Seizures and Epilepsy in Dementia: Diagnosis and Management

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List of Abbreviations

AD	Alzheimer's Disease
ADL	Activities of daily life
AED	Antiepileptic drugs
APP	Amyloid-beta precursor protein
CBZ	Carbamazepine
CJD	Creutzfeld-Jakob Disease
CR	Controlled-release
CSF	Cerebrospinal fluid
CT	Computed tomography
DLB	Dementia with Lewy bodies
DMN	Default mode network
EEG	Electroencephalogram
FTD	Frontotemporal dementia
HD	Huntington's Disease
IED	Interictal epileptiform discharges

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K. S. Frederiksen, G. Waldemar (eds.), *Management of Patients with Dementia*,
https://doi.org/10.1007/978-3-030-77904-7_12

IL	Interleukin
LEV	Levetiracetam
LTG	Lamotrigine
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NCSE	Non-convulsive status epilepticus
PB	Phenobarbital
PDD	Parkinson's disease dementia
PS1	Presenilin 1
PSP	Progressive supranuclear palsy
SE	Status epilepticus

Pathophysiology of Epilepsy in Dementia

A wide range of pathologies can cause dementia, these include vascular, infectious, traumatic, metabolic, and inflammatory causes. For the purposes of this chapter, we will focus on the most common neurodegenerative aetiologies, which is where much of the epidemiological and experimental evidence originates.

A large body of epidemiological studies suggests that late-onset epilepsy is common [1, 2]: ~25% of new onset epilepsy occurs in individuals older than 65 years [3]. After cerebrovascular disease (~50–70% of late-onset epilepsy; [4, 5]) and trauma (~20% [6, 7], dementia and neurodegenerative disorders are the third most common causes of late-onset epilepsy, with 10–20% of cases attributed to these aetiologies [8]. Furthermore, individuals with a recent diagnosis of epilepsy (under 10 years), have an increased relative risk of developing dementia (RR 2.5) and being diagnosed 1 year after epilepsy diagnosis: this risk not thought to be due to cumulative effect of seizures [9, 10]. Conversely, patients with dementia are known to have an increased risk of epilepsy [11]. Patients with Alzheimer's Disease (AD) and those aged >65 years have a tenfold higher risk of epilepsy and seizures [12, 13]. This is also the case in patients with a diagnosis of vascular dementia [14].

Seizures and Dementia Share Common Risk Factors and Pathological Features

An important observation that may explain the common co-occurrence of epilepsy and dementia is that both share common risk factors [15]: these include hypertension, diabetes mellitus, obesity, smoking, and low physical activity levels [16, 17]. Whilst patients with early [18] and late-onset epilepsy have higher burden of cerebrovascular disease [19], it remains unclear if modification of vascular risk factors would reduce seizures (beyond prevention of strokes) and/or mitigate cognitive decline. Interestingly, a recent study in religious groups that refrain from alcohol

and tobacco showed reduced incidence of AD but not epilepsy [20]. A further important observation is that epilepsy and AD-type dementia share pathological markers: temporal lobectomy tissue from temporal lobe epilepsy patients harbours increased levels of amyloid-beta precursor protein (APP) [21]. Of note, seizures are particularly prominent in patients with AD due to APP duplication. Temporal lobe epilepsy specimen also showed age accelerated presence of senile amyloid plaques [22], and abnormal hippocampal tau immunohistochemistry [23]. Increased tau was also found in surgical specimens with focal cortical dysplasia lesions [24]. Conversely, hippocampal sclerosis, which is sometimes reported in patients with AD (but also frontotemporal dementia, primary age-related tauopathy, and limbic-predominant age-related TDP-43 encephalopathy) differs regarding pathology and subfield localization in the hippocampus, relative to hippocampal sclerosis seen in temporal lobe epilepsy [25, 26].

It remains to be elucidated, how this variety of risk factors interact, although some pathologies appear to be worse than others for cognition and seizures (e.g. vascular risk factors) [15].

A Bidirectional Relationship: Dementia Increases Risk of Seizures and Seizures Worsen Cognitive Function

More recent evidence suggests that rather than just sharing the same risk factors, the pathophysiology underlying dementia itself increases the risk of seizures, and that frequent seizures worsen cognitive performance, as has been widely studied in patients undergoing epilepsy surgery [27]. Seizures can therefore be interpreted as one manifestation of the pathophysiological process underlying dementia. For example, seizures are common in the prodromal phase of neurodegenerative disease [28]. Cognitive decline may begin several years earlier in individuals with AD who suffer from seizures compared to those who do not [29, 30]. In patients with familial AD, seizures occur in >45% cases [31], suggesting that younger people (50–59 years) with AD are at highest risk of developing seizures, and that therefore disease duration in itself is not crucial for epileptogenesis. In late onset AD, epilepsy may be associated with faster cognitive decline [32], but overall, lack of population based studies and common definitions of dementia used in studies make estimates difficult [33]. Whether epilepsy, especially late-onset epilepsy may lower brain reserve and facilitate manifestation of dementia [15] or if epilepsy in itself produces dementia (e.g. by frequent seizures and subsequent network disruption) remains unclear.

Animal Models of Network Disruption and Epilepsy in Alzheimer's Disease

Much of the preclinical evidence of epileptogenesis and dementia comes from animal models of AD. These are characterized by overexpression of amyloid precursor protein (APP), presenilin 1 (PS1) or both, and therefore mimic familial forms of AD

[34, 35]. Within the same individual, the relative contribution of amyloid beta, APP and its metabolites, and tau, however, remain unclear [35]. Box 12.1 summarizes currently available evidence from experimental data (Box 12.1).

Epileptogenesis in mouse models of AD is different from other experimental models of epilepsy [35]. Firstly, fibrillary amyloid beta appears to act as a trigger for epileptiform activity, disrupting neuronal membranes [36, 37] and the balance of excitation and inhibition across brain networks [38]. Secondly, both endogenous and experimentally mutated tau (in order to increase tau production/reduce clearance) modulates seizure susceptibility and network excitability in a dose-dependent manner [35]. Interestingly, knocking out tau improves deficits in spatial memory and protects mice against excitotoxicity in a human APP (hAPP) mouse model, without effect on amyloid deposition [39].

Recent evidence suggests that amyloid beta initiates neuronal hyperactivation by suppressing glutamate reuptake [40]: Active neurons at baseline are particularly susceptible to excessively increased activity. Further evidence indicates that neuronal hyperactivity increases amyloid beta and tau secretion, thereby establishing a vicious cycle of disease protein secretion and aberrant aggregation [41, 42].

Finally, it is interesting to note that antiepileptic drugs (AED) interfere in the disease process: Levetiracetam and Topiramate reduced amyloid plaques in a double transgenic mouse model of AD (APP23xPS45: overexpressing APP and mutant PS1) and improved spatial memory in the water maze [43]. In the hAPP model, Levetiracetam but no other AEDs reduced abnormal spike activity on electroencephalogram (EEG) and improved memory performance in vivo, whereas, in acute slices, levetiracetam reversed deficits in synaptic transmission restoring long-term potentiation [44].

Box 12.1 Proposed Mechanisms of Epileptogenesis in Alzheimer's Disease

1. Extrasynaptic glutamate spillover due to impaired glial or neuronal glutamate transporters [45, 46]
2. Tau-induced enhancement of presynaptic glutamate release [47].
3. Reduced axonal and dendritic transport of cargoes (e.g. mitochondria) that regulate neuronal excitability [48–50]
4. Altered trafficking and surface expression of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and *N*-methyl-D aspartate receptors [51, 52]
5. Altered amounts of voltage-gated ion channels in the brain [52–54]
6. Fyn-mediated alterations in *N*-methyl-D aspartate activity [39, 51, 55, 56]
7. Selective impairment of GABAergic interneurons in the hippocampus and parietal cortex [46, 53, 57–60]
8. Shortened dendrites, lowering threshold for action potential generation [61]
9. Impaired cortical input to the reticular thalamic nucleus and subsequent disinhibition of thalamic relay nuclei and their cortical and limbic targets [62]

10. Increases in cholinergic tone before the degeneration of cholinergic pathways [63]
11. Induction of intracellular neuronal expression of ApoE4 in GABA-ergic interneurons and subsequent ApoE4-mediated toxicity through a tau-dependent mechanism, which leads to their dysfunction and eventual death, with resulting network hyperexcitability [64]

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The Role of Interictal Epileptiform Discharges

Whilst it is widely appreciated that recurrent seizures and status epilepticus impact upon cognition regardless of their aetiology [65], more recent findings in animal models and humans suggest that even interictal epileptiform discharges (IED) can affect cognitive function [66, 67]. During the presurgical evaluation of 67 patients, IEDs worsened recall on a memory task even if originating outside the ictal onset zone [68]. These findings suggest that both seizures and IEDs can affect cognition by long-range network disruption. Whether cognitive function is affected if network disruption involves critical areas, has been the subject of recent investigations and the default mode network (DMN) has emerged as a critical ensemble [69]. The default mode network comprises the posterior cingulate cortex, precuneus, lateral parietal, and medial frontal regions with strong links to the hippocampus [70]. Blood oxygen level-dependent signals detected on functional magnetic resonance imaging (MRI) demonstrate that the DMN is active at rest and deactivates during goal-directed behaviour [71]. Greater DMN deactivation and stronger functional connectivity within DMN regions correlate positively with better cognitive performance [15, 72, 73]. Intriguingly, simultaneous functional MRI-EEG studies of temporal lobe epilepsy patients, detected hippocampal hyperactivity during IEDs, as well as decreased resting functional connectivity of the DMN [74–76]. A similar pattern has also emerged in individuals with mild cognitive impairment (MCI) and therefore at risk of developing AD [77, 78]. Furthermore, greater hippocampal hyperactivity and reduced DMN deactivation correlates with greater amyloid deposition even in healthy individuals [79, 80].

