 4 to almost 60%, but is estimated to be 10.7% in community-dwelling elderly individuals based on a recent systematic review [10]. In contrast, in the nursing home population, as high as one-half of elderly residents are frail [11].

One expects a different management of epilepsy in the frail elderly compared with a relatively healthy individual of the same age. Some authors have proposed subdividing elderly individuals with epilepsy into nine subgroups based on chronological age, presence or absence of multiple medical comorbidities, and frailty [12].

3. Descriptive epidemiology

Older age has been shown to be an independent risk factor for both acute symptomatic seizures and new-onset epilepsy [13].

3.1. Incidence of acute symptomatic seizures

Seizures that occur in association with an acute event that temporarily alter the metabolic or structural homeostasis of neurons are named "acute symptomatic seizures". The incidence of acute symptomatic seizures linearly increases with age after age 35 years, reaching 1.23 per 1000 person-years among people aged 75 years and older [14].

3.2. Prevalence and incidence of epilepsy

The point prevalence of active epilepsy increases with age, from 0.7% for those aged 55–64 years to 1.2% for those aged 85–94 years [15]. Recent USA Medicare beneficiaries' data including over 95% of the US population above age 65 years reported a point prevalence of 10.8/1000 [16]. The incidence of epilepsy is represented by a U-shaped curve, with the highest estimates at both extremes of the age spectrum (Fig. 1) [13]. Estimates of the incidence of new-onset epilepsy in the elderly vary between 1 to 3/1000 person-years [13,16–19].

3.3. Drug-resistant epilepsy

Drug-resistant epilepsy (DRE) is the failure to respond to at least two appropriate and well-tolerated antiepileptic drugs (AEDs) [20]. Individuals with late-onset epilepsy (after age 60 years) generally achieve seizure freedom with lower doses and fewer AEDs [21]. We found one study that specially examined the prevalence of DRE in adults age 60 years and older and found that they were less likely to meet DRE criteria as compared with younger patients (21% vs 51%, $p = 0.001$) and were more likely on AED monotherapy [22].

4. Etiology and risk factors

4.1. Acute symptomatic seizures

Causes of acute symptomatic seizures in the elderly are summarized in Table 1. Acute cerebrovascular events account for half of acute symptomatic seizures in older individuals [14]. Risk factors of early poststroke seizures (EPS, seizures occurring within the first 7–14 days of a stroke) are described in Table 2. The majority (over 60%) of EPS occur either at the time of stroke onset or within the first 24 h [14,23].

Acute metabolic disturbance and toxic (drug-related) etiology each explain approximately 15% of acute symptomatic seizures in the elderly [17]. Elderly individuals are at an increased risk of metabolic disturbances and drug toxicity because of increased comorbidities, polypharmacy, and age-related changes in hepatic and/or renal function. Examples of acute metabolic disturbances associated with seizures include hyper- and hypoglycemia, hypocalcemia, hypothyroidism, as well as uremic and hepatic encephalopathy [14].

Several medications can lower the seizure threshold in an elderly individual. Most drug withdrawal seizures in the elderly are related to alcohol or benzodiazepines. The peak incidence of a first alcohol withdrawal seizure is in the fifth and sixth decades of life [24].

4.2. The etiology of new-onset epilepsy in the elderly and associated risk factors

The high prevalence of many important epilepsy risk factors accounts for a proportion of the increased risk of epilepsy of the elderly. Cerebrovascular disease, dementia, cerebral neoplasms, and head trauma are the most common central nervous system (CNS) disorders associated with new-onset epilepsy in elderly people (Table 1) [25]. Despite neuroimaging advances, the underlying cause of epilepsy remains unknown among more than one-third of older individuals [21].

4.3. Cerebrovascular disease

Cerebrovascular disease is by far the strongest independent predictor for both acute symptomatic seizures and new-onset epilepsy in individuals over 65 years of age [14,19]. Up to 65% of elderly people with new-onset epilepsy have evidence of prior cerebrovascular disease, a more than fivefold higher prevalence compared with age-matched individuals [19]. Individuals aged ≥65 years with a history of stroke have a relative hazard of developing new-onset epilepsy more than threefold greater than individuals of the same age group [18].

The distinction between EPS (first 7–14 days after a stroke) and late poststroke seizures (LPS) is important because of the difference in presumed pathophysiology and risk of recurrence. Early poststroke seizures are caused by cellular membrane instability and the release of glutamate-mediated excitotoxicity. Late poststroke seizures, on the

