LATE-ONSET EPILEPSY IN THE ELDERLY: DIFFICULTIES OF DIAGNOSIS AND PERSONALIZED PHARMACOLOGICAL MANAGEMENT, WITH PARTICULARITIES TO COVID-19 PANDEMIC – SYSTEMATIC REVIEW OF LITERATURE

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Abstract

In the actual demographic and pandemic context, epilepsy in people over 65 years is a multidimensional issue and a challenge to public health care. Systematic reviews and meta-analyses on the subject are scarce. A systematic and synthetic analysis of the literature published in the last 10 years (2011 - 2020) was performed, using the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) paradigm. All identified papers were subjected to a standardized related filtering endeavour, in five steps, using PRISMA inspired selection methodology. Ultimately, there were selected 56 eligible articles; nonetheless, we enlarged our bibliographic base with additional resources related to the subject, freely discovered in the literature. The paper emphasizes elements of descriptive epidemiology, clinical presentations, differential diagnosis, and special issues in the treatment and prognosis of late-onset epilepsy in the elderly. The therapeutic decision in late-onset epilepsy is considered in the holistic frame of the neurologic pathology, pharmacological and pharmacokinetic issues specific for the old persons. The elderly is susceptible to drug-induced acute seizures because of the high prevalence of co-morbidities or polypharmacy. Special considerations were focused on COVID-19 associated seizures. Management of elderly patients with late-onset seizures/epilepsy requires special considerations concerning the positive and differential diagnosis, aetiology, prognosis and treatment.

Rezumat

În contextul demografic și pandemic actual, epilepsia la persoanele peste 65 de ani este o problemă multidimensională și o provocare pentru serviciile de sănătate publică. Recenziile sistematice și meta-analizele pe acest subiect sunt rare. A fost efectuată o analiză sistematică și sintetică a literaturii publicate în ultimii 10 ani (2011-2020), folosind paradigma de raportare pentru revizuiri sistematice și meta-analize (PRISMA). Toate lucrările identificate au fost supuse unui efort de filtrare standardizat, în cinci pași, folosind metodologia de selecție inspirată de PRISMA. În cele din urmă, au fost selectate 56 de articole eligibile; cu toate acestea, s-a lărgit baza bibliografică cu resurse suplimentare legate de subiect, descoperite liber în literatură. Lucrarea subliniază elemente de epidemiologie descriptivă, prezentare clinică, diagnostic diferențial și probleme speciale în tratamentul și prognosticul epilepsiei cu debut tardiv la vârstnici. Decizia terapeutică în epilepsia cu debut tardiv este considerată în cadrul holistic al patologiei neurologice, problematicii farmacologice și farmacocinetice specifice vârstnicilor. Vârstnicii sunt susceptibili la convulsii acute induse de medicamente din cauza prevalenței mari a comorbidităților sau poli-pragmaziei. Considerații speciale s-au concentrat asupra convulsiilor asociate cu COVID-19. Managementul pacienților vârstnici cu convulsii/epilepsie cu debut tardiv necesită considerații speciale privind diagnosticul pozitiv și diferențial, etiologia, prognosticul și tratamentul.

Keywords: late-onset epilepsy, elderly, seizures, COVID-19, comorbidities

Introduction

People over 65 years represent the fastest-growing age group globally, estimated to rise up to 1.2 billion in 2025 [1]. In the European Union, it is predicted to rise from 87.5 million in 2010 to 152.6 million in 2060 [2].

Many neurological conditions, such as stroke, Alzheimer's, or Parkinson's diseases are typically

nomological entities attributed to the elderly; other diseases, such as epilepsy or traumatic brain injury have a second peak at old age [3-9]. During the last 40 years, the age-related incidence of epilepsy significantly increased among old individuals (from 57 *per* 100,000 to 217 *per* 100,000) [10].

Global and regional variations in epileptogenesis are recorded all over the world and depend on socio-demographic, respectively country-specific socio-economic factors. Socio-economic and educational status create disproportionate discrepancies between high- *vs.* lower-middle-income economies, regarding incidence, prevalence, mortality, disability, and the quality of life of epileptics. In low-income populations, the global burden of epilepsy is higher and access to performant medication is limited [8, 9, 11-18].

Patients 70 - 80 years old have seizures twice or three times more frequently than in childhood [4, 6]. The annual incidence of recurrent unprovoked epileptic seizures is 90/100,000 in people 65 - 69 years old, and estimated to be more than 150/100,000 for those over 80 years [4].

