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Epilepsy (E Waterhouse, Section Editor)

Treatment of Epilepsy in the Setting of Cognitive Decline in Older Adults

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Abstract

Purpose of Review Discuss the state of the literature for the treatment of comorbid epilepsy and cognitive dysfunction, specifically focusing on the older adult.
Recent Findings Epilepsy and cognitive dysfunction are neuronal network disorders with converging molecular underpinnings. Anti-seizure medication is not obligatory after the first instance of a seizure in the setting of cognitive dysfunction. In the absence of randomized controlled trials, current practice is largely based on individual clinical presentation and estimated risk of recurrence. Screening for epilepsy in the context of cognitive dysfunction and cognitive dysfunction in the context of epilepsy should occur early and often throughout treatment.
Summary Decreasing central nervous system polypharmacy is highly recommended in elderly patients, and early cognitive/epilepsy screening may improve both treatment and clinical outcomes. Neuromodulatory techniques and diet modifications are promising treatments that would benefit from additional research. Overall, elucidating the pathological mechanisms that connect epilepsy and cognitive impairment in this population could help direct future treatments.

Introduction

Changes in cognition and epilepsy are highly correlated manifestations of the diseased brain [1, 2]. Symptoms of cognitive dysfunction have long been recognized as part of the disease of epilepsy. Cognitive impairments are even found early in the disease progression of epilepsy. The incidence of cognitive dysfunction in patients newly diagnosed with epilepsy ranges between 58 and 75%. This cognitive dysfunction appears to be worse than what is found in the early courses of other diseases such as Parkinson's disease or multiple sclerosis [3, 4, 5•, 6]. The Atherosclerosis Risk in Communities ($N = 15{,}792$) study concluded that patients with the diagnosis of late-onset epilepsy had an elevated risk of developing dementia [7], demonstrating a bi-directional association between epilepsy and dementia with common neuropathological effect. The molecular links between dementia and epilepsy remain unclear but are proposed to involve models of long-term potentiation, kindling, inflammation, tau proteins, and hippocampal degeneration [1, 5•].

Those with epilepsy and cognitive dysfunction could represent a unique subset of patients with a different and/or more severe pathology as compared to their peers. For example, those with a prior history of adult onset epilepsy experienced onset of cognitive decline 3.6 years earlier than those with no history of epilepsy [8]. The risk for developing epilepsy in those with dementia is highest among those who are younger and who have poorer cognitive function scores at the time of diagnosis. This is consistent with the hypothesis that increased risk is not due solely to neurodegeneration as a progression of the disease but that the underlying disease pathology leads to epileptogenesis. Conversely, patients with dementia were not at a greater risk for seizure recurrence after the first seizure episode as compared to controls [9, 10]. Therefore, having one seizure alone could be the result of general disease related neurodegeneration and is not enough to predict the risk of epilepsy development in a heterogeneous population where there are differing etiologies and disease progression trajectories. It follows that, while both epilepsy and cognitive dysfunction are disorders marked by patients with varying underlying etiologies, a subset of these populations appear to have a related underlying disease of neuronal networks [5•].

Currently, there are major gaps in knowledge and methodological problems that limit recommendations for treatment. In working with this population, early screening for seizure-like activity is indicated, and some non-pharmacological methods, such as diet, that have been successful in epilepsy and cognitive dysfunction are tentatively suggested. Anti-seizure medication use and brain stimulation–based methods are discussed in the following review based on the limited evidence available to date. In the future, teasing out the neurobehavioral phenotypes of those that suffer from both epilepsy and cognitive decline, and eventually, the molecular pathways that link cognitive dysfunction and epilepsy will likely help to guide treatment choices.