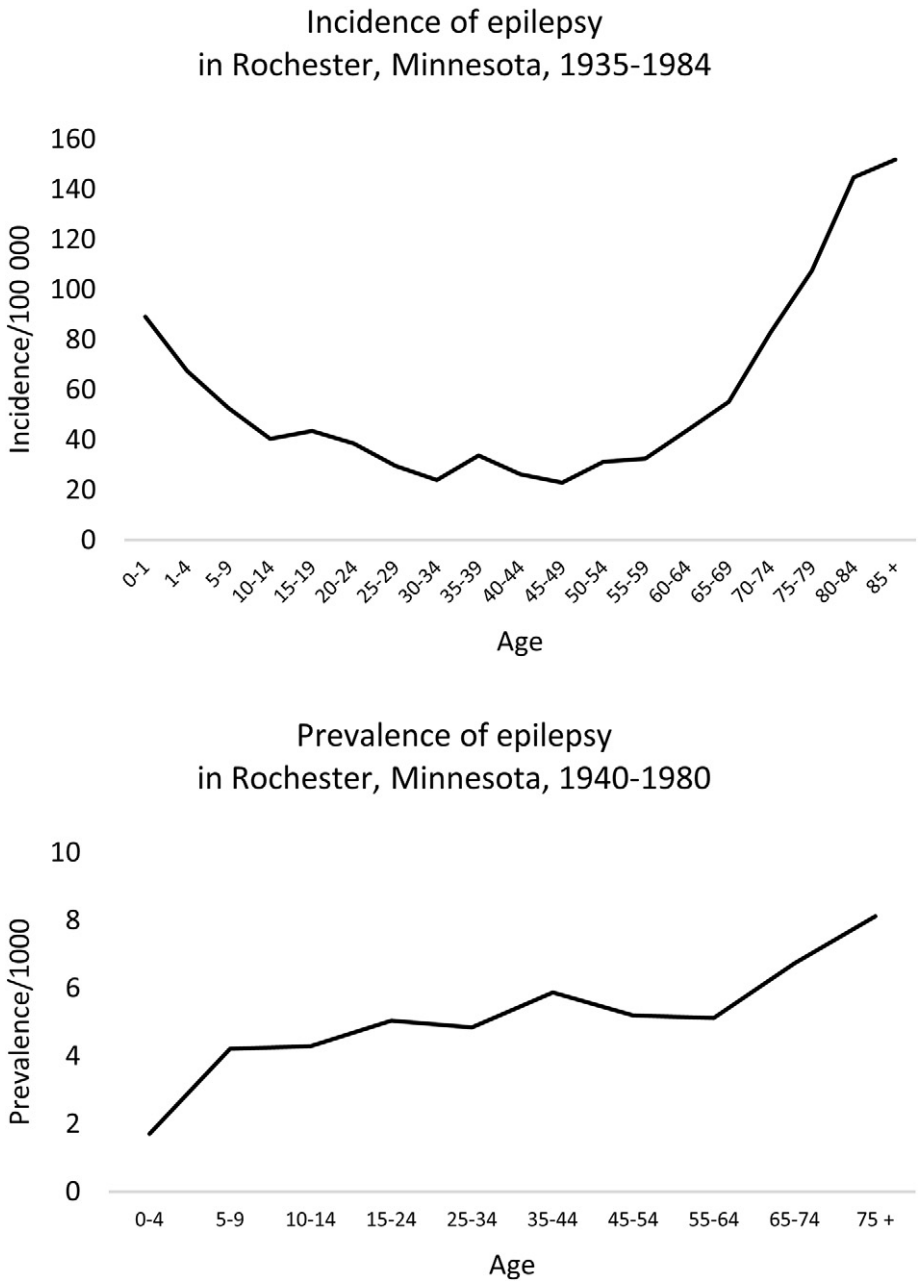

Fig. 1. Incidence and prevalence of epilepsy across age groups.
Footnote: Adapted from Hauser et al. [95] and Hauser et al. [13].

other hand, are caused by gliosis, neuronal deafferentation, and collateral sprouting [23]. Because EPS are the result of an acute cerebral insult, they carry a lower risk of recurrence. In hospital-based studies, adults develop epilepsy after approximately a third of EPS but after over 90% of LPS [26]. Up to 6% of elderly individuals will experience an EPS after a stroke and a similar proportion will experience LPS [23,27]. Independent seizure predictors are summarized in Table 2.

Epilepsy appears to also predict the future development of cerebrovascular disease. Elderly individuals with a previous history of seizures have a relative hazard of stroke of 2.89 [95% confidence interval (CI): 2.45, 3.41] as compared with age-matched individuals with no history of seizures [28]. Some have termed this phenomenon "vascular precursor epilepsy". Adults with epilepsy have a greater burden of vascular risk factors and disease as compared with their peers, even in the absence of stroke [29]. People with childhood-onset epilepsy also have greater magnetic resonance imaging (MRI) cerebrovascular changes at 45 years of follow-up as compared with controls [30].

4.4. Dementia and epilepsy

Neurodegenerative diseases predispose to epileptogenesis because of various CNS structural and biochemical changes, such as the loss of inhibitory neurons in hippocampal and neocortical areas, glutamate-mediated excitotoxicity, disturbances in neurotransmitters, and ion channel dysfunction [31].

Elderly individuals with dementia have a two to tenfold increased risk of developing new-onset epilepsy [25,32]. Similar risk estimates are reported in Alzheimer's disease and vascular dementia [33]. Ten to 22% of individuals with Alzheimer's disease will have at least one lifetime unprovoked seizure. Contributing risk factors include early-onset Alzheimer's disease (before age 65 years) and familial presenilin I or

Table 1
Causes of acute symptomatic seizures and new-onset epilepsy in elderly people.

Cause	Approximate proportion
Acute symptomatic seizures (provoked) seizures	
Acute hemorrhagic and ischemic stroke (within 7–14 days) [14,17]	40–55%
Acute metabolic illness (e.g., electrolyte disturbances) [17]	15%
Toxic: alcohol, drugs, and drug withdrawal [17]	15%
Recent traumatic brain injury [14,17]	4–10%
CNS infection [14,17]	2–3%
Others or unknown (e.g., subdural hematoma) [14,17]	5–20%
New-onset epilepsy	
Cerebrovascular disease	30 to 65%[a]
Dementia [19,24,31]	10–20%
Cerebral neoplasm [19,21,24]	3–11%
Remote traumatic brain injury [19,24,40]	1–7%
Remote infection [24]	0–1%
Vascular malformation [21]	0–3%
Others or unknown [24,40]	30–50%

[a] 30% for a documented history of stroke and up to 65% for any evidence of cerebrovascular disease (e.g., subcortical microvascular disease on neuroimaging) [19,40].

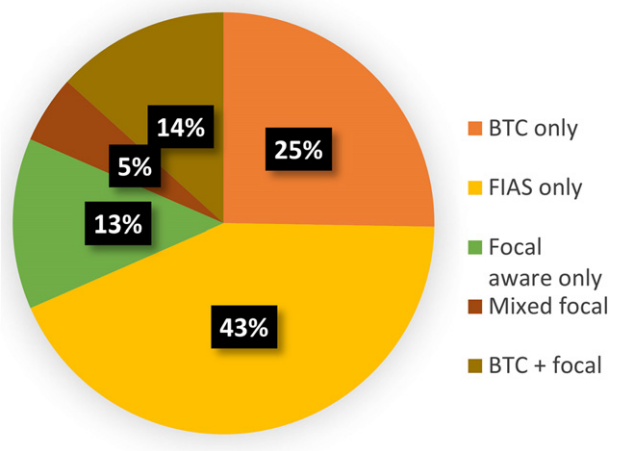

Fig. 2. Seizure semiology in new-onset epilepsy in the elderly. BTC = Bilateral tonic–clonic; FIAS = Focal onset with impaired awareness seizure.
Footnote: Adapted from Rowan et al. [40].

amyloid precursor protein gene mutations (as described in late-onset myoclonic epilepsy in Down syndrome) [31].