In two patients with established AD but no clinical seizures, EEG recordings employing foramen ovale electrodes revealed not only the presence of IEDs but also of silent hippocampal seizure activity [81]. Recording patients with standard EEG overnight increases the yield in detecting IEDs: Vossel et al. demonstrated that ~42% of patients with established AD and no history of seizures had detectable IEDs on overnight Video-EEG [82]. Patients with IEDs did not differ clinically from those without, nor was there any significant differences in brain atrophy, suggesting that the severity of AD is not useful in distinguishing between the two [82].

An important question arising from these investigations is whether excessive hippocampal activity is pathological or represents an early compensatory

mechanism. Bakker et al. addressed the hypothesis that suppressing excessive neuronal activity leads to improved cognitive performance: 2 weeks of low dose levetiracetam (LEV 62.5 or 125 mg BD but not 250 mg BD) suppressed aberrant hippocampal dentate gyrus/cornu ammonis 3 blood oxygen level-dependent signal and significantly improved memory performance in early MCI [78]. These results suggest that hippocampal hyperactivity more likely represents abnormal activity, in keeping with similar findings in animal models of AD [83].

Epilepsy in Other Forms of Dementia

The incidence of epilepsy in other forms of neurodegeneration and dementia is higher than in the general population [84]: Epidemiological studies reveal tenfold increased seizure incidence rates in AD and dementia with Lewy bodies (DLB), and sixfold in frontotemporal dementia (FTD) [85]. Myoclonus is also more common in these disorders with an increase in relative myoclonus rates with earlier age at onset of dementia in AD, DLB, and FTD [85]. Seizures may be an important feature in patients with frontotemporal dementia (FTD) with hippocampal sclerosis and FTD and parkinsonism linked to chromosome 17 with a P301S MAPT gene mutation [86]. Patients with progressive supranuclear palsy (PSP) may also be at higher risk of developing seizures [84, 87].

Whilst the pathogenesis of epilepsy in these forms of neurodegeneration is less extensively studied, a transgenic mouse model of FTD with parkinsonism linked to chromosome 17 recapitulates some of the clinical features, including a propensity for spontaneous seizures on EEG [88]. In this model of human mutant tau overexpression, reactive microglia and astrocytes in the hippocampus precede the appearance of neurofibrillary tangles, and epilepsy develops in the absence of Aβ pathology.

Seizures can be a presenting feature of sporadic Creutzfeld-Jakob Disease (CJD), with focal onset seizures, generalized convulsive and non-convulsive status epilepticus (NCSE) all reported, in addition to myoclonic jerks which are a very common feature in CJD. Animal models of CJD demonstrate that loss of the prion protein (nPrP knockout mice) leads to neocortical and hippocampal hyperexcitability and synchronized activity [89], possibly through facilitated *N*-methyl-D aspartate receptor-mediated excitation in the hippocampus. A more recent study in a mouse model expressing a mutated and misfolding prion protein (Tg(CJD) mice) has shown that abnormal hippocampal *N*-methyl-D aspartate-dependent synaptic plasticity and susceptibility to seizures results from a combination of both gain and loss of function of the prion protein [90]. In addition, astrocytic interleukin (IL)-1beta plays an important role in modulating susceptibility to seizures, as treatment with the IL1 antagonist anakinra, reduces seizure susceptibility and normalizes hippocampal neurotransmission, thereby establishing an important link between neurodegeneration and inflammation [90].

Epilepsy may also be feature of Huntington's Disease (HD) [91], with a 30–40% incidence in juvenile HD [92]. Higher number of CAG repeats are correlated with younger age of onset and increased seizure risk [91], although the exact mechanism

by which seizures are caused remains unknown. In adult onset HD, incidence of epilepsy is only 1–2% [92], with an adult onset HD phenotype with epilepsy more commonly caused by dentato-rubro-pallido-luysian atrophy.

Opportunities for Translational Research

Past research on the pathophysiology of epilepsy in dementia highlights a number of important areas for future research with immediate translational potential. These include the investigation of whether more aggressive management of vascular risk factors is protective for both development of dementia and epilepsy, and whether antiepileptic drug therapy in AD patients without seizures has beneficial effect on cognitive function. Ongoing trials may yield important information in due course (NCT02002819, NCT01044758). Finally, some of the difficulties in developing good epilepsy and dementia guidelines arise from the heterogeneous data available from clinical trials, e.g. using a multitude of cognitive scales to define cognitive impairment. Large-scale patient registers, harmonized cognitive assessments and multi-centre collaborations [93] will be instrumental in achieving better quality and meaningful data.

Clinical Seizure Semiology and Differential Diagnosis

Seizure Semiology

As new-onset epilepsy in dementia can be considered a structural form of epilepsy, the clinical features of seizures will depend on the anatomical location of seizure onset and whether there is secondary spreading to adjacent regions or both hemispheres. In both AD and FTD, the underlying neurodegenerative pathology can be present in large parts of the brain at an early stage, providing a basis for seizure generation outside the brain regions involved at onset of cognitive symptoms [94]. In AD, seizures usually originate in the medial temporal or frontal lobes [30, 95–97], with corresponding seizure semiology as described below [35]. There is less data on seizure semiology in frontotemporal dementia (FTD), although the distribution of the underlying pathology would suggest that seizures will usually start in the frontal or temporal lobes [85, 98]. In vascular dementia, cortical infarcts commonly cause post-stroke seizures and can be located in different cortical regions. The diagnosis of specific types of dementia does not rest on the presence or type of seizure. In a large retrospective study of almost 2000 patients with AD, DLB, and FTD, seizures lacked distinguishing clinical features, providing no evidence for specific seizure semiology in different types of neurodegenerative dementia [85]. In clinical practice, many patients will present either after generalized tonic-clonic seizures or non-motor seizures with decreased consciousness, which will not allow the clinician to determine in which brain region the seizures started. On the other hand, it is important to be aware of the common types of seizures in dementia, especially in

AD [35]: based mostly on studies in AD, the most common clinical presentation of epilepsy are focal impaired awareness seizures (previously termed complex partial seizures) with or without secondary generalization [35]. Focal onset aware seizures (i.e. without impairment of consciousness, previously called simple partial seizures) are less common [35].

In AD, focal impaired awareness seizures (complex partial seizures) with non-motor onset and can manifest as recurrent, stereotyped attacks of decreased awareness, speech arrest, more pronounced amnesia, déjà vu, unexplained expressions of emotion, or sensory symptoms [35]. Seizures can induce tachycardia, bradycardia, or even asystole requiring pacemaker implantation, possibly due to involvement of insular cortical regions [30]. These attacks reflect epileptic activity in the hippocampus and medial temporal lobes and have similar features as in common temporal lobe epilepsy in patients without dementia. The recognition of these symptoms as possible epileptic seizures will depend on the degree of cognitive impairment, especially amnesia, changes in emotion and, to some degree, decreased verbal fluency are common cognitive features in AD.

While transient changes in consciousness and behaviour will often be a manifestation of epilepsy in persons with normal cognition and recognized as such by both bystanders and clinical professionals, similar symptoms in persons with dementia might go unnoticed or be misinterpreted by carers and clinicians. In addition, cardiac or other causes for transient loss of awareness or alertness are common, especially in certain types of dementia as described below.

Generalized seizures may be more common in DLB [85], but data on this disease is scarce. In a study on Huntington's disease with juvenile onset, generalized tonic-clonic seizures were the most common types of seizures, followed by tonic seizures and seizures with spells of staring [91].