The incidence, prevalence, and mortality of epilepsy vary in well-defined populations, and across countries with different economies [16, 17]. Disparity results from methodological problems, possible seizure remission and/or premature mortality, socioeconomic factors, and social stigma [19].

Epilepsy is the third most prevalent neurological condition affecting the elderly, after stroke and dementia-related diseases [20]. The elderly is prone to multiple comorbid diseases that may be risk factors for late-onset epileptic (LOE) seizures, such as stroke, neuro-degenerative diseases, brain tumours, traumatic brain injury, neuroinfections [12, 20-22].

According to the ILAE (International League Against Epilepsy), seizures and epilepsy are not the same, and the onset of a single seizure does not mean epilepsy [23]. For example, heavy alcohol consumption is associated with epilepsy, whereas alcohol withdrawal can cause seizures, but not epilepsy [24, 25].

Seizure is a paroxysmal neurological event and epilepsy is a "disease involving at least two unprovoked (or reflex) recurrent seizures, occurring more than 24 hours apart or after one seizure, if risks of recurrence are "high" (> 60%)" [23].

Seizures are short-term events, frequently occurring in the absence of witnesses, so old persons living alone might have seizures that can remain unknown [4, 7, 26, 27] and in about half of the cases, no obvious aetiology can be detected [7, 22, 23].

Both seizures and epilepsy manifest with paroxysmal episodes, characterized by aberrant (excessive or hyper-synchronous) bio-electrical cerebral activity, in the form of sudden and recurrent stereotypical clinical events [20, 23].

Epilepsy at old age has two main clinical and etio-pathogenic aspects: a chronic illness from an early year's diagnosis, or late-onset (LOE/or new-onset) seizures in the elderly. LOE means occurrence of first time (*de novo*) seizures after the age of 65, in a person with no previous epileptic history.

Typically, up to 70% of LOE have focal onset, with or without secondary generalization [22, 28-30], triggered by the local/regional structural cerebral modifications and aetiology. Onset with tonic-clonic convulsions is relatively rare [22, 31].

According to the Epilepsy Foundation, up to 10% of people may have a lifelong seizure, while 1/26 of subjects will develop epilepsy [32]. Establishing a correct differential diagnosis between epilepsy and other seizure disorders in the elderly has tremendous importance [5].

LOE represents a unique challenge in an increasingly prevalent population [33], due to the frailty of age, the complexity of comorbid medical and neurological disorders, and has become a worldwide public health problem [13, 27, 34].

Materials and Methods

A systematic and synthetic analysis of the literature published in the last 10 years (2011 - 2020) was performed, using the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) paradigm. The following medical databases were interrogated: WoS, Elsevier, NCBI/PubMed, NCBI/PMC, PEDro, using a series of keywords combinations/syntaxes. All identified papers were subject to a standardized related filtering endeavour, in five steps, using PRISMA-inspired selection methodology.

Results and Discussion

Ultimately, there were selected 56 eligible articles; nonetheless, we enlarged our bibliographic base with additional resources related to the subject, freely discovered in the literature.

Endogenous and exogenous risk factors for seizures and epilepsy in the elderly. The predisposition to further development of symptomatic convulsions and epilepsy is miscellaneous: systemic and extracerebral disorders (metabolic or electrolyte disturbances, toxic factors, inappropriate administration or sudden discontinuation of psychotropic drugs or within 48 h of cessation of prolonged drinking, hypothyroidism, pneumonia, urosepsis and hepatic failure) [4, 25, 32, 35].

Many old persons may have dysbiosis of gut micro-flora and inflammatory bowel disease. Dismicrobism predisposes to dysregulation of the gut-brain inter-relations and possible LOE [36].

Reactive psychological issues (depression, anxiety and sleep deprivation) or long-term morpho-pathological sequelae of brain injuries are the most common co-morbidities and risk factors for recurrent seizures [7, 21, 29, 37]. Cerebrovascular diseases, including stroke,

account for 30 - 50% of LOE in the old age population [38].

Older people are more sensitive to the neurotoxicity of specific drugs and susceptible to drug-induced acute seizures, because of the high prevalence of comorbidities and polypharmacy [29, 37].