Treatment

Need for Neuropsychological Testing/Seizure Screening in Cognitive Decline and Epilepsy

A recent study of a large population-based cohort ($N = 4906$) by Stefanidou et al. reported that there is a bi-directional association between epilepsy and dementia, and patients are at a twofold risk of developing either condition in the existence of the other. Moreover, the same study reported that the risk of developing dementia among people with epilepsy who have post-high school education increases fivefold when compared to control patients with dementia but no epilepsy with the same educational attainment [11•]. Schnier et al. found that the incidence of dementia in people with epilepsy is higher than people without epilepsy, including vascular dementia (hazard

ratio 3.1) and Alzheimer's disease (hazard ratio 1.6) [12]. In addition, the risk of having a new diagnosis of dementia increases by 187% for people who develop epilepsy after the age of 50 [13]. Patients with dementia have a 2.5-fold increased risk of developing epilepsy [9]. Ranges of the prevalence of epilepsy in the setting of cognitive dysfunction vary based on specific diagnosis, from 4–5% in those with dementia, 3% in those with frontotemporal dementia, 5 to 10% in those with Alzheimer's disease and up to 20% in those with Lewy body dementia [14]. Both cognitive dysfunction and epilepsy are also associated with psychiatric comorbidities such as depression, anxiety, and psychosis [4, 15].

Despite the association between cognitive dysfunction and epilepsy and its impact on quality of life of people with epilepsy, cognitive dysfunction can often go undiagnosed and untreated in the epilepsy population [6, 15]. Similarly, seizure activity can often go unrecognized in those with cognitive dysfunction [14, 16]. General convulsive seizures are the most reported in those with Alzheimer's disease, but reports are often dependent on caregivers that may or may not have witnessed or been aware of witnessing the seizure activity [2, 14]. Non-convulsive seizures are the most difficult to identify, less likely to be reported, and more common in older patients than in younger individuals [17]. In clinical studies of those with Alzheimer's disease or dementia, EEG's were not commonly performed or reported on, which is critical considering that the recommendation for anti-seizure drugs in people with Alzheimer's disease or dementia is controversial without documented abnormal EEG results [2, 18].

The bidirectional association between epilepsy and cognitive dysfunction indicates that there is a need for standardized testing after initial diagnosis of either disease. And because patients tend to under report cognitive symptoms, subjective data is insufficient. For example, in a study of 247 newly diagnosed patients with epilepsy, deficits in attention and memory were only reported by 28.7 and 25.1% of patients, respectively. When screened with objective measures, 49.7% of patients had attention and executive function impairments, and 47.8% had memory impairments [3, 6].

In a series of recent reviews, Helmstaedter and Kanner et al. also discuss the need for early standardized screening of cognitive function in the setting of epilepsy and describe recommended neuropsychological tests [5, 15]. Helmsaedter et al. recommends specific assessments that might be useful, such as the Montreal Cognitive Assessment, Trail Making Test (TMT) A&B, Boston Naming Test (BNT), quality of life in neurological disorders (Neuro-QoL), and the Wechsler Adult Intelligence Scale (WAIS) [5•]. Cognitive impairment can be present early in the stages of epilepsy, emphasizing the need for early screening procedures [4]. Standardizing screening for cognitive dysfunction at the time of initial epilepsy diagnosis could provide a baseline for future assessments of cognitive decline over the course of the disorder and allow for early intervention [4, 15, 19]. Standardized screening for epilepsy in the setting of cognitive dysfunction can allow for the early diagnosis of epilepsy which can help to better manage and even prevent seizure activity [9]. Furthermore, those with early onset and rapidly progressive dementia, regardless of etiology, appear to have the highest risk for developing epilepsy

in the future, further supporting the need for early and repeated screening for cognitive dysfunction and epilepsy in these populations [9].

Although screening for seizure activity in the context of cognitive dysfunction is critical, it is often fraught with methodological issues. Even if routine EEG's are performed, many of the seizures experienced in the setting of cognitive decline may have nondiagnostic EEG results that do not meet the threshold for diagnosis, requiring costly and challenging long-term EEG monitoring [14, 18]. Nevertheless, capturing neuronal electrical abnormalities with EEG monitoring and using it to define seizure activity remains the gold standard before pharmacological treatment in people with Alzheimer's disease or dementia [14, 18]. Studies have found that EEGs performed for an 8-h period (awake) or 1 h during sleep were sensitive enough to detect epileptiform activity in five patients with Alzheimer's disease and epilepsy [16]. In fact, in this sample, 82% of epileptiform activity occurred during non-REM sleep. Therefore, prolonged EEGs including overnight sleep might produce the most sensitive recordings in this patient population [16].