The risk of developing dementia in people with epilepsy is less clear, although some data point to a bidirectional association. Temporal lobe resections have revealed hyperphosphorylated tau pathology in older individuals with DRE and progressive cognitive decline [34]. In addition, people with childhood-onset epilepsy have greater amyloid deposition at 50-year follow-up compared with controls [35]. In one prospective population-based study, individuals aged at least 50 years with epilepsy had a relative risk of 1.5 (95% CI: 1.4, 1.7) of developing dementia over 8 years [36].

4.5. Other CNS lesions: cerebral neoplasms and remote traumatic brain injury

Elderly individuals with cerebral neoplasms or remote traumatic brain injury (TBI) are about two times as likely to develop new-onset epilepsy [25]. Seizures are the presenting sign in 20–40% of cerebral neoplasms in adults [37]. Older individuals are more vulnerable to TBI because of the increased risk of falls in old age [38].

5. Presentation

5.1. Type of seizures

Focal impaired awareness seizures (FIAS, previously known as "complex partial seizures") represent about 40–50% of new cases of seizures in the elderly (Fig. 2) [24,39,40]. On electroencephalogram (EEG) recordings, a temporal localization is most frequent [41]. Table 3 summarizes the differences in epilepsy semiology between elderly and younger adults.

Table 2
Risk factors for seizures after stroke.

Early poststroke seizures	Late poststroke seizures and epilepsy
Hemorrhagic transformation of ischemic stroke [23,97]	Age below 65 [27]
Hyperglycemia [23]	Recurrent stroke [98]
Alcoholism [97]	History of early poststroke seizures [98]
Risk factors for early and late poststroke seizures	
Size of total anterior circulation infarct [23,27,98]	
Hemorrhagic stroke (subarachnoid hemorrhage, intraparenchymal hemorrhage)[a] [27,97]	
Cortical involvement with risk lower in lacunar and posterior circulation infarcts [27,97]	
Clinical stroke severity (NIH stroke scale >14) [23,27,97]	

[a] Hemorrhage is considered a long-held risk factor for late poststroke seizures although a recent meta-analysis failed to confirm this association [97].

5.2. Late-onset generalized epilepsy

A few cases of generalized epilepsy of presumed genetic origin (formerly called idiopathic generalized epilepsy) starting after the age of 60 years have been described. A prospective multicenter study identified only one participant (1.3%) with generalized epilepsy of presumed genetic origin among 79 elderly with late-onset epilepsy; compared with 9 cases (13%) among elderly with early-onset epilepsy; versus a significantly higher proportion (18%) in younger adults (<50 years old) [21]. Elderly people with early-onset generalized epilepsy of presumed genetic origin usually have long quiescent periods in adulthood before relapsing in older age [42].

5.3. Status epilepticus (SE)

In hospital-based studies, about 30% of first seizures in the elderly present as status epilepticus (SE) [43]. The overall mortality of SE in the elderly is estimated at 35% and increases to up to 50% after age 80 years [43]. Predictors of mortality include de novo status, status severity and duration, presence of an underlying CNS structural lesion, and a higher number of comorbidities [43,44].

Table 3
Proposed differences in presentation between the elderly and younger adults.

Feature	Elderly	Younger adults
Auras[a] [55]	Less reported	More common
Automatisms[a] [55]	Less observed	More common
Motor features (focal and/or generalized) [41]	Infrequent	Frequent
Semiology of FIAS [21]	Simpler and shorter	More elaborate
Subtle episodes of transient confusion [99]	More frequent	Less frequent
Postictal state (confusion, aphasia, paresis) after a secondarily generalized seizure [21]	Hours–days	5–15 min

FIAS = focal impaired awareness seizure.
[a] Some conflicting data.

Ischemic stroke is the most common cause of SE in the elderly [43]. The majority of SE in the elderly present as nonconvulsive status epilepticus (NCSE) with impaired awareness (83%), while the minority (17%) present with motor symptoms [44]. The prevalence of NCSE may be overestimated due to the effect of comorbid medical conditions on the neurological status of an individual (e.g., a failure to regain consciousness following a prolonged seizure due to an intracranial hemorrhage) as well as controversies regarding the electrophysiological criteria for epileptic seizures on EEG [45]. Nonconvulsive status epilepticus can manifest as a prolonged confusional episode mimicking delirium, psychosis, or unexplained coma, with a paucity of distinguishing features. Risk factors for SE in the elderly include a previous history of seizures, cerebrovascular disease, nonvascular dementia, and acute medical illness (cardiac, respiratory or hepatic, hyper- or hyponatremia) [44].

Late-onset absence SE is generally described in the elderly as a reactivation of a previous generalized genetic epilepsy (previously known as idiopathic generalized) [46]. De novo late-onset absence SE (with no prior history of seizures) has also been reported in older individuals (most commonly women) after benzodiazepine or alcohol withdrawal, or initiation of medications that lower the seizure threshold [46–48], and more rarely without any identifiable triggers [42]. A correct diagnosis of absence SE has important therapeutic implications since worsening can occur with the administration of intravenous (IV) phenytoin (PHT) [49].

According to a recent systematic review, very few studies have examined the treatment of SE in the elderly [50]. A reversible etiology should be sought promptly since more than half of NCSE in the elderly are precipitated by acute illness. Aggressive administration of AEDs may lead to greater neurotoxicity in the elderly than in a younger adult. Choice of AED should be individualized according to age, previous response to AED, potential for drug interactions, and comorbidities. Progressive AED escalation may include monitoring of AED serum levels for efficacy and toxicity [50].