A wide range of medications commonly used by the elderly have proconvulsant side effects and precipitate drug-induced symptomatic acute seizures: antibiotics such as carbapenems (mero-/; erta-/; imipenem); high-doses of penicillin; antihistamines (desloratadine); pain medication (tramadol or high-dose opiates); initiation or withdrawal of antipsychotics or anti-depressants (clomipramine, bupropion); theophylline, Levodopa and even Ginkgo biloba herbal remedies [32].
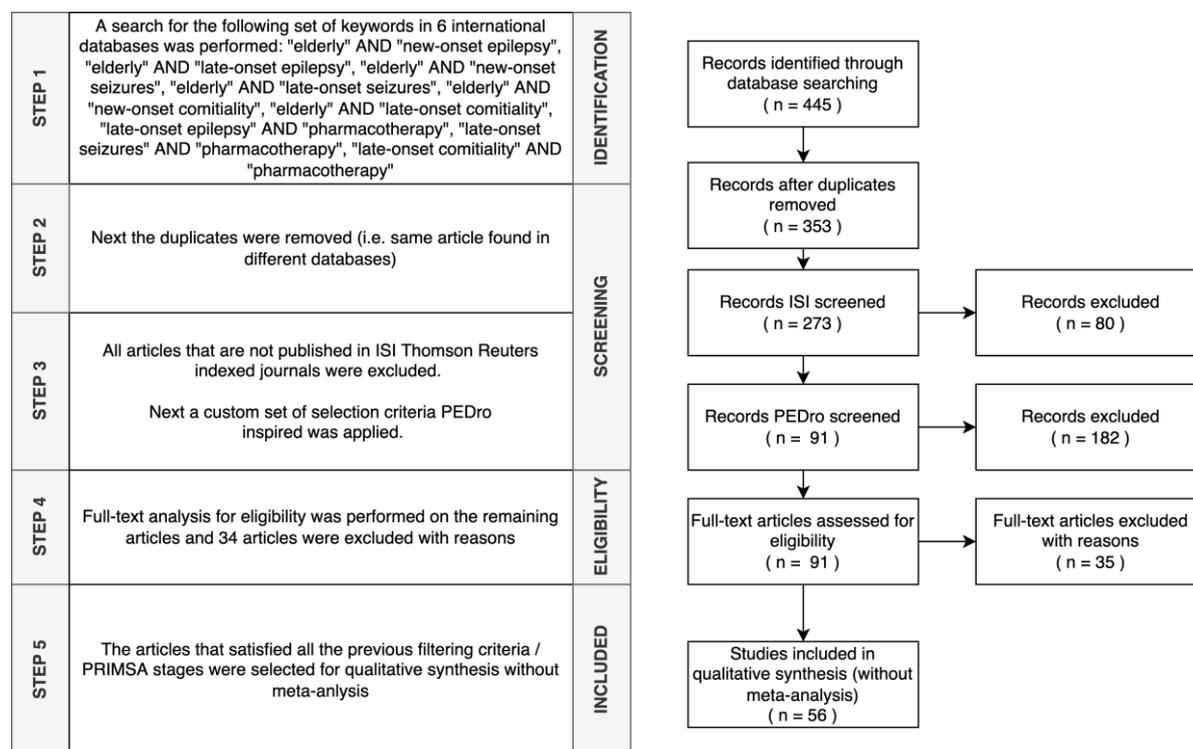

Figure 1.
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of the literature search

Antihypertensive, diuretics, some antidepressants, even anti-epileptic drugs (such as carbamazepine (CBZ), or the newer one oxcarbazepine (OXC), particularly when co-administered with diuretics) can induce hyponatremia in the elderly, although this might be asymptomatic [3, 4, 35]. Sodium concentrations below 125 mmol/L are associated with an increased seizure risk in the elderly [35].

Neurotrophic agents have no active role in epilepto-genesis and may be used to treat patients who share epilepsy as a co-morbidity (e.g., elderly epileptic patients with stroke). Strict patient monitoring is required to ensure appropriate choice and effective doses of antiepileptic treatments [39].

Epilepsy can be caused by many conditions that affect the brain. Acute symptomatic seizures in older patients are common in close temporal association with brain injuries [21, 26, 40-44]. About 1 - 2% of the geriatric population has epilepsy secondary to cerebrovascular diseases, which means a third of the identifiable causes of seizures and epilepsy in older people [12, 22, 29, 31].

Stroke (mainly ischemic) is a common cause of adult and elderly-onset epilepsy [12, 13, 21, 38, 41, 42, 45, 46], and incidence of early post-stoke seizures (PSS) varies from 2% to 33% [47]. Focal-onset seizures in the elderly occurred most commonly (84%) after stroke [13].