Myoclonus is a common feature in early-onset (<65 years) and atypical forms of AD, as well as in DLB [85]. Whilst myoclonus can be expression of either cortical or subcortical hyperexcitability, in patients with dementia and stereotyped cognitive or behavioural changes, it should prompt an evaluation for possible seizures. Although most seizures will be self-limiting, non-convulsive status epilepticus (NCSE) is not uncommon and can be particularly difficult to both diagnose and treat [4].

Obtaining a Good Seizure History in Dementia Patients: Common Challenges

Reliance on information and observations from caregivers play a central role for reliable information on seizure activity. While generalized seizures will always be noted, partial or nocturnal seizures might go unnoticed. It is important to ask specifically for signs of fluctuating cognition or consciousness, speech arrest, staring, motor automatisms, and if these episodes are followed by unusual tiredness. However, all these signs could have other causes than epilepsy as is further detailed below and in Table 12.1.

Table 12.1 Differential diagnoses of seizures in dementia

Diagnosis	Clinical features	Useful investigations
Epilepsy (seizures)	*Duration*: Short (seconds-minutes; longer in Todd's paresis[a]) *Characteristics*: Acute onset, recurring, stereotypical, unprovoked *Symptoms*: Episodes of confusion or behavioural change, loss or impairment of consciousness, involuntary movements or sensory disturbances in a body part, visual disturbances, agitation, anxiety, recurrent episodes of sleep disturbances (motor, vocal), frequent falls which the patient does not remember afterwards	EEG
Epilepsy (NCSE)[b]	*Duration*: Medium-long (hours-weeks) *Characteristics*: Acute or gradual onset, fluctuating symptoms *Symptoms*: Change in cognition and behaviour, varying degrees of impaired consciousness	EEG
Transient global amnesia (TGA)	*Duration*: Medium (hours, <24 h) *Characteristics*: Acute onset, isolated amnesia, often provoked by mental or physical stress *Symptoms*: Isolated anterograde and varying degrees of retrograde amnesia	
Cardiac arrhythmia	*Duration*: Brief to short (seconds-minutes) *Characteristics*: Acute onset, recurring, provoked, or unprovoked *Symptoms*: Syncope, dizziness, feeling faint, shortness of breath	ECG Holter-ECG
Postural hypotension	*Duration*: Short to medium (depending on severity) *Characteristics*: Positional, always in a standing position (in very severe cases also while sitting) *Symptoms*: Syncope, dizziness, feeling faint, confusion, cognitive worsening, leg weakness	Orthostatic BP or tilt testing
Transient ischemic attacks (TIA)	*Duration*: Short to medium (minutes-hours, <24 h) *Characteristics*: Acute onset, single to multiple episodes, varying severity and symptoms *Symptoms*: Mostly preserved consciousness, manifestations vary (motor, sensory, speech etc.)	CT/MRI
Stroke	*Duration*: Long (days-months) *Characteristics*: Acute onset, duration >24 h *Symptoms*: Manifestations vary (motor, sensory, speech, visual, brain stem etc.)	CT/MRI
Migraine aura	*Duration*: Medium (hours up to 1–2 days) *Characteristics*: Gradual onset (minutes), first attack onset <50 years *Symptoms*: Visual, motor, sensory (headache phase can become less prominent with ageing)	
Delirium	*Duration*: Long (days-weeks) *Characteristics*: Gradual onset, often provoked by infection, metabolic or environmental factors *Symptoms*: Cognitive or behavioural change, impaired attention, perception, and consciousness, Hallucinations	Blood tests EEG Lumbar puncture

(continued)

Table 12.1 (continued)

Diagnosis	Clinical features	Useful investigations
Psychosis	*Duration*: Long (weeks-months) *Characteristics*: Gradual onset, often permanent part of pre-existing condition (psychiatric illness or dementia), varying degrees of severity *Symptoms*: hallucinations, delusions, agitation, anxiety	
Fluctuations in dementia	*Duration*: Short to medium (minutes-hours) *Characteristics*: Acute or gradual onset, fluctuating condition *Symptoms*: worsening of cognitive problems, impaired attention and speech, normal muscle tone	EEG
Metabolic disturbance[c]	*Duration*: Short to long depending on condition *Characteristics*: Sudden or gradual onset depending on condition *Symptoms*: Feeling faint or dizzy, syncope (in hypoglycaemia), worsening of cognitive problems	Blood tests
Paroxysmal movement disorders[d]	*Duration*: Short to medium depending on condition *Characteristics*: Focal, stereotypical, varying in severity, duration, and distribution *Symptoms*: Brief (myoclonus) or fluctuating motor symptoms (tremor, dyskinesia, dystonia)	
Intoxication[e]	*Duration*: Medium to long (days-weeks) *Characteristics*: Attacks occur, but mostly fluctuating change in general condition *Symptoms*: Variable, attacks occur, but usually fluctuating change in cognition, behaviour, attention, consciousness	Blood and urine tests
Sleep disorder[f]	*Duration*: Brief (seconds) to short (minutes) *Characteristics*: Recurring, nocturnal *Symptoms*: Complex movements and speech in sleep (REM-sleep behaviour disorder; RBD) or twitching focal leg movements (Periodic leg movements in sleep; PLS)	Polysomnography Video-EEG

[a]Todd's paresis is a transient paresis during the post-ictal phase after an epileptic seizure, not caused by ischaemia
[b]Non-convulsive status epilepticus
[c]Hypoglycaemia, hyperglycaemia, electrolyte disturbance
[d]Tremor, myoclonus, dyskinesia, dystonia
[e]Drugs or toxins
[f]REM-sleep behaviour disorder (RBD), Paroxysmal leg-movements in sleep (PLS)

Persons with dementia might have varying degrees of language impairment or lack of insight. In these cases, it might be even more difficult for the patient and carers to recognize changes in awareness, speech and behaviour, and consultation due to possible seizure activity will not be sought unless in cases of partial motor seizures, loss of consciousness, and generalized tonic-clonic seizures. In progressive supranuclear palsy (PSP), verbal fluency can be severely impaired, with periods

of speech arrest that can be misunderstood as partial seizures. In the presence of other clinical features of PSP such as postural problems with falls, vertical gaze palsy, and general psychomotor slowing, episodes of speech arrest should be seen as a cognitive symptom and not a manifestation of epilepsy.

Persons with dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and vascular dementia, often have pronounced subcortical dysfunction which often leads to fluctuations in cognition, awareness, and even consciousness that can last from a few minutes to almost an hour. Muscle tone is often preserved, and the patient can remain in a sitting position but is unable to respond to the environment. These manifestations of decreased cortical activation are difficult to distinguish from epileptic seizures and a common reason for misdiagnosis of epilepsy in these types of dementia. The key to diagnosis is the presence of a subcortical type of dementia, concomitant fluctuations in cognition often lasting several hours and the absence of other suspected epileptic features, such as motor manifestations.

Differential Diagnosis

Diagnosing epilepsy in dementia can be challenging due to many factors. Patients are often elderly, have single or multiple comorbidities, including cardiovascular disease, polypharmacy, and the inherent cognitive impairment, which makes it more difficult to distinguish changes in cognition and behaviour. Possible differential diagnoses are summarized in Table 12.1. In general, and irrespective of age or underlying conditions, epileptic seizures tend to be brief in duration (minutes), stereotypical, recurring, and not dependent on situation or body position. The most important differential diagnoses to identify or exclude are cardiac arrhythmias, postural hypotension, stroke or transient ischemic attacks, and delirium. After a generalized seizure, patients with dementia can have a prolonged post-ictal phase lasting from a few days up to 2 weeks [99, 100]. On the other hand, NCSE can present as delirium which can be misinterpreted as worsening of cognitive decline inherent to a progressive dementia disorder. Stroke can present with focal symptoms from an area of cerebral ischaemia, which at the same time can provoke an epileptic seizure (acute symptomatic seizure [101]). An epileptic seizure can result in a Todd's paresis, which in dementia may be prolonged and can mimic a stroke. The coexistence of neurodegenerative and ischemic pathology in mixed AD and vascular dementia increases the risk of epilepsy and further complicates the differential diagnosis and treatment of the different conditions.

Status Epilepticus in Patients with Dementia

Although most seizures in patients with dementia are self-limiting, some seizures may continue unabated, and are then considered a separate entity, status epilepticus (SE). SE is a condition "resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to

abnormally prolonged seizures. It is a condition that can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [102]. While convulsive SE is clinically apparent and a medical emergency which requires immediate and rapidly escalating therapeutic interventions, non-convulsive status epilepticus (NCSE) can be challenging to diagnose, as it might manifest only as delirium or a slightly decreased level of awareness or consciousness [103], and its diagnosis relies on EEG criteria [104, 105]. The incidence of non-convulsive status epilepticus increases with age [103]. Up to 16% of persons older than 60 years that present in the emergency department with confusion or an altered mental state were found to have NCSE [106] and it is of great importance to perform an EEG early in the diagnostic process, to determine whether NCSE is present. Treatment can be very difficult for both convulsive and non-convulsive status, as patients often are old and frail, and may not tolerate higher doses of AEDs, sedatives, or anaesthesia. EEG is also helpful to identify if SE has been successfully treated. Admission to an intensive or an intermediate care unit (preferably with the possibility of continuous or repeated EEG monitoring) may become necessary if SE is not controlled with first- or second-line agents. In younger persons, NCSE frequently results as an exacerbation from the patient's pre-existing underlying epilepsy and has a better prognosis [107]. In contrast, in older people with NCSE prognosis is much worse, with significant morbidity and a mortality of up to 50% [103, 106].