The use of first-line (benzodiazepines) and second-line AEDs [e.g., PHT, valproate (VPA)] has been inferred from data in the general adult population with SE. Phenobarbital (PB) should be avoided because of its greater potential for adverse events (AEs) and drug interactions [50]. Small studies with few participants have documented the efficacy and tolerability of IV levetiracetam (LEV) [51,52], IV VPA [53], and IV lacosamide (LAC) [54] in the elderly with SE.

6. Differential diagnosis

6.1. Challenges in diagnosing epilepsy in the elderly

Making an accurate diagnosis of epilepsy in the elderly is challenging, as demonstrated by an average delay of 1.7 years from the time of symptom onset to a formal diagnosis [24]. In a large study in older veterans, epilepsy was a diagnostic consideration after initial evaluation by a primary care physician or internist for only 73% of individuals ultimately diagnosed with epilepsy. Initial diagnoses included altered mental status, confusion, blackout spells, memory disturbance, syncope, dizziness, and dementia [55].

Challenges may arise from unreliable history-taking in the presence of cognitive deficits. Obtaining reliable witnesses is essential but often problematic since the elderly, based on studies in the USA, are more likely to live alone [56]. Seizures are often difficult to observe. Subtle FIAS can be misattributed to comorbid dementia or delirium [31]. Nonepileptic episodes of unresponsiveness can be seen in Alzheimer's disease and dementia with Lewy Bodies. Delirium and seizures may coexist in the same patient with an acute CNS insult (e.g., metabolic illness). Myoclonus and hallucinations can be features of both delirium and seizures. Postictal Todd's paresis may be misdiagnosed as stroke, while postictal confusion may be mistaken for delirium [21].

Comorbid cerebrovascular and cardiovascular disease (stroke or syncope) can be misidentified as seizures and vice versa [57]. Focal cerebral ischemia caused by high-grade carotid stenosis can produce limb-shaking transient ischemic attacks (TIAs) resembling focal clonic movements. Sudden speech arrest or aphasia can be a manifestation of either seizures or TIAs. Sleep disorders such as rapid eye movement sleep behavior disorder (RBD) increase in prevalence with age and can be mistaken for nocturnal seizures. Undiagnosed RBD coexists in up to 13% of the elderly with epilepsy [58].

The differential diagnosis of epileptic seizures in an elderly individual is provided in Table 4. Conditions that will be discussed in more detail are the following: syncope, amyloid spells, and transient epileptic amnesia (TEA).

6.2. Syncope

In an elderly individual presenting with falls, the initial step is to determine whether consciousness was impaired. In the presence of unwitnessed falls with an unreliable history (cognitive impairment or amnesia), syncope and epilepsy remain diagnostic possibilities. Compared with a younger adult, syncope in the elderly is more likely to result in incontinence or injury [59]. Cardiac syncope can occur in the supine position [59]. During recovery, sustained hypotension can result in prolonged confusion, resembling a postictal state [57]. Elderly individuals with impaired cognition may fail to recognize or remember prodromal symptoms. The frequency of autonomic prodromal and postdromal symptoms (e.g., nausea, feeling of cold) reported by the elderly is much lower than in younger individuals. During the syncopal phase, tonic posturing and myoclonic movements occur in the majority of people [60], although these are less frequently observed in the elderly as compared with the younger adult [59]. Different types of syncope with suggestive features are described in Fig. 3.

A cardiovascular evaluation should include a physical examination with orthostatic blood pressure measurements, and a 12-lead electrocardiogram (ECG) [61]. Additional cardiac testing (e.g., ECG, tilt-table test) is performed based on the degree of clinical suspicion. False-negative routine ECGs are common and a more prolonged recording (i.e., 24–48 h Holter) may be considered if episodes are recurrent and frequent [61]. Interictal EEG has an extremely low diagnostic yield in distinguishing seizures from syncope, and rarely results in significant subsequent change in management [62]. Tilt-table testing can be used to confirm neutrally mediated syncope or autonomic dysfunction [61]. Recent guidelines from the European Society of Cardiology recommend intensive and prompt evaluation (in an observation unit or hospitalized) for individuals with high-risk history, examination, or ECG findings [61]. These guidelines present a comprehensive list of what are considered “high” as opposed to “low” risk items [61].

6.3. Transient focal neurological episodes (TFNEs) in cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a vascular disease defined by the progressive deposition of beta amyloid in the wall of cortical and leptomeningeal small arteries of older individuals. Common presentations include lobar intracerebral hemorrhage and progressive cognitive deficits. Transient focal neurological episodes (TFNEs), also named “amyloid spells”, are a less common presentation of CAA (present in 14% of cases at presentation) [63]. They can equally present with positive neurological symptoms, mimicking focal seizures, or negative neurological symptoms, mimicking TIAs. Positive symptoms are usually described as recurrent, stereotyped, spreading paresthesias (marching smoothly over contiguous body parts over 1–15 min), positive visual phenomena (flashing lights, “zig-zags”), or limb-jerking. Episodes typically last fewer than 30 min [63].

6.4. Transient global amnesia vs transient epileptic amnesia

In TEA, elderly individuals present with brief episodes of anterograde and/or retrograde amnesia, which are often misdiagnosed as

Table 4
Differential diagnosis of seizures in the elderly.