Approximately 45% of the *de novo* seizures over the age of 60s are attributed to ischemic or haemorrhagic strokes [12]. There are two peaks in occurrence: during the first days (24 - 48 hours) or during the first 7 [12, 48], up to 14 days [13]. Early-onset PSS could be a presenting feature and common cause of emergency hospitalization, or a complication that occurred within the first 14 days after the cerebral accident, and are reported in about 4.2% of patients [12].

Intracerebral and/or subarachnoid hemorrhage and hyponatremia are risk factors for early PSS [38].

The second pick of incidence occurs remotely at 6 - 12 months after stroke [12, 42, 48]. Epileptogenesis in the aforementioned clinical situations has different morpho-pathological substrates [42].

A previous history of ischemic stroke is the leading putative cause (22.6%) for seizures recurrence and LOE [12, 13, 21, 42] in more than 72 - 80% of cases [21].

Epidemiological evidence suggests a bidirectional relationship between epilepsy and stroke; in the elderly who develop LOE, the risk for a possible subsequent stroke is 3 times higher [21, 49] although this pathophysiological relationship remains unclear [50].

Post-stroke seizures/epilepsy can be managed using long-term anti-seizure medications (AEDs), associated with good seizure outcomes [13].

Most issues (40%) were controlled with monotherapy (i.e., sodium valproate VPA) [13, 14, 21], initiated promptly after the first seizure [13, 21], although it is more cautious to avoid VPA in elder patients due to its adverse effects.

Seizure recurrence induces neurobiological insults in the central nervous system, respectively cognitive, psychological and social consequences. Prophylaxis with AEDs should be administered in post-stroke late epileptic attacks, because recurrence is double (54%) in patients without AEDs treatment, during the first-year post-stroke [48].

Although AEDs failed to prevent recurrence and freedom of crises in all persons at risk [13, 14, 21], overall effectiveness was satisfactory in 80.5% of patients, who achieved significant seizure reduction at the two-year follow-up evaluation [13].

New-generation AEDs levetiracetam (LEV) and lamotrigine (LTG) – where available [13] – have the best tolerance and are appropriate for managing post-stroke seizures [42, 47].

Gabapentin (GBP) and LTG were approved and are considered to be more effective than CBZ because they do not interact with anticoagulants and antiplatelet drugs, prescribed in the elderly with post-stroke epilepsy [45].

A large study comparing over 3,000 Taiwanese patients with late-onset post-stroke epilepsy revealed that in those treated with VPA or new AEDs (OXC, vigabatrin, tiagabine, LTG, LEV, topiramate, GBP and pregabalin) used as a first-line therapeutic option, exacerbation of seizures and hospitalizations were lower compared to patients treated with phenytoin (PHT) or CBZ [51].

Post-critical partial or complete motor deficit (Todd`s paralysis) is a temporary neurological condition experienced after a seizure and must be differentiated from stroke recurrence [52].

Dementia and late-onset epilepsy (LOE)

Primary neurodegenerative disorders associated with cognitive impairment (especially Alzheimer's disease and vascular dementia) are at significantly higher risk of developing epileptic seizures than in the general elderly population [53-56].

Approximately 10 - 22% of older people with Alzheimer's dementia have at least one unprovoked seizure that occurs in later stages (usually after 6 years of disease) [57]. A cohort study of over 3 thousand patients with mild to moderate Alzheimer's evaluated the risk for new-onset seizures, and estimated an incidence rate of 484 *per* 100,000 persons [56]. Neurodegenerative processes expose the elderly with Alzheimer`s disease to a 5 - 10-fold higher risk of developing epilepsy, than their non-Alzheimer's counterparts [20, 58, 59].

LOE in older adults with Down syndrome and dementia, carriers for APOEε4 alleles was associated with a 7 - 10-fold increased risk for mortality [60].

Seizures can be an early clinical presentation of autosomal dominant Alzheimer's familial disease [61], particularly if there are gene mutations in presenilin (PSEN1, PSEN2) or amyloid precursor protein (APP) genes [57]. Evidence suggests common morpho-pathological connections between Alzheimer's disease and LOE, possibly mediated by the underlying vascular changes and/or tau pathology [53, 55, 62-64]. Loss of GABA interneurons in the hippocampus (selectively vulnerable to apoE4-mediated neurotoxicity) leads to deficiency of inhibitory neural networks and cognitive decline. Damage to GABA interneurons induces aberrant network hyperexcitability and hypersynchrony in the hippocampus and cortex, respectively seizures [58, 59].