Making a Diagnosis

As discussed in section "Clinical Seizure Semiology and Differential Diagnosis", the diagnosis of epilepsy in patients with dementia can be challenging and may be delayed, particularly in the elderly population: in a subgroup analysis of the Veterans Affairs Cooperative Study of seizures in people >60 years old, the time to correct diagnosis was significantly delayed, with a mean of 2.3 years [108]. Whilst there is no evidence base to guide which investigations to adopt in patients with dementia and possible seizures, the following pragmatic approach appears sensible, by extrapolating from research in younger people and elderly patients without dementia [109]: We recommend routinely enquiring about seizure markers at each clinic appointment and to teach carers to detect and document possible ictal features. After careful history taking in the presence of a caregiver, preferably a person who has regular contact with the patient and who observed the suspected seizure (section "Clinical Seizure Semiology and Differential Diagnosis"), a thorough clinical examination should establish if there is residual focal neurological involvement, evidence of cardiac disease (e.g. a heart murmur, an arrhythmia) or additional clues as to the underlying diagnosis (e.g. a rash, liver stigmata) and potential risk of seizure recurrence (e.g. signs of meningism or raised intracranial pressure). Further, routine baseline observations, such as heart rate, blood pressure, and temperature should be part of the clinical assessment. History and clinical examinations are aimed at establishing an aetiological diagnosis but also, importantly, at excluding

causes for acute symptomatic seizures (acute brain and metabolic precipitants). With this in mind, whilst there is no evidence supporting extensive laboratory tests in patients who have fully recovered, a basic set of investigations is recommended [109–111] to rule out easily treatable precipitants. These include serum glucose, electrolytes (Na, K, Ca), and urea, as well as a routine screen including baseline markers of renal and liver function and a septic screen including a full blood count and C-reactive protein. A 12-lead electrocardiogram should always be performed to rule out cardiac arrhythmias or any abnormalities precluding the use of certain anticonvulsants.

Recommended Investigations

Acute Setting

Residual focal neurology should prompt urgent brain imaging: Computed tomography (CT) is the preferred imaging modality, as it is easily available, rapid, detects bony abnormalities (e.g. fractures), and identifies blood earlier than MRI. A lumbar puncture should be considered in the acute setting, if the differential diagnosis includes infection, subarachnoid haemorrhage, or malignancy [112].

Outpatient Setting

A patient with dementia who has fully recovered from a seizure, and where acute precipitants have been excluded, should be referred to an appropriate outpatient setting with expertise in epilepsy within an acceptable time frame (2–4 weeks depending on national guidelines [110, 113]).

Whilst the diagnosis of epilepsy is predominantly clinical, the following investigations may help ruling out non-epileptic and dangerous causes of transient loss of consciousness, if suggested by the clinical history: carotid and basilar artery ultrasonography, orthostatic blood pressure measurement, and Holter monitoring of the electrocardiogram. A useful aid for the clinician may also be a video capture of the event, e.g. on a mobile phone, and family and carers should be encouraged to video the suspected seizure, providing the patient's safety is maintained. However, despite extensive investigations, often the diagnosis will be uncertain, unless a typical event is recorded with simultaneous EEG and electrocardiogram monitoring.

Imaging

MRI of the brain is the imaging modality of choice in epilepsy, as it demonstrates higher sensitivity than CT [114] and is particularly important in patients with refractory focal onset seizures. Despite the lack of prospective data on the diagnostic yield of imaging in the population with dementia and seizures, it should be recommended in any new-onset epilepsy patient regardless of age, to rule out hippocampal sclerosis, tumours, or dual pathology [115].

Despite these recommendations, a few points relevant to clinical practice are worth discussing: Firstly, many patients with dementia may already have undergone a recent MRI in the work-up for dementia. Secondly, a typical epilepsy protocol

MRI takes 15–20 min to acquire: the requirement to lie immobile for such an extended length of time in a noisy environment may be unattainable for some patients, especially in more advanced stages of disease. Finally, MRI may not be ubiquitously available and may be expensive. In such cases, we feel CT imaging may be a viable option to exclude new or acute causes of seizures, keeping MRI (possibly with general anaesthesia or sedation) as an option only if there is a pressing clinical need.

Electroencephalography

To correctly determine the value of electroencephalography in evaluating a patient with dementia and suspected seizures, the following important points need to be highlighted: Firstly, interictal routine scalp EEG (i.e. 20–30 min) recordings greatly underestimate subclinical hyperexcitability in AD: in patients with episodic confusion, a fluctuating course or a seizure-like event, a normal EEG does not exclude epilepsy or subclinical seizures [81]. Secondly, subclinical seizures and spikes are activated in sleep [81]. In a study of 33 patients with AD and no seizures, subclinical epileptiform activity was detected in 42.4% of AD patients on overnight video telemetry [82]: AD patients with epileptiform activity did not differ clinically from those without such activity but showed faster rates of cognitive decline. Whilst subclinical seizures and spikes can cause significant cognitive impairments [67, 116], it is currently unknown whether treatment of interictal epileptiform discharges improves cognitive function in patients with dementia or mild cognitive impairment and is the subject of ongoing clinical trials (see Sect. “The Role of Interictal Epileptiform Discharges”).

Finally, misdiagnosis of “benign” EEG patterns (e.g. wicket spikes, *hypnagogic* hypersynchronicity, hyperventilation induced slowing) is common when EEGs are interpreted by physicians without specialized training [117, 118]. In addition, non-specific patterns are commonly seen in the elderly, making a distinction between “normal” and “abnormal” even more challenging [119].

In conclusion, the “gold-standard” investigation in problematic cases is to capture a typical event on video-EEG. Whilst this may not be ubiquitously feasible, available or indicated, the EEG evaluation in the population with dementia should at minimum include sleep [35] and be reported by a certified electroencephalographer, especially in difficult cases.

Diagnosing Non-convulsive Status Epilepticus

As discussed in section “Clinical Seizure Semiology and Differential Diagnosis”, a diagnosis of non-vascular dementia is an independent risk factor for status epilepticus [120]. Diagnosing non-convulsive status epilepticus (NCSE) can be particularly challenging in the elderly population, and even more so in patients with dementia. Diagnosing non-convulsive status is difficult, but whilst there are now consensus electrographic criteria [121], there are no defining clinical parameters. Elderly patients may simply present with confusion of unknown origin or delirium [122–124], although acute onset (i.e. within 24 h) and lack of clinical response to simple

commands were reported to be associated with NCSE rather than an alternative diagnosis [122]. Prion Disease Dementia has been reported to be associated with NCSE [125–127] and generalized status epilepticus [128, 129].

In conclusion, whilst NCSE should be considered in all elderly patients when sudden and transient cognitive fluctuations appear [130], diagnosing NCSE in dementia patients, who frequently have cognitive fluctuations at baseline, remains challenging. A low index of suspicion remains key: quick progression of cognitive deterioration or subtle ictal features (minor twitching of the face or limbs, nystagmoid eye movements) should be screened for and Video-EEG monitoring instituted as the best and probably only modality helping to make a diagnosis.

Management Approaches

General Principles of Epilepsy Management in Dementia

The general principles for management of epilepsy in persons with dementia are not different from other patient groups. However, there are many factors to take into consideration in new-onset epilepsy in the elderly population, which are especially important in persons with cognitive impairment and dementia. The ageing brain, in combination with coexisting focal lesions or regional neurodegeneration found in dementia, is especially sensitive to both the effects of seizures and the pharmaceutical treatments given to prevent further seizures. In addition, elderly patients, commonly suffer from comorbidities affecting their general physical condition, including balance, gait, and muscle strength, which will further increase the risk of falls and fractures in connection with seizures. Falls may also be related to adverse events from antiepileptic drugs (AED). Medication taken to treat medical comorbidities, also increases the risk for interactions with AEDs. Other considerations to take into account include the consequences of the cognitive problems (e.g. strategies to remember to take medication) and different psychosocial factors (e.g. education of carers, safety of accommodation) involved in dementia.