Category	Diagnosis	Features
Falls without altered consciousness	Accidental falls	• Witnessed/reliable history with no impairment of consciousness
Falls with altered consciousness	Syncope	• See Fig. 3
Confusion and memory disturbances	Delirium	• Structural or metabolic CNS insult (e.g., infection, hypoglycemia) • May coexist with seizures
	Dementia [64]	• Progressive cognitive deficits with functional impairment • Episodic unresponsiveness or decreased alertness in LBD and AD • Possible frontal release signs, myoclonus, or parkinsonism • May coexist with seizures
	TGA [66]	• See Table 5
	Drug AEs, intoxication, or withdrawal [100]	• New medication or change in dosing • Myoclonus described with various medications • Classic toxidrome with certain drugs (e.g., cholinergic) • Other systemic signs (disturbance in vital signs, acid–base balance, renal, cardiac) or positive drug screen
Focal neurological symptoms	TIA	• Sudden loss of function (weakness, numbness, aphasia, visual loss) with maximal intensity at onset (no evolution) • Loss or impairment of consciousness is uncommon • Less likely if multiple recurrent stereotyped episodes occur without sequelae • Duration ≤5 min is more suggestive of epilepsy • Limb-shaking TIA (in carotid stenosis) may mimic focal clonic jerks, but occurs in the upright position
	Amyloid spells [63]	• Positive or negative symptoms (motor, sensory, or visual), spreading over contiguous body parts over 1–15 min • Duration ≥6 min in over 50% of cases (but usually <30 min) • Associated cognitive deficits may be present • Positive iron-susceptibility MRI sequences
	Migraine aura [96]	• Known history of headaches: new-onset migraines after age 60 are rare (rule out giant cell arteritis and CNS lesion) • Visual or sensory symptoms with slow onset (over ≥5 min) • Prolonged duration (20–60 min) • Migraines with aura often lose the headache element in elderly
Sleep disorders [96]	RBD	• Second half of sleep (instead of first half) • Often able to recall vivid or frightening dreams
	Parasomnias	• Longer duration (>5 min), rare in frequency, and without clustering • Stage 3–4 non REM sleep: 1–2 h after falling asleep • May wander outside the bedroom and perform complex-directed behaviors (e.g., picking up objects, dressing) • Nonrepetitive and nonstereotyped • No clear recollection of the event
	PLMS	• Repetitive stereotyped lower limb movements (great toe extension, dorsiflexion, hip and knee flexion) • Short duration: 0.5–4 s at intervals 20–120 s
Movement disorders [96]	Nonepileptic myoclonic jerks	• Usually in the presence of toxic/metabolic encephalopathy • More often proximal, bilateral, or multifocal • May also respond to certain AEDs
	Tremor	• Preserved consciousness despite bilateral motor activity • Additional neurological signs (e.g., parkinsonism in PD/LBD or task-specific tremor with dystonia) • Family history in essential tremor
Psychiatric	Psychogenic nonepileptic seizures [50,96]	• Represent about 20–50% of paroxysmal nonepileptic events in video-EEG monitoring studies • Forced eye closure is the most reliable sign (PPV: 94.3%) • Normal vital signs during the episode • Asynchronous motor activity or pelvic thrusting • Preserved awareness despite bilateral motor activity • Complex behaviors such as screaming or crying • Often occurs in front of a witness • Trauma, incontinence, or tongue-biting are rare • History of psychological health-related trauma
	Panic disorder	• Longer duration (>5 min) than mesial temporal lobe seizures

Abbreviations: CNS — central nervous system; LBD — Lewy body dementia; AD — Alzheimer's disease; TGA — transient global amnesia; TEA — transient epileptic amnesia; AEs — adverse events; TIA — transient ischemic attack; sx — symptoms; RBD — rapid eye movement sleep behavior disorder; PLMS — periodic limb movement in sleep; AEDs — antiepileptic drugs; PD — Parkinson's disease; PPV — positive predictive value.

nonepileptic transient global amnesia (TGA). Typical attacks last less than 1 h and are often accompanied by olfactory hallucinations, automatisms, and a brief loss of responsiveness [64]. Features distinguishing TEA and TGA are summarized in Table 5. A recent study provided evidence that the duration of episodes was not helpful in distinguishing TEA from TGA, but rather recurrences, associated confusion and language disorders, as well as 24-hour EEG are the most helpful in distinguishing TGA from TEA [65]. Transient epileptic amnesia commonly begins in late-middle to old age and is most associated with temporal lobe epilepsy. Transient epileptic amnesia has been captured on EEG recordings both as an ictal and/or a postictal epileptic phenomenon. Interictal cognitive symptoms, such as accelerated long-term forgetting, are frequently reported. Individuals usually respond to low doses of AED monotherapy [66].