Dementia-associated epilepsy is a two-way relation-ship and the prevalence of cognitive decline in epilepsy ranges from 8.1% to 17.5% [13, 63, 64].

Oestrogens and serotonergic neuromodulator drugs targeting 5-HT1A and 5-HT3 receptors have potentially neuroprotector proprieties, and might ameliorate seizure-induced neurodegeneration and the recurrent, aberrant hyper- synchronous neuronal activity [65].

Pre-existing dementia does not exempt the clinician from ruling out other causes of symptomatic seizures [54].

Meningitis and cerebral abscesses can affect vulnerable old persons and can have a fulminant evolution with lethargy, nausea, vomiting, nuchal rigidity, new-onset seizures, possible focal neurologic deficits and death [52].

Sometimes seizures have no obvious clinical causes, so diagnosing, respectively managing elderly-onset epilepsy could be challenging [8, 66].

Complex focal brain pathology induces mainly complex partial seizures (47.1% cases) than simple focal ones [28]. It's possible to have just one type of seizure, or more than one type [32] without secondary generalization (47.1%), mainly in patients with temporal lobe epilepsy [38]. New-onset complex partial seizures may have misleading clinical presentations, with atypical features (episodes of paroxysmal confusion, periods of in-attention and memory lapses) mimicking transient

ischemic attacks, syncope, or transient global amnesia [7, 26, 28, 38, 67].

Postictal altered state of consciousness, confusion and memory lapses are particularly prolonged in the elderly after an epileptic seizure [13].

Status epilepticus (SE), especially refractory SE, represents a medical emergency, and life-threatening condition, with a high mortality rate [68, 69].

It is defined as any clinical and/or electrophysiological epileptic activity that lasts for more than 5 minutes, or recurrence of at least two seizures within a 5-minute period, without remission to the normal level of consciousness, between these acute episodes [13, 47, 68].

Its annual incidence is 27.1 *per* 100,000 elderly people, approximately 4 - 5 times higher than in nongeriatric adults, due to specific aetiologies and structural brain issues [44, 70]. Stroke, neurodegenerative diseases, brain tumours (typically gliomas, meningiomas, and brain metastases), traumatic and/or post-surgical brain lesions/sequelae, encephalitis are leading putative causes of LOE and SE [7, 13, 22, 70, 71].

About 30% of LOE (new-onset acute) seizures in old persons will present as new-onset refractory SE, with a mortality rate approaching 40% [44, 68, 69]. In the prehospital settings, anti-seizure management consists of rectal administration of diazepam, or midazolam (intranasal or buccal) [8]. Experts recommend IM injectable midazolam, as the drug of choice for out-of-hospital, as well as an emergent alternative for hospitalized patients with SE [71].

Non-convulsive status epilepticus (NCSE) may be evoked by an acute (prolonged) episode of confusion, fluctuating awareness, and/or behavioural changes [5, 70, 72-74], certified by continuous bioelectrical monitoring and video recordings [13].

The electroencephalogram (EEG) is the most useful diagnostic method in epilepsy. Standard EEG findings are fairly typical, and if EEG shows clear epileptiform discharges, the risk for seizure recurrence is considerably high [73].

On the other hand, EEG patterns can be highly variable and sometimes difficult to distinguish an NCSE (frequently encountered in the elderly) from a metabolic or infectious encephalopathy [73].

In many cases, EEG is usually recorded late after the ictal episode, and the absence of epileptic discharges does not exclude epilepsy [8, 73].

Intensely abnormal EEG grafo-elements could predict mortality in severe ICU or palliative care patients [73, 74].

Prolonged or continuous and automated quantitative EEG monitoring, teleneuro-electrodiagnosis could detect ictal and/or interictal bioelectrical abnormalities, useful in the differential diagnosis of NCSE from other non-convulsive seizures (complex partial seizures but they are not routinely available [8, 42, 70].

The therapeutic paradigm in (refractory) SE aims at burst pattern suppression and reducing coma duration, using intravenously AEDs administration [70]. LCM (lacosamide) might be a first-choice drug against post-stroke NCSE in the elderly [47].

De novo seizures in older patients infected with SARS-CoV-2. The coronavirus disease 2019 (COVID-19) represents a global public health issue. The virus exhibits neurotropic properties and can invade the central nervous system (CNS).

Infected patients may develop various clinical manifestations, including headache, dizziness and severe CNS related manifestations (such as impaired consciousness, encephalopathy, encephalitis, seizures and acute cerebrovascular events), and peripheral nervous system issues (such as hyposmia/anosmia, hypogeusia/ageusia, muscle pain and Guillain-Barre syndrome) [18, 72, 75].