When a diagnosis of epilepsy is made in a person with dementia there are several issues that have to be addressed. Due to the patient's cognitive impairment, information about the diagnosis and its consequences should be given both orally and in writing, not only to the patient, but also to family and other caregivers. It is important to educate caregivers on signs that can indicate seizures, in which circumstances emergency medication should be given (if relevant) and when it is important to seek medical advice or call an ambulance. Contact information to a specialist service should be available, especially if the patient is living at home. Rapid follow-up should be arranged, either at a clinic or by phone, to ensure that the information given has been understood, to check whether there are repeated seizures and, if treatment with AEDs has been started, ensure that there is no worsening of cognitive function or the general condition due to adverse effects, see further below.

As with all cases of newly diagnosed epilepsy, treatment with an AED should be started if there are frequent generalized tonic-clonic seizures (especially nocturnal,

as this increases the risk of sudden unexpected death in epilepsy [131]). Further, treatment should be commenced if there is a risk for recurrent seizures that might increase the risk for falls or other traumatic events, accentuate the cognitive impairment, or lead to behavioral disturbances that could be negative to the patient or caregivers. However, these risks have to be balanced against the risk of side effects from the treatment, which is especially common in cognitively impaired patients and might lead to poor compliance to treatment. While the primary goal of treating epilepsy in a cognitively healthy and independent person will always be to achieve seizure freedom, this goal has to be modified in persons with dementia and one should always take into consideration the risk of decreasing the quality of life when treating with an AED. In a person with moderate-to-severe dementia with occasional focal seizures that do not lead to falls, severe behavioural changes, or other potentially dangerous situations, active treatment can be postponed. On the other hand, it is important to inform patients and caregivers that if treatment with an AED is initiated, seizure freedom on low or moderate doses of AEDs can often be achieved. In the elderly, seizure freedom of 60–90% with treatment has been reported [132]. There is also some evidence that treatment with an AED can improve cognitive function in some patients [35, 133]. This could be due to a decrease in interictal seizure activity or a direct positive effect on hippocampal function as demonstrated with low doses of levetiracetam in one study in patients with mild cognitive impairment [134]. Drug treatment, including choice of AED, is discussed in more detail below.

Due to their cognitive problems, patients with dementia often find it difficult to self-report seizures, recognize and express the nature of adverse events, and remember to take their medication. Arrangements should be made both for supervision of the patient's general condition, signs of new seizures and to ensure that prescribed medications are taken. The latter can be facilitated by using drug dispensers or supervision of drug intake. A driving ban due to epilepsy is seldom an issue in patients with an established dementia diagnosis but might need to be addressed in patients with mild cognitive impairment and seizures. Both patients and caregivers should be given practical and psychological support to handle other psychosocial aspects of newly diagnosed epilepsy in dementia: Issues include anxiety both for the patient and for the caregiver, due to fear of new seizures and possible side effects of AEDs, social isolation, stigma and uncertainty concerning the diagnosis and its practical aspects for daily life. Some of these issues might have a greater impact on the caregiver's situation and general well-being than on the person with dementia and epilepsy. Clear written information and contact details to a specialist service will decrease worry and increase confidence in those affected.

General Aspects of Drug Treatment

After deciding to treat a person with epilepsy in dementia with an AED, there are a number of factors to consider. While drug absorption, protein binding, and hepatic clearance are not substantially affected by normal ageing [4], this is often the case

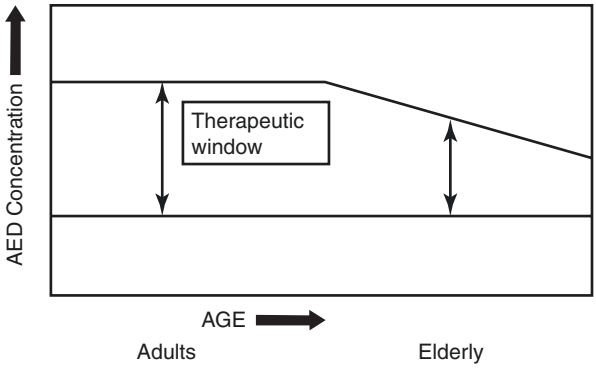

Fig. 12.1 Effect of age on therapeutic ranges: The elderly have a narrower therapeutic window (the range between the lowest effective concentration and the maximal tolerated concentration (Source: Bergey [135]; reproduced with permission from Wolters Kluver Health)

in patients with dementia that are frail, possibly malnourished, and often have comorbidities that might affect these aspects of the patient's condition. Renal clearance decreases with age and dosage need to be adjusted for AEDs that are primarily metabolized by renal excretion, such as levetiracetam and gabapentin. Pharmacodynamic aspects are also very important. Due to a decline in homeostatic mechanisms in the ageing brain, older people are very sensitive to adverse effects of psychoactive drugs [4]: the therapeutic window is typically narrower in the elderly (Fig. 12.1, reproduced from [135]). This is even more important in dementia, where the cerebral changes of ageing are compounded by neurodegenerative or other lesions.

Polypharmacy is common in persons with dementia, due to multiple concomitant medical conditions. For example, secondary prophylactic treatment is given after transient ischaemic attack/stroke, while the cognitive, affective and behavioural symptoms in dementia might require symptomatic treatment with antidepressants, anxiolytics, antipsychotics, and antidementia medications (choline esterase inhibitors, memantine). In addition, persons with dementia are often older and are prone to general medical comorbidities such as cardiovascular disease, diabetes, gastrointestinal conditions, and pain. Consequently, a careful review of the patient's list of medications is needed before initiating treatment with an AED. Especially the risk for interactions and additive adverse effects on cognition and wakefulness need to be taken into account.Additionally, patients with epilepsy who receive long-term monotherapy with enzyme inducing AEDs (carbamazepine, phenytoin, or valproate) exhibit altered circulatory markers of vascular risk (increased total cholesterol and homocysteine, reduced folate, increased common carotid artery intima media thickness), which is significantly associated with the duration of AED monotherapy and may contribute to acceleration of the atherosclerotic process [136]. Recent large population-based cohort studies have also demonstrated that persons with AD treated with AEDs are at increased relative risk of death (mainly due to dementia and more so on older AEDs) [137] and of stroke (regardless of AED used) [138], highlighting the need to use AEDs judiciously in this vulnerable population. Box 12.2 summarizes desirable features of AEDs for dementia patients (reproduced from [135]).

Box 12.2 Summary of Desirable Features of an AED for Use in the Elderly and Persons with Dementia

No interaction with other medications
No interaction with other AEDs
Can be introduced at therapeutic doses
No metabolism
No protein binding
Once or twice daily dosing
Laboratory monitoring not necessary
Excellent safety record
Good side-effect profile
High therapeutic index
Little effect on cognitive function
Psychoactive benefits

Source: Bergey [135]; reproduced with permission from Wolters Kluver Health

AEDs with minimal interactions should be chosen (see further below) and decreased dosage of other psychoactive drugs should be attempted when starting treatment with an AED. Newer AEDs have lower cognitive and sedative effects than older AEDs and should be drugs of first choice [133, 139–142]. Finally, oral intake might be compromised by dysphagia, decreased appetite, or behavioural issues in the patient with dementia. In these cases, AEDs where tablets can be divided in smaller pieces or crushed, or are available as granules or liquid formulations, might be preferred.

The following steps should be followed when starting treatment with an AED in dementia:

1. *Assess cognitive function before starting treatment*. In order to evaluate whether introduction of an AED affects the patients' cognition and general condition, baseline assessment of cognitive and activities of daily living (ADL) functions should be performed before starting treatment. Depending on whether the patient has a mild, moderate, or severe dementia, different methods of assessment can be utilized. As a minimum, this should include a cognitive screening test such as Mini-mental state evaluation (MMSE) and a structured interview with family members and other caregivers.
2. *Treatment is started with a low dose and titrated slowly to a minimum effective dose*. When treating epilepsy in dementia a lower dose of AED can be used than which is usually required in younger or otherwise healthy older patients with epilepsy. For example, a daily dose of 100 mg lamotrigine or 500 mg levetiracetam is often sufficient [133]. Careful evaluation of efficacy and adverse effects should be made before further increases in dosage.