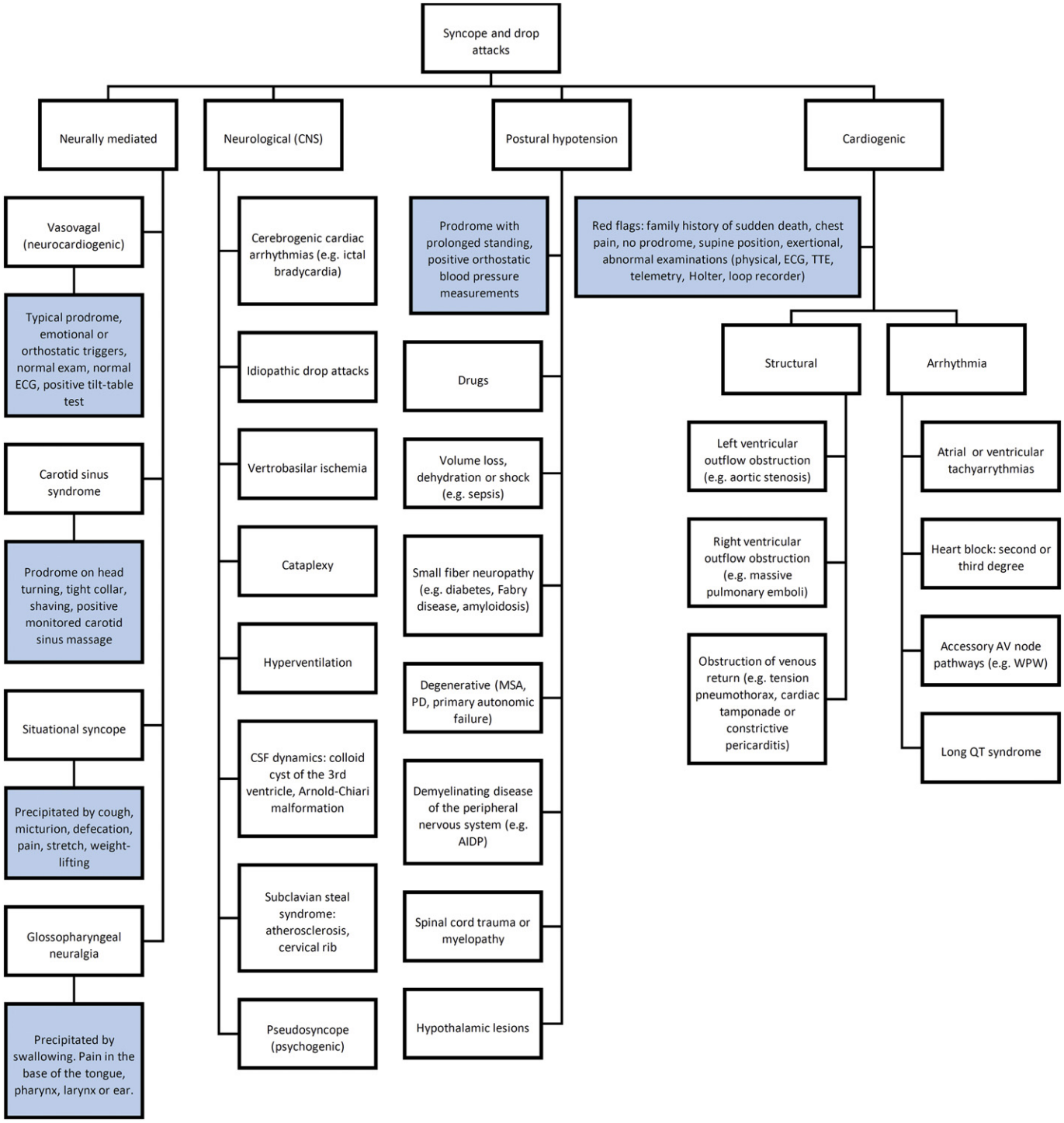

Fig. 3. Differential diagnosis of syncope and drop attacks. Abbreviations: CNS — central nervous system; CSF — cerebrospinal fluid; MSA — multiple system atrophy; PD — Parkinson's disease; TTE — transthoracic echocardiogram; ECG — electrocardiogram; AIDP — acute inflammatory demyelinating polyneuropathy; WPW — Wolff–Parkinson–White syndrome. Footnote: Adapted from Crompton and Berkovic [96].

7. Evaluation

7.1. The diagnostic evaluation of a first seizure and new-onset epilepsy in the elderly

When a first seizure is suspected in an elderly individual, the first step is to obtain an accurate history from an eyewitness and perform a thorough neurological examination to exclude a seizure mimic. A cardiovascular evaluation should be performed if syncope is suspected, whereas a routine EEG can be misleading and is not essential in the elderly (see EEG and video-EEG section below). If a seizure is likely, one should first rule out a reversible etiology, starting with routine blood tests (complete/full blood count, complete electrolytic profile, thyroid studies, renal, and hepatic function) [14]. An infectious work-up, including lumbar puncture, is performed when there are symptoms or signs suggestive of a CNS infection. Brain imaging (computerized tomography (CT) and/or MRI) should be obtained. Polysomnography can help differentiate parasomnias from nocturnal frontal lobe seizures [58].

Table 5
Features distinguishing transient global amnesia from transient epileptic amnesia. Adapted from Bilo et al. [66].

	Transient global amnesia	Transient epileptic amnesia
Duration of attacks	1–24 h (average 4–6 h)	<1 h (in >70% individuals)
Interictal abnormalities on routine EEG	Usually normal	Epileptiform abnormalities in temporal or frontotemporal regions in minority (30%)
Disturbance of consciousness	No (preserved awareness and alertness)	Possible (brief loss of responsiveness or clouding of consciousness)
Repetitive questioning	Yes, with anxiety	No
Type of amnesia	Anterograde amnesia with variable retrograde amnesia; no memory of the episode after its resolution	Severe retrograde amnesia with incomplete anterograde amnesia (partial memory of the episode after its resolution)
Other ictal symptoms	No	Majority of cases (motor automatisms, olfactory hallucinations)
Precipitant	Emotional or physical stress	Upon awakening
Recurrence	Rare	Frequent
Response to AEDs	No	Yes

AEDs — antiepileptic drugs; EEG — electroencephalogram.

Performing a cognitive screening test (e.g., Mini mental status exam) should also be part of the routine evaluation of older adults with new-onset epilepsy, since they have increased cognitive deficits even before AED initiation [64].

7.2. EEG and video-EEG

On routine EEG, normal variants occur in up to half of elderly individuals [67] and are often mistaken as epileptiform abnormalities. Routine EEG detects interictal epileptiform abnormalities in only about 35% of elderly with preexisting epilepsy and 26% of elderly with new-onset epilepsy [68]. Prolonged video-EEG monitoring (mean: 3–4 days) in the elderly can be used to differentiate epileptic from nonepileptic events (such as psychogenic seizures) [39], but the cost of such an ancillary test may be prohibitively high.

7.3. Brain imaging

Brain imaging using CT or MRI should be performed in all elderly individuals with possible seizures given the high frequency of structural etiologies [69,70]. Brain CT is faster, less expensive, and more accessible in emergency situations, while MRI is considered more sensitive and preferred in nonemergency settings. About half of CTs and MRIs of the brain performed in geriatric-onset epilepsy identify an underlying focal lesion, most commonly ischemic stroke [70]. No studies have yet examined whether common age-related MRI findings such as leucoaraiosis are predictive of epilepsy in old age.

7.4. Autoimmune-mediated seizures

Clinicians and investigators increasingly recognize that immune-mediated seizures and epilepsies are an important diagnostic consideration. Investigators have identified more than 15 intracellular and surface antigen-targeting autoantibodies that can be responsible for epilepsy [71]. Antibodies directed at the voltage-gated potassium complex (e.g., LGI1 and CASPR2) are especially pertinent to older adults although if the possibility of a paraneoplastic syndrome appears to be high, anti-Hu antibodies are a major consideration (along with other onconeural antibodies such as anti-Ma and anti-Amphiphysin) [71,72]. Autoantibody testing, in serum and cerebrospinal fluid, should be carried out in individuals at risk. Clinical features that are predictive of positive autoantibody testing include autonomic dysfunction, a viral prodrome, faciobrachial dystonic seizures, and associated oral dyskinesias [73].