A study by Tolchin et al. demonstrates that ambulatory EEGs can be useful in differentiating geriatric non-epileptic seizures from other disorders. The use of ambulatory EEG might be more convenient because of its substantially lower cost than inpatient EEG. Moreover, older individuals with a history of cognitive impairment and dementia might prefer the use of ambulatory EEG in the home environment over inpatient EEG [20]. In addition, emerging technologies such as medical wearable system devices can improve the ability to detect epileptic seizure activity by monitoring physiological parameters and cardiorespiratory function [21].

If prolonged EEG recording is not possible, extensive standardized questioning that specifically asks about seizure activity known to occur in this population could be utilized [14, 16]. For example, Baker et al. used a standardized interview technique to diagnose epilepsy in patients with diagnoses related to cognitive dysfunction. They conducted the interview in the patient's home, included the patients care giver, and asked specifically about generalized tonic–clonic seizures, behavioral arrest, amnesia on waking, olfactory hallucinations, and abnormal movements [16]. From this interview, they were able to diagnose 37 out of 144 patients with epilepsy, where only 10 of these patients had been suspected to have epilepsy prior to screening [16].

In addition to an EEG, brain imaging with CT or MRI should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure [22]. For example, an MRI-based study identified that deficits in visuospatial skills, decreased blood flow to the parietal lobe, and degeneration of the parietal lobe could be sensitive markers of those with Alzheimer's disease and epileptic seizures [23]. Sinha et al. describe that this kind of brain imaging can help to discern etiology and assist in medical decision making related to therapeutic options [23].

Need for Psychiatric Comorbidity Screening and Treatment in Cognitive Decline and Epilepsy

In epilepsy, identifying and treating underlying psychiatric and cognitive impairments can be just as critical as treating the seizures themselves. Psychological factors such as anxiety and depression can modify treatment outcomes in epilepsy and cognitive dysfunction [4, 24]. Because depressive symptoms themselves can induce cognitive dysfunction, treatment of the depression can alleviate cognitive symptoms in both epilepsy and cognitive dysfunction. Furthermore, if a person has mood disorder or depression, it may significantly increase the risk of suicidality. For psychogenic non-epileptic seizures in particular, a more comprehensive battery to assess cognitive and emotional systems that might be involved in PNES could advance understanding and in the development of treatment options [25]. Mood and anxiety disorders, however, tend to go underdiagnosed [4, 15].

The Beck Depression Inventory-II, Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Study Depression Screen, and the Neurologic Disorders Depressive Inventory in Epilepsy are all screens that are recommended to assess for depression [4, 15], although the PHQ-9 may be more feasible as a routine measure in the clinical setting. These screenings are suggested to be done at least once a year [4, 26].

In both epilepsy and cognitive dysfunction, depression could be associated with neuronal dysfunction. The clinical presentation of depression and/or anxiety, however, in these patients, is likely multifactorial. Mood and anxiety disturbances likely result from both the consequence of living with a chronic disease and a pathological predisposition towards neuronal dysfunction [4, 14].

Pharmacological

The Veteran's Health Administration and the American Psychological Association do not have a specific guideline for those with cognitive dysfunction and epilepsy. They do, however, suggest psychotherapy and second-generation antidepressants, particularly SSRI's, as first line treatments for older adults [27, 28]. Rudzinski and Meador suggest that in people with epilepsy and cognitive dysfunction, depression should be treated aggressively, even if they fail to meet diagnostic criteria for major depressive disorder [4], which is in line with the recommendations of the American Psychological Association for older adults with subclinical depression [27].