3. *Rapid follow-up of the patient after starting treatment.* The importance of rapid follow-up cannot be overemphasized and should be performed within 2–3 weeks, much faster than is often the case in follow up of epilepsy treatment in cognitively intact patients who can self-report any adverse events. The initial follow-up can be done by phone and should include an interview with a caregiver, focusing on cognitive and general ADL function, as well as sedative and other adverse effects. The same principle should be applied when starting treatment with other psychoactive drugs such as antidepressants or antipsychotics. Adherence issues should also be addressed. Check if the patient is taking the medication and if supervision or a drug dispenser is needed.
4. *Long-term follow-up*. Follow-up in person should be scheduled within 1–3 months and include assessment of further seizures, cognition (with renewed cognitive screening test for objective comparison), ADL function, changes in behaviour (e.g. sedation, apathy, depression, irritability, disinhibition), balance and general well-being. Always interview a caregiver who knows the patient well, in person or by phone, as an accompanying person at a clinic visit might not be closely acquainted with the patient. Provide caregivers with contact details and encourage them to contact the clinic if there are changes in the patient's condition.
5. *Length of treatment.* Seizure control is often good when treating epilepsy in patients with dementia and older people in general, with 60–90% of patients becoming seizure free or have a greater than 95% reduction in seizure frequency and less than 3 seizures per year (up to 79% in a retrospective study of 39 patients with various dementia syndromes [95]). However, seizure recurrence is possible and should be carefully monitored for [95, 132]. In addition, the underlying dementia disorder remains and progresses, and treatment should most often be continued long-term providing there are no adverse effects or other factors that might require stopping or reducing the dose of the AED.

Antiepileptic Drugs Used in Patients with Dementia

The evidence base to guide the choice of antiepileptic treatment in patients with seizures and dementia is limited due to paucity of randomized clinical trials [143], and relies mainly on other studies in the elderly with or without dementia.

Taken together with limited data from randomized controlled studies in older people [139, 142, 144, 145] the newer anticonvulsants (including levetiracetam and lamotrigine) should be considered as a first line in the treatment of epilepsy in patients with dementia due to their lower potential for drug interactions, lower incidence of adverse effects and linear pharmacokinetics [93].

The following section and Table 12.2 summarize commonly used AEDs in patients with dementia, their metabolism, interactions, efficacy and tolerability, and adverse effects [35, 146].

Table 12.2 Commonly prescribed antiepileptic drugs in older patients with cognitive impairment

	Dose (mg per day)	Tolerability	Efficacy	Metabolism/ Excretion/ Elimination half-life (hours)[a]	Cognitive side-effects?	Adverse reactions (including those of concern in cognitive impairment)	Other uses
Levetiracetam	250–500	Excellent	Excellent	Enzymatic hydrolysis of acetamide group/ renal unchanged/6–8	No	Aggression, asthenia, dizziness, fatigue, headache, irritability, and nausea	Treatment of myoclonus
Lamotrigine	25–500	Excellent	Excellent	Liver (mostly UGT1A4-mediated)/ urine (70%), faeces (2%)/2–5	No	Asthenia, ataxia, blurred vision, diarrhea, diplopia, dizziness, hypersensitivity reaction, incoordination, insomnia, nausea, rash, somnolence, Stevens-Johnson syndrome, and tremor	Mood stabilization
Gabapentin	300–1500	Good	Good	Not significantly metabolized/ renal/5–9	Possible	Ataxia, dizziness, fatigue, nystagmus, nausea, peripheral oedema, somnolence, and weight gain	Treatment of insomnia, peripheral neuropathy, postherpetic neuralgia, and migraine prophylaxis
Carbamazepine	600	Fair	Good	Hepatic (CYP3A4)/ urine (72%), faeces (28%)/5–26 (autoinduction and reduced half-life on repeat dosing)	Yes	Agranulocytosis, asthenia, ataxia, blurred vision, cardiac dysrhythmia, constipation, decreased bone density, dizziness, hepatotoxicity, hypersensitivity reaction, hyponatraemia, nausea, rash, somnolence, and xerostomia	Mood stabilization, and treatment of trigeminal neuralgia

	Dose (mg per day)	Tolerability	Efficacy	Metabolism/ Excretion/ Elimination half-life (hours)[a]	Cognitive side-effects?	Adverse reactions (including those of concern in cognitive impairment)	Other uses
Valproic acid	250–1000	Fair	Good	Hepatic-glucuronidation (50%), beta-oxidation (40%), hydroxylation (10%)/renal/13–16	Yes	Alopecia, asthenia, ataxia, constipation, diarrhoea, diplopia, dizziness, gait disturbance, headache, hepatotoxicity, indigestion, nausea, nervousness, nystagmus, peripheral oedema, rash, somnolence, tinnitus, tremor, weakness, and weight gain	Mood stabilization, migraine prophylaxis, and treatment of myoclonus
Phenytoin	200–300	Poor	Good	Hepatic/mainly bil, <5% unmetabolized in urine/7–80 (mean 20 at 10–20 mg/L)	Yes	Ataxia, constipation, decreased bone density, dizziness, dysarthria, gingival hyperplasia, hepatotoxicity, hypersensitivity reaction, incoordination, lethargy, muscle hypotonia, nausea, nervousness, nystagmus, and sedation or drowsiness	None
Phenobarbital	50–100	Poor	Excellent	Liver (CYP2C19)/ renal (25%)and Feacal/70–130	Yes	Asthenia, barbiturate withdrawal, decreased bone density, hypersensitivity reaction, somnolence, and syncope	Long-term sedation

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[a]Elimination half-life in healthy adults (from Shorvon et al. [146])

Newer Antiepileptic Drugs

Levetiracetam

Levetiracetam (LEV) is a broad-spectrum AED thought to exert its function by binding synaptic vesicle protein 2A [147], thereby reducing neurotransmitter release during repetitive stimulation on rapidly firing neurons [148]. Its main advantages are the broad-spectrum activity, the availability of oral and parenteral formulations, and the lack of clinically significant drug interactions.

The use of LEV in the treatment of seizures in patients with AD is supported by strong evidence [133, 149]: In an open-label observational study of LEV, Belcastro and colleagues [149] administered LEV daily (1000–1500 mg) to 25 patients with advanced AD and new-onset epilepsy: 72% were seizure free for at least 1 year, 16% discontinued due to side effects, 8% were unresponsive, 4% were lost to follow-up. Cumbo et al. [133] performed a prospective, randomized, three-arm parallel-group, case-control study of 95 patients with AD and seizures: Three treatment groups (LEV $n = 38$, phenobarbital $n = 28$, lamotrigine $n = 29$) were compared to a control group ($n = 68$) to evaluate cognitive effects of AEDs. The study revealed that LEV (500–2000 mg/day) is effective in treating focal onset seizures in patients with AD: at 12 months, 71% were responders (seizure reduction of at least 50%) and 29% had become seizure free. Importantly, efficacy was observed at low doses (mean 1343.7 mg/day), justifying the use of lower doses in elderly patients with dementia. There was no difference in the efficacy of all three anticonvulsants but LEV was associated with fewer adverse events. Additionally, LEV improved cognitive performance (especially attention level and oral fluency) measurable clinically by MMSE and Alzheimer's disease Assessment Scale-cognitive scoring. Patients treated with LEV experienced less depression than patients treated with phenobarbital, but more so than those treated with lamotrigine.

LEV is available as modified release formulation, useful in patients who have compliance issues. Serum level monitoring and blood monitoring are usually not required, although it would be advisable to determine serum creatinine and creatinine clearance prior to starting in the elderly to establish correct dosing [150].

Lamotrigine

Lamotrigine (LTG) is another broad-spectrum anticonvulsant with efficacy against multiple seizure types and with good tolerability [151]. It exerts its action predominantly by blocking voltage-dependent sodium and calcium channels, preventing action potential propagation [152, 153] and the release of neurotransmitters, mainly excessive glutamate [154, 155] from excitatory neurons, which may be a relevant mechanism in the pathophysiology of AD.

With LEV, LTG is supported by the strongest available evidence for the treatment of focal onset seizures in AD: as mentioned in the section above, Cumbo et al. [133] demonstrated that LTG (25–200 mg/day) is equivalent to LEV and phenobarbital (PB) at achieving seizure reduction at 1 year (LTG response rate 59%). Like LEV, LTG has fewer adverse effects and a better cognitive outcome compared to PB. Additionally, LTG improved mood. In a small crossover trial of LTG, Tekin

et al. [156] demonstrated that 300 mg/day of LTG improved word recognition, naming, and depressed mood in AD patients without epilepsy on Alzheimer's disease Assessment Scale behavioural subscale after 8 weeks of treatment. In the Veterans Administration Cooperative Study, Rowan and colleagues [140] showed that LTG (150 mg/day) and gabapentin (1500 mg/day; see section below) were better tolerated than carbamazepine (CBZ) (600 mg/day) in a 12-month efficacy and tolerability study of 593 adults (mean age 72 years) with new-onset epilepsy. Efficacy and seizure freedom rates of around 50% were comparable in all three groups.

LTG is non-sedating and does not cause significant cognitive dysfunction [157, 158]. LTG is not highly protein bound, nor an hepatic enzyme inducer, resulting in minimal drug interactions except for when it is given with enzyme-inducing drugs (lowering LTG levels) or valproate (resulting in two to threefold higher LTG levels) [151]. The main disadvantage of lLTG is the need for slow dose escalation, due to the risk of hypersensitivity reactions if the dose is escalated too rapidly [159].