8. Treatment

8.1. When to initiate AED treatment (risk of recurrence after a first seizure)

In the general population, adults with a first unprovoked seizure have a seizure recurrence risk of 21–45% over the following 2 years [74]. Some authors have reported numbers as high as 90% in individuals 65 years and older [55] that were likely inferred from studies of LPS [26]. Large prospective observational studies have shown a similar risk of

Table 6
Summary of recommendations for AEDs in elderly individuals with epilepsy.

Guideline	Country	Date	Geriatric AED recommendation	Class of recommendation and/or level of evidence[a]
SIGN (Scottish Intercollegiate Guidelines Network)	UK	2015	New-onset focal epilepsy: LTG or LEV GBP as an alternative mono- or adjunctive therapy	Level B Level C
International League Against Epilepsy (ILAE)	Int.	2013	New-onset focal epilepsy: GBP and LTG CBZ TPM and VPA	Class III Level A Level C Level D
National Institute for Health and Care Excellence (NICE)	UK	2012	Lower doses of usual AEDs (as general adult population) Attention to comedications and comorbidities If using CBZ, offer CBZ-CR	NR
American Academy of Neurology (AAN) and American Epilepsy Society (AES) practice guidelines	USA	2018	New-onset epilepsy (focal or unclassified TCS): LTG GBP as an alternative choice	Class I, level B Class II, level C
Critical Care Services Ontario (CCSO)	Canada	2015	Focal epilepsy first choice: LTG, GBP, CLB	NR

AED = antiepileptic drug; NR = not reported; TCS = tonic–clonic seizure LTG = lamotrigine; LEV = levetiracetam; GBP = gabapentin; CBZ = carbamazepine; CBZ-CR = carbamazepine controlled-release; TPM = topiramate; VPA = valproate; CLB = clobazam.

[a] Class I = a masked randomized controlled trial (RCT), meeting all key variable criteria for low risk of bias (detailed guidelines available in each individual study); Class II = a masked prospective-matched group cohort study in a representative population that meets all key variable criteria OR a RCT in a representative population that lacks one of the key variable criteria; Class III = all other controlled trials in a representative population, where outcome assessment is independent of patient treatment; Class IV = evidence from uncontrolled studies, case series, case reports, or expert opinion; Level A = established as effective (≥2 Class I studies); Level B = probably effective (≥1 Class I or ≥2 Class II studies); Level C = possibly effective (≥1 Class II or ≥2 Class III studies).

recurrence at 1 year in the elderly (aged ≥65 years) as compared with younger age groups [75]. At 5 years of follow-up, the cumulative risk of recurrence becomes higher in the elderly, but the difference remains modest [75]. Independent seizure predictors (risk of recurrence ≥60%) are similar to those found in younger adults: epileptiform abnormalities on EEG, abnormal neurological examination, nocturnal seizures, and a remote symptomatic cause [74,75]. Although the risk of recurrence after a first seizure may be comparable with younger adults, the consequences of seizures in the elderly may differ, however, such as a potentially higher propensity for falls and fractures.

8.2. Considerations about AED treatment in the elderly

With newer agents available, the choice of the initial AED in the elderly with new-onset epilepsy is evolving. A recent US survey of epilepsy experts demonstrated a rise in the preference for lamotrigine (LTG) or LEV in the elderly with epilepsy, with a decline in preference for PHT comparing 2005 with 2016 [76].

Data from randomized controlled trials (RCTs) concur with the majority of guidelines favoring LTG, LEV, or gabapentin (GBP) as first-line AEDs in the elderly with new-onset epilepsy (Table 6). A recent comprehensive meta-analysis of RCTs of AEDs in the elderly with epilepsy demonstrated that LTG is better tolerated than carbamazepine (CBZ) with no differences in measures of efficacy [77]. There were no differences in tolerability between LEV and LTG although LEV-treated participants had a marginally higher probability of achieving seizure freedom. There were fewer data regarding the use of other AEDs in the elderly with epilepsy [77]. Table e-2 summarizes data about efficacy and tolerability data of AEDs commonly used in the elderly as well as their practical advantages and disadvantages.

The selection of an AED in an elderly person with epilepsy should be individualized. Dosage-dependent AEs (confusion, dizziness, lethargy, unsteadiness, visual disturbance) and drug-specific AEs (hyponatremia, tremor, cardiotoxicity, ataxia, polyneuropathy, and osteoporosis) should be carefully addressed. Considerations include the route of drug metabolism or elimination, the method of administration, the frequency of administration, cost, a person's comorbidities, and comedications (Table e-2).

Some experts suggest a target geriatric AED dose of about 50–75% of that used in a young adult [78]. Monotherapy is preferred over polytherapy to minimize drug interactions [78]. In the elderly with cognitive deficits, adherence is better with a lower frequency of administration (once or twice daily) [79].

An additional concern associated with enzyme-inducing agents (e.g., PHT, CBZ, PB), and VPA, is an increased risk of osteoporosis and bone fractures [80]. Community-dwelling elderly women treated with continuous PHT have a 1.8-fold greater mean rate of bone loss with a 29% increased risk of hip fracture over 5 years as compared with age-matched individuals [81]. Enzyme-inducing AEDs are also associated with an increased risk of vascular disease, including increased carotid intima thickness [82]. This may account for the increased risk of sudden cardiac death observed in people with epilepsy [83].

Table 7
Epilepsy surgery in the elderly.