In treating cognitive impairment in the setting of epilepsy, it is important to take into consideration the effect of anti-seizure medications on cognitive function. Renal and hepatic function diminishes with age, and age is associated with a decrease in muscle to body fat ratio, resulting in potential changes in the pharmacokinetics and pharmacodynamics of anti-seizure medications. These changes may lead to anti-seizure medication toxicity and more adverse effects of anti-seizure medications [29, 30]. Anti-seizure medications with hepatic metabolism are particularly problematic due to

the possibility of drug interactions with medications commonly used in older patients (e.g., statins, anti-depressants) [30]. When polypharmacy is needed, the use of medications with less severe side effect profiles is preferred. For example, one study has shown that second generation agents anti-seizure medications such as lamotrigine and levetiracetam might be better for elderly patients on polypharmacy treatments [18, 30, 31]. These agents are also associated with less severe drug interactions and may be suitable choices for minimizing drug interactions in populations with multiple co-morbid conditions [18, 30]. Additionally, common side effects of anti-seizure medications include cognitive impact, but some anti-seizure medications have a more significant impact than others [32]. Topiramate has been found to have the greatest risk of cognitive impairment with long-term use [10]. Gabapentin, lamotrigine, and levetiracetam have demonstrated fewer cognitive impacts compared to carbamazepine and could be preferable in this population [33].

When a first unprovoked seizure occurs in the setting of cognitive impairment, the decision whether or not to treat with anti-seizure medication is largely based on clinician judgment of individual assessment in lieu of a lack of more defined studies [9]. In general, these decisions can be based on an individualized assessment of the risk for future seizures, a careful history of relevant co-morbidities, and the results of diagnostic tests. Future studies that further assess seizure recurrence risk in specific circumstances would help to further refine when medication is an appropriate choice [9].

When pharmacological options are deemed necessary, a 2016 Cochrane review found lamotrigine and levetiracetam to be equivalent in their ability to reduce seizures in people with Alzheimer's disease [34]. A recent systematic review and network metanalysis of drug monotherapy for epilepsy in the elderly analyzed data from five randomized clinical trials (1425 patients) and concluded that no significant difference in efficacy was found between Lamotrigine, levetiracetam, and lacosamide for achieving seizure freedom in adults (≥ 60 years old). Carbamazepine (both immediate release and controlled release) had a poor tolerability profile [35]. Levetiracetam was found to be the best at improving cognitive symptoms but tended to negatively impact mood while lamotrigine had a negative impact on cognitive symptoms [31, 34, 36, 37]. Similarly, in elderly patients with Alzheimer's disease, levetiracetam has good efficacy with a low-risk side effect profile but should be avoided in patients with mood disturbance as it can make aggressive behaviors worse [18, 38•]. Certin et al. provide an extensive review of the current second- and third-generation anti-seizure medications in patients with various forms of dementia. That review also concluded that levetiracetam is the agent of choice in patients with dementia [38•].

Bruun et al. assessed the outcome of anti-seizure medication monotherapy regimens in patients with newly diagnosed epilepsy and who were 65 years and older ($N = 529$). Results concluded that, unlike younger adults with newly diagnosed epilepsy, older patients with epilepsy were more likely to respond to monotherapy with approximately 64% of older individuals in their sample being seizure-free with the first monotherapy [39]. Moreover, approximately 50% remained seizure free for at least 2 years following the first monotherapy [39].

Nonpharmacological

Neuromodulatory treatments and diet modifications are non-pharmacological treatment options that have shown promise in both epilepsy and cognitive dysfunction settings. Deep brain stimulation, transcranial magnetic stimulation, vagus nerve stimulation therapy (VNS), and responsive neurostimulation system (RNS) have been demonstrated to improve cognitive function and to treat seizures [18]. A 5-day course of transcranial direct current stimulation decreased depressive symptoms and improved memory function in patients with temporal lobe epilepsy [34]. VNS has been recognized for the management of chronic depression and cognitive improvement [40]. VNS has also been approved for adjunctive treatment for medically refractory focal-onset seizures since 1997 [41] and could be especially useful in drug-resistant epilepsy. Furthermore, VNS was found to be cost effective when used in conjunction with anti-seizure medications because it was effective in reducing seizure frequency reducing costs associated with health care resource use as a result [42]. A controlled clinical trial among patients with focal seizure showed 75% reduction in seizure frequency after 9 years of RNS treatment resulting in improvement in quality of life and cognitive function [43]. These neuromodulatory treatments are promising in that they could directly target dysfunctional neuronal networks [18]. Punia et al. assessed the outcomes of resective epilepsy surgery (RES) among older adults (≥ 60 years old) and found that RES had good surgical outcomes without notable surgical or cognitive morbidity in their sample of older adults. Despite the considerable burden of comorbidities, later age at seizure onset, and longer duration of epilepsy, the outcomes were comparable to younger adults [44].