Gabapentin

Gabapentin (GBP) is a well-tolerated anticonvulsant with modest efficacy, which has good tolerability, including in the elderly and lacks major drug interactions [160]. The predominant effect of GBP is as a selective inhibitor of voltage-gated calcium channels containing the α2-δ1 subunit [161]. Additionally, GBP reduces the release of a number of neurotransmitters, including, among others, glutamate, noradrenaline, and acetylcholine, but their effect on seizures remains to be elucidated [162]. The Veterans Administration Cooperative Study [140], a randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures, demonstrated that GBP (up to 1500 mg/day) was better tolerated than carbamazepine (CBZ) and was as efficacious as both LTG and CBZ at seizure control, with more than 50% of participants seizure free at 12 months.

GBP is renally excreted without being metabolized in the liver, and does not induce hepatic enzymes. The only reported drug interactions are antacids containing aluminium or magnesium hydroxide, as they reduce absorption of the drug by about 20%. Their administration should be separated by at least 2 h [163].

Oxcarbazepine and Eslicarbazepine

Oxcarbazepine (OXC) is a 10-keto analogue of CBZ [164], whilst eslicarbazepine (ESL) is a prodrug of (*S*)-(+)-licarbazepine [165, 166]. Both act mainly via inhibition of voltage-gated sodium channels. Both are licensed for adjunctive and monotherapy of focal-onset and secondarily generalized seizures [166]. OXC can be more rapidly uptitrated than CBZ, and is also available as extended-release formulation that can be administered once daily. Eslicarbazepine only requires once daily dosing, too. No evidence is available on the safety and efficacy of these two drugs in patients with dementia, although both are being used successfully in the treatment of elderly patients. Efficacy of OXC appears to be similar to CBZ when used in older patients, whilst ESL showed improved efficacy (62% in >65 years vs. 48.8% in 65 years, ESL was found to cause low rates of hyponatraemia [168], possibly due to the lower mean doses used in this subgroup (850 mg/day in >65 years

vs. 1032.6 mg/day in <65 years), hence serum sodium monitoring is always recommended when using OXC and ESL in the elderly population. Discontinuation rates due to adverse effects among elderly patients were similar to those of younger individuals for OXC [169], but higher for ESL [168]. The most common adverse effects for both drugs included dizziness and nausea [164, 168]. The tolerability profile improved in patients who switched from CBZ or OXC to ESL due to adverse effects [168].

Enzyme-inducing antiepileptic drugs reduce levels of the active metabolite monohydroxycarbazepine and of ESL [164], whilst both may increase serum levels of phenytoin.

Lacosamide

Lacosamide (LCS) is a later generation antiepileptic drug, which enhances the slow inactivation of voltage-gated Na channels with comparable efficacy to other antiepileptic drugs licenced in the last decade [170]. There is no available evidence of its use in patients with dementia. Most of the evidence of its use in the elderly comes from retrospective case series [171–173], a subgroup analysis of a non-inferiority trial vs. controlled-release (CR) carbamazepine [174] and from its use in neuropathic pain trials, which enrolled higher numbers of elderly patients [175]: Overall LCS is well tolerated and no dose reduction is recommended in older patients (unless there are known renal problems). LCS has similar efficacy to CBZ-CR (6-and 12-month seizure freedom) and is better tolerated than CBZ-CR. There is, however, a higher incidence of cardiac disorder adverse effects with higher discontinuation rates because of any adverse effect in the 400–600 mg/day groups. LCS can induce a dose-dependent prolongation of the PR interval, with occasional reports of atrioventricular block and alterations in cardiac rhythm reported when the drug was used at high doses in patients with pre-existing cardiac disease risk factors, in which caution is mandated in using this drug. Psychiatric side effects including psychosis, agitation, and suicidality have rarely been reported in post-marketing studies [176]. LCS has several properties that make it an attractive choice in patients with dementia and their comorbidities: LCS is available as tablet, syrup, and iv preparation with bioequivalence between the formulations making direct conversions possible [177]. Further, LCS has linear pharmacokinetics, is not affected by food and has a low potential for clinically relevant pharmacokinetic drug–drug interactions with AEDs and other common medications [167].

Topiramate, Perampanel, and Brivaracetam (BRV)

Of the newer anticonvulsants, Topiramate (TPM) and Perampanel (INN) are less suitable for treatment of seizures in dementia due to their cognitive and psychiatric side effects.

TPM alleviates behavioural deficits in mouse models of AD [43] and is effective in older adults as monotherapy or add-on for the treatment of one or more focal seizures [178]. However, cognitive side effects are a significant disadvantage: they appear to impact particularly on working memory, short-term verbal memory, language skills, verbal IQ, attention/concentration, processing speed, complex

visuomotor ability, and perception [179]. Cognitive side effects can be minimized by slow uptitration but there is a proportion of patients very sensitive to cognitive side effects of TPM regardless of how cautiously it is introduced. Furthermore, cognitive side effects, albeit reversible on drug withdrawal, may appear at low doses and persist throughout treatment. TPM can also have negative side effects on mood and cause psychosis [180].

INN is a selective non-competitive antagonist at the α-amino-3-hydroxy-5--methyl-4-isoxazolepropionic acid receptor (AMPA) receptor, an ionotropic glutamate receptor. Its mechanism of action is unique among anticonvulsants and it requires only once daily dosing. No data is available to support its use in older patients with epilepsy, as there were not sufficient numbers of subjects aged 65 years and over enrolled in the trials. A significant drawback is the occurrence of common psychiatric side effects [181] including aggression, but also thoughts of harming others, physical assault, threatening behaviour, and suicidal ideation, which prompted the FDA to issue a black box warning against INN. Careful consideration of these important side effects and particular care should be taken when considering INN for patients with dementia.

BRV is one of the latest anticonvulsants licenced, where no or very little data exists on its use in the elderly population: BRV is the 4R-propyl analogue of LEV. Like LEV it binds to synaptic vesicle protein 2A but with 15- to 30-fold higher binding affinity than LEV, possibly at a different binding site and interacting with different conformational states of the synaptic vesicle protein 2A protein [182]. Its efficacy in older adults is comparable to that in younger subjects and no dosage adjustment is required [183]. One of the major advantages of BRV is that no initial dose titration is needed and efficacy is seen on day 1 of oral use in a significant percentage of patients [182]. Parenteral and oral formulations are available and side effect profile is similar to that of LEV, with irritability, agitation, anxiety, insomnia, aggression, and depression the commonest dose-dependent side effects, which are typically mild to moderate. Whilst post-marketing data is being collected, to date, the psychiatric side effects of BRV have been reported as being perhaps less frequent and less severe compared to LEV [182].

Older Antiepileptic Drugs

Carbamazepine

Carbamazepine (CBZ) is a blocker of voltage-sensitive sodium channels and a widely prescribed anticonvulsant [184]. In respect to the elderly and patients with dementia, it has a less than favourable pharmacokinetic profile: as a hepatic enzyme inducer it may have numerous drug–drug interactions, and hyponatraemia has been more frequently reported in elderly patients taking CBZ [185]. In the Veterans Administration Cooperative Study [140], Rowan and colleagues demonstrated that cCBZ (600 mg/day) was less well tolerated than lLTG or gGBP for the treatment of new-onset seizures in older patients, although the efficacy rates were comparable among the three groups.

Phenytoin

Data on the use of phenytoin (PHT), a potent blocker of voltage-gated sodium channels, in AD derives from observational studies, which have demonstrated high rates of adverse effects (up to 40% [186]) including worsening of cognitive symptoms, ataxia, delirium and sedation [30, 95, 187] and variable efficacy on seizure control. Individuals with Down Syndrome and epilepsy, for example, respond well to PHT when treated early in life but develop cognitive side-effects when treated for late-onset seizures [187]. The adverse effects of PHT on cognition and seizures may be due to blockage of NaV1.1 channels predominantly in parvalbumin-positive inhibitory interneurons, thereby causing network hyperexcitability, findings replicated in the APP–J20 mouse model [53].

Phenobarbital

The use of phenobarbital (PB) in patients with AD was evaluated in a randomized three-group parallel case control study [133] of LEV, LTG, and PB (described in the previous section): There were no differences in responder rates among the 95 patients treated with either of the three AEDs. There was, however, higher incidence of adverse events on PB (43%), most commonly somnolence and asthenia, and high withdrawal rates (17%). More than half of patients on PB experienced side effects (61%). The authors concluded that despite its efficacy, due to its side effects of ataxia, somnolence, and central nervous system depression causing further cognitive impairment, PB is not a good choice in elderly patients [133].