Study[a]	Setting	No (old/young)	Age of old vs young in years ± SD (range)	Surgery	F/U	Efficacy	Complications and morbidity
Sirven et al. (2000) [91]	Scottsdale, USA	370 (340/30)	54.2 ± 4.7 (50–66) vs 32.8 ± 7.7 (18–49)	ATL for refractory TLE	≥1 year Mean: 4 years	Engel I: 52% in older vs 75% in younger group ($p < 0.008$)	No difference in neuropsychological outcomes and driving status
Boling et al. (2001) [88]	Montreal, Canada	218 (18/200)	54 (50–64) vs 30 (10–49)	Cortical AH or selective AH for refractory nontumoral TLE	≥2 years Mean: 64 mo	No difference in seizure remission (83% Engel I–II in older subjects)	No difference in complications (6%): quadrantanopsia, infections
Grivas et al. (2006) [93]	Bonn, Germany	373 (52/321)	55.9 ± 3.5 (50–71) vs NR (<50)	AH-HS, AH-Les, or LX + AH or ATL, for refractory TLE	≥1 year Mean: 33–34 mo	No difference in seizure remission (Engel I–II ≥90%).	No mortality; higher neurological complications in older: 3.8% dysphasia, 3.8% hemiparesis, and 5.9% hemianopia; worsening in neuropsychological testing in the older group postop.
Murphy et al. (2010) [89]	Melbourne, Australia	124 (21/103)	54.9 (50–72) vs 34.6 (20–48)	ATL for HS	≥5 years Mean: 9.57 ± 2.4 years	No difference in seizure remission (Engel I–II ≥90%)	No difference in complications and neuropsychological outcomes
Srikijvilaikul et al. (2011) [92]	Bangkok, Thailand	200 (16/184)	55.5 (50–72) vs 32.9 (16–49)	ATL for HS	≥1 year	Engel I: 56% in older vs 79% in younger ($p = 0.041$)	Higher surgical complications in the older age group (6%, $p = 0.009$): subdural hygroma and chronic subdural hematoma; No difference in morbidity or mortality
Punia et al. (2018) [90]	Review of case series Plus own single-center retrospective analysis: Cleveland, USA	168 (58 elderly in case series review; own center: 51/50)	Case series: ≥60 yo Own center: 65 ± 4 (≥60) vs 35 ± 5 (25–45)	Case series: ATL; AH; AH-Les, LX, frontal resection Own center: temporal or extratemporal lesionectomy	Case series: ≥1 year Own center: 3.2 ± 2.2 years	Engel I: 72.4% (case-series) and 80% (own center) of older adults; similar to 68% of younger adults (own center)	No difference in surgical complications or neuropsychological outcomes, except for confrontational naming

Abbreviations: SC = single center; ATL = standard anterior temporal lobectomy; AH = amygdalohippocampectomy; HS = hippocampal sclerosis; TLE = temporal lobe epilepsy; AH-HS = amygdalohippocampectomy for hippocampal sclerosis; AH-Les = amygdalohippocampectomy for mesiotemporal lesion; LX = lesionectomy; LX + AH = lesionectomy + amygdalohippocampectomy; Engel I = seizure freedom; Engel II = rare seizures (1–3 per year); NR = not reported; SD = standard deviation.
The 58 elderly patients included in case series identified by Punia et al. do not overlap with the participants in the studies listed above.
[a] All studies are single-center retrospective analyses except Punia et al., which also included a systematic review.

8.3. Cognitive adverse events

Many elderly individuals with epilepsy have comorbid dementia and/or are on drugs with potential cognitive AEs. Starting a new AED in an elderly individual can also unmask or exacerbate preexisting cognitive deficits. A recent systematic review of the treatment of epilepsy in people with Alzheimer's disease identified only one RCT [84]. Compared with similar LEV- or LTG-treated individuals, elderly patients with Alzheimer's disease and new-onset epilepsy started on PB experienced a deterioration of cognitive performance at 6- and 12-month follow-up. In one RCT of 15 healthy elderly participants, CBZ immediate-release was associated with more cognitive AEs compared with GBP although the difference was modest [85]. One RCT comparing LTG with topiramate as adjunctive AEDs in older adults (mean age: 57.7 ± 8.9) found no significant differences in cognitive AEs [86]. Phenytoin is associated with greater cognitive AEs when compared with CBZ in the general adult population [87].

8.4. Epilepsy surgery

Limited data regarding epilepsy surgery in individuals over 50 years show mixed results (Table 7). Some studies have shown a similar probability of seizure freedom and risk of postoperative complications in elderly patients, as compared with younger age groups [88–90]. Other studies show a lower efficacy in older adults [91,92], as well as a slightly higher probability of cognitive, neurological, and other medical sequelae postoperatively [92,93]. While older age is not an absolute contraindication to epilepsy surgery, the decision should be balanced against the presence or absence of cognitive or functional deficits and comorbidities.

9. Future directions

Despite neuroimaging advances, the etiology of approximately one-third to one-half of new-onset epilepsy in the elderly remains unknown [25,40]. The mechanisms linking epilepsy and dementia, including Alzheimer's disease, remain opaque. Further work into epilepsy mechanisms and risk factors in the aging individual could help guide clinical practice as well as provide new insights about epileptogenesis in this population. The elderly population is rapidly growing in high-income countries, and the incidence of epilepsy in this age group is great, but there remains a dearth of high-quality evidence to inform its management. Randomized controlled trials and high-quality observational studies examining the efficacy and tolerability of the newest AEDs (such as LAC, perampanel, clobazam, and brivaracetam) could expand our therapeutic arsenal in older adults with epilepsy. Chronological age should not be the only issue when choosing an appropriate AED in the elderly with epilepsy. Future studies should examine the impact of particular comorbidities, such as neurodegenerative disease and cerebrovascular disease, on outcomes. These comorbidities may increase the susceptibility of the aging brain to drug-related AEs, as well as influence drug adherence (in the setting of cognitive deficits) and the method of administration (in the setting of dysphagia) [94]. Amyloid spells can resemble focal seizures, and their pathophysiology is poorly understood [63]. Large studies are needed to assess the diagnostic utility of amyloid-positron emission tomography for TFNE. The design of a standardized frailty measurement in elderly people with epilepsy could help identify individuals at higher risk of adverse outcomes. Frailty is likely an important determinant of an individual's response to an AED as well as their overall prognosis, may help inform the choice of AED as well as dose, but research into this area is lacking [12]. Further work is needed to determine which elderly patients benefit most from epilepsy surgery.

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Appendix A. Supplementary data

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