Ketogenic diets restrict carbohydrate intake to less than 20 g per day and have a higher fat intake as compared to protein consumption [45]. A modified ketogenic was developed to make the ketogenic diet more flexible for patients and typically involves 10–30 g of carbs per day, a 1:1 fat to combined protein and carbohydrate intake, and no limitation on fluid or protein intake [45]. Ketogenic diets have been suggested as an effective treatment for neurological disorders in general [46]. The ketogenic diet can improve benefits in refractory epilepsy by decreasing the frequency of seizures across age groups [47]. In addition, the ketogenic diet has had extensive success in the treatment of children with epilepsy with 52% of those that stayed on the diet for up to 24 months achieving greater than or equal to 90% seizure control with similar results for the modified Atkins diet [45]. Mechanistically, it has been proposed that a ketogenic diet, through the promotion of ketogenesis, reduces neuroinflammation [48], and alters the excitability of neurons at a cortical level [49, 50].

Other diets have also been found to improve neurocognitive function. Fasting to induce a state of ketogenesis was the first approach historically before the ketogenic diet [51]. Intermittent fasting is a popular diet for weight loss that has been proposed to have positive overall all health benefits [52, 53]. Diets that target omega 3 fatty acids/omega 6 fatty acid dietary ratios have also been effective at improving symptoms of mood and cognitive impairments, reducing psychological distress, and improving quality of life

[54–56]. The Mediterranean-Dash diet intervention for neurodegenerative delay (MIND) diet (included either extra-virgin olive or mixed nuts) has been suggested as a non-pharmacological treatment in the cognitive setting [57]. Although it is linked to neuroprotection and dementia prevention, it is unknown if this diet modification would be helpful for patients with epilepsy and cognitive dysfunction.

Diet modification is a promising treatment in that it tends to have benefits for overall health and work to improve outcomes for multiple co-morbidities. It does, however, tend to involve behavioral modification strategies and nutritional psychoeducation to be co-implemented to ensure success. The long-term benefits and negative side effects that are avoided with this approach, however, could make up for this front loading of resources. Overall, more research is needed to determine a diet intervention that would be ideal for this patient population.

Conclusions and Future Directions

While the current literature provides suggestions for treatments in individuals with epilepsy and/or dementia, more randomized control trial studies are needed before firm recommendations or practice guidelines can be put in place. Early standardized screening of cognitive function in the setting of epilepsy is, however, highly recommended [5•]. Cognitive function can be tested through standardized neuropsychological assessment. In screening for epilepsy, a combination of standardized interviewing techniques, wearable devices, and overnight EEG tests might be optimal to proceed with early screening for epilepsy in those with cognitive dysfunction [14, 16, 21]. Continued screening and assessment throughout the disease process could help in establishing guidelines specifically for those with epilepsy and cognitive dysfunction. Creating these guidelines for patients with multiple neurological co-morbidities could help in improving outcomes and reducing polypharmacy, particularly for older adults [58].

Beyond measuring outcomes that can guide the treatment progression of an individual, understanding the underlying molecular mechanisms of neuronal hyperexcitability and deficits in learning and memory could play an important role in establishing treatment guidelines [1, 59]. Implementing rigorous, standardized neuropsychological testing can help to further this goal. For example, cognitive phenotypes derived from neuropsychological testing can be associated with anatomical differences identified with CT and MRI that could reveal groups of patients with unique pathological etiologies [5•, 60–62]. This not only expands our resources for screening but also helps to elucidate the underlying neuronal mechanisms driving pathology. Ultimately, understanding the related pathology between epilepsy and cognitive dysfunction may play a critical role in identifying appropriate treatments in the future.

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Compliance with Ethical Standards

Disclaimer
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Competing Interests
The authors declare no competing interests.

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