Valproic Acid

Valproic acid (VPA) was evaluated in a multicentre, randomized, double-blind, placebo-controlled trial of 313 patients with moderate AD without epilepsy, to determine whether treatment with VPA 10–12 mg/kg/day could delay/prevent the onset of agitation or psychosis [188]. This study revealed not only that VPA did not delay onset of agitation and psychosis but showed that the valproate group had higher rates of toxic effects including somnolence, gait disturbance, tremor, diarrhoea, and weakness. It also showed that there was greater hippocampal volume loss in the valproate group when imaged at 12 months [189]. These results should caution on the use of VPA at these doses in patients with AD with or without epilepsy. A further concern is a development of valproate-induced parkinsonism and of valproate encephalopathy, an idiosyncratic drug reaction, characterized by impaired cognition, drowsiness, and apathy, which typically resolves on stopping the drug [112, 190, 191]; see section “Valproate Encephalopathy”).

Benzodiazepines: Chronic Use

Chronic benzodiazepine use in older patients remains high in developed countries (7–43% [192]), although international guidelines [193] discourage its use due to the inherent risks of withdrawal symptoms, making dose reduction difficult, and the risk of withdrawal seizures on forgetting medication even in healthy individuals. A recent study has additionally shown a 50% higher risk of developing dementia upon lifetime use of >90 doses of benzodiazepines, equivalent to two doses a week for

1 year [192]. The use of chronic benzodiazepines is therefore discouraged in the management of epilepsy in dementia, whilst acute benzodiazepine use maintains its role in treating prolonged seizures in the acute phase (see section "Acute Seizure Treatment with Benzodiazepines").

Aspects Requiring Special Consideration

Bone Health

Several AEDs have negative effects on bone metabolism and might increase osteoporosis in the already susceptible population of older people, especially in dementia where physical activity often is limited. A recent meta-analysis found that first-generation AEDs, including valproate, phenobarbital, phenytoin, and carbamazepine, as well as the second-generation AED lamotrigine, could decrease bone density, while levetiracetam did not [4, 194]. This may be especially important in patients with manifest osteoporosis. Due consideration for follow-up of bone density and risk for fractures is needed during long-term treatment with an AED, and prophylaxis with calcium and vitamin D started as needed. On the other hand, in patients with progressive dementia and shorter expected survival, this issue might not be of major importance.

Acute Seizure Treatment with Benzodiazepines

Elderly patients are very sensitive to the sedative effects of benzodiazepines, especially long-acting ones. If given in the acute setting to curtail an ongoing seizure, in a hospital, or by an ambulance service, iv formulations are often used. This may lead to depression of respiration and might result in intubation and need of intensive care. Benzodiazepines should therefore be used with caution and ideally reserved for cases of convulsive status epilepticus. In prolonged seizures or seizure clusters, short-acting bensodiazepines such as alprazolam and iv treatment with, e.g. LEV, VPA, or LCS should be considered as first-line treatment. Diazepam easily accumulates in the elderly with risk for long-term sedation, while LEV, VPA, and LCS have less risk for acute falls in blood pressure compared to phenytoin or fos-phenytoin, which is another commonly used iv treatment for prolonged seizures and status epilepticus. In a person with dementia with frequent generalized seizures, it can be advisable to have acute medication available that can be given in cases of prolonged seizures. Traditionally, rectal diazepam has been given, but entails some problems with administration. Liquid midazolam is available in syringes and can more easily be administered orally between the teeth and the inside of the cheek. Although respiratory depression is less of an issue with rectal or oral administration, post-ictal sedation and delirium remain problematic.

Valproate Encephalopathy

A number of case reports and smaller case series have described cognitive decline and extrapyramidal motor symptoms during long-term treatment with valproic acid [195–199]. Although rare, valproate encephalopathy can affect both younger and older patients. The clinical symptoms of valproate encephalopathy are usually related to introducing the drug but onset can occur several years after starting treatment. As VPA concentrations most often are within the therapeutic range, the reaction appears to be idiosyncratic, although the exact mechanism remains to be determined. Valproate encephalopathy is unrelated to derangement in liver function tests, but is typically associated with raised levels of ammonia, which can be screened for. Valproate encephalopathy is a reversible condition and often accompanied by pseudoatrophy, with normalization of brain volumes and cognitive function after valproate is discontinued [199]. In summary, a diagnosis of valproate encephalopathy should be considered in patients with more rapid cognitive decline and ammonia levels screened for. Treatment with VPA should be avoided in the elderly, especially in patients with dementia.

Case Scenarios and Summary Teaching Points

The final section of this chapter presents three real-life case scenarios to illustrate and summarize the major teaching points arising from the sections above.

Case 1

An 85-year-old man with mixed AD and vascular dementia had a self-limiting generalized seizure of 1–2 min duration and a post-ictal state lasting several hours. He was admitted to hospital and started on treatment with levetiracetam 500 mg daily. After discharge, he was followed up by a general practitioner at the care facility where he lived. There were no further seizure episodes during the following year.

Teaching Points
Epilepsy in dementia is common and risk of seizure recurrence is fairly high. The institution of treatment with an AED should therefore be considered already after a first seizure. Low doses of a newer AED are often sufficient and leads to seizure freedom in a majority of cases.

Case 2

An 82-year-old single woman was referred to the Neurology Outpatient Clinic after two episodes of generalized seizures. She was started on carbamazepine but developed severe lethargy and stopped the medication. After having a few focal onset

impaired awareness seizures (complex partial seizures), she was started on lamotrigine 100 mg daily but again developed sedative adverse effects, as well as dizziness. Treatment was changed to gabapentin 300 mg three times daily, which was well tolerated. There remained occasional short-lasting focal onset impaired awareness seizures but no further generalized seizures during 2 years of follow-up.

Teaching Points
Elderly people, with or without dementia, can be very sensitive to adverse effects of AEDs, even at low doses. A risk-benefit assessment should always be made when starting, changing, or terminating treatment. Complete seizure freedom cannot always be attained.

Case 3

A 68-year-old male was admitted to hospital for new-onset delirium and urinary voiding. He was married, university educated, a non-smoker with moderate alcohol consumption. He had localized prostate cancer and a 4-year history of progressive problems with gait, general psychomotor slowing and problems with executive function. He had been operated on for a lumbar spinal stenosis 1 year previously with improvement of pain but not gait.

On admission, EEG showed focal epileptiform activity in both frontal lobes but no signs of NCSE. He was diagnosed with epilepsy and treatment with valproate was initiated. This led to cognitive worsening and lethargy and his AED treatment was changed to carbamazepine. His condition improved and he was discharged to his home with assistance and alternate-weekly stays in a care facility. He was referred to a Memory Clinic pending follow-up of his epilepsy at the Neurology Outpatient Clinic. During the hospital stay an MRI was performed that showed mild atrophy of the frontal lobes and mesencephalon, while cerebrospinal fluid (CSF) analysis showed no signs of inflammation but a mildly raised level of Neurofilament light protein of 3740 ng/L (<1850 ng/L) and an increased Albumin CSF/serum ratio, while biomarkers for AD were normal.

On examination at the Memory Clinic, 3 months after he was started on carbamazepine but before follow-up at the Neurology Outpatient Clinic, he showed severe psychomotor slowing and could not participate in conversation or cognitive testing. He had a horizontal and vertical gaze palsy, bilateral but asymmetric rigidity and bradykinesia. He could only stand and walk with the aid of two persons. A diagnosis of a neurodegenerative disorder caused by probable progressive supranuclear palsy (PSP) was made. The patient was also suspected to have an encephalopathy caused by carbamazepine (700 mg per day), in spite of carbamazepine levels of 30 μmol/L (therapeutic range 20–40), with worsening of preexisting gait and cognitive symptoms. An EEG was repeated and showed a slight increase in the focal bifrontal epileptiform activity seen previously but no electrographic seizures. The patient's AED treatment was changed to levetiracetam 1000 mg daily.

At follow-up 1 month after the switch to levetiracetam, the patient was much better, and he talked and joked spontaneously. He did not want to spend time in a respite home any longer and home assistance had been stopped. He walked independently but with a broad-based gait and had decreased postural reflexes, but showed no bradykinesia, rigidity, or gaze palsy. A cognitive screening test showed MMSE 23/30, but he was unable to draw a three-dimensional cube or a clock. He had no further seizures but progressed in his cognitive and motor symptoms. After 6 years, he had progressed to the same clinical state as he had originally presented with and he died of pneumonia 7 years after onset of epilepsy and first presentation to our Memory Clinic. No autopsy was performed but the clinical diagnosis of PSP was maintained.

Teaching Points

When starting treatment with an AED in patients with an underlying neurodegenerative disorder, rapid clinical follow-up is essential to exclude adverse effects, especially worsening of cognitive function. Severe cognitive side effects are common and can occur in spite of AED levels within the therapeutic range. The risk of negative effects on cognition is more common with older AEDs.

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