De novo seizures in confirmed COVID-19 may occur in patients without a history of epilepsy, in both sexes and of all ages. Yet, the prevalence of new-onset seizures associated with COVID-19 is 0.08% [76] (less than the prevalence rate of epilepsy in the general population, reported to be 0.7 - 1.0%) [77].

When compared to the mild forms, severe infections are more likely to induce neurological complications (30% *versus* 45.5%) [75].

Critically ill patients are at high risk for encephalopathy, delirium and possible *de novo* symptomatic seizures/status epilepticus. The pathological mechanisms of these complications are multifactorial. Epileptogenesis might be the consequence of hypoxic respiratory distress, metabolic derangements and multi-organ failure, sepsis with dysregulated immunomodulation (the "cytokine storm") and autoimmunity against neuroglia, or a direct SARS-CoV-2 neuronal damage, chronic cerebral issues (associating pre-existing low-grade chronic inflammation and downregulated ACE-2 levels), but it can also be induced by the side effects of medications [72, 75, 76, 78-80, 94].

Acute symptomatic seizures in critically ill infected with COVID-19 could be the first viral manifestation or a severe neurologic event during hospitalization, being associated with hypoxemia, fever and other risk factors triggering convulsions [76, 78, 81].

Previous chronic (multiple) comorbidities (obstructive pulmonary disease, diabetes, obesity, dysmetabolic causes, hypertension, coronary heart disease, liver or kidney diseases, pre-existing neurological issues, including stroke, and/or cognitive decline and cancer) are risk factors that make older individuals – who's characteristic bio-pathological status is multi-morbidity – highly vulnerable for developing severe COVID-19 infections, complicated with multiple organ failure, and a greater mortality rate.

The neurovirulence and neuroinvasive potential of SARS-CoV-2 can affect the cardio-respiratory regulatory nuclei of the brainstem and merge the deadly

pathological vicious cycle, explaining the very high mortality rate (80%) among patients with seizures [76].

Some reports suggest that COVID-19 might increase the risk of sudden unexpected death in epilepsy (SUDEP) [75].

Detailed clinical, neurological, imaging and electro-physiological investigations are mandatory in SARS-CoV-2 positive old patients with pre-existing cognitive decline, who present altered mental status, convulsive status epilepticus, or refractory non-convulsive status epilepticus with generalized periodic discharges.

Najjar S *et al*. reported a 71-year-old female SARS-CoV-2 positive [72], who presented with altered mental status and new-onset convulsive seizures, then aggravated to non-convulsive SE, despite sedation with propofol and intubation for respiratory difficulty. The refractory non-convulsive SE with altered EEG pattern (persistent generalized periodic discharges) was treated with several AEDs and was associated with a severe, rapid rise in serum CRP. MRI-DWI imaging revealed numerous minuscule foci of cerebral ischemia, distributed bilaterally in the cerebral sub-cortical white matter.

Although there is no panacea, some drugs were tested for the treatment SARS-CoV-2 infection: atazanavir (ATV); chloroquine (CLQ); hydroxychloroquine (HCLQ); favipiravir (FAVI); lopinavir/ritonavir (LPV/r); ribavirin (RBV); remdesivir (RMD); tocilizumab (TCZ) and interferon β-1a (IFN-β-1a).

Common anti-seizure medications might have potential pharmacological interactions with medications tested against SARS-CoV-2. Some anti-virals (such as RBV and LPV) can have cytochrome-based interactions with AEDs [82]. Interactions between drug combinations may be assessed by clinical studies, or predicted based on their metabolic profiles [83].

The following clinical situations could be expected: the AEDs – anti-COVID drugs should not be co-administered (due to potentially high toxic levels of COVID drugs and/or of AEDs); potential clinically significant interaction, that is likely to require additional monitoring, alteration of drug dosage or timing of administration; potential interactions, likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required; no clinically significant interactions expected.

Some AEDs might potentially decrease the exposure to COVID drugs. This pharmacological effect is provoked by anti-seizure drugs with hepatic enzyme inducing effects – such as phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB) – metabolized by cyto-chrome P450s in the liver). They might decrease remdesivir (RMD) antiviral efficacy [83].

Cytochromes P450, a superfamily of hepatic enzymes (CYP3A4, CYP2C19, CYP2C9 and CYP1A2) are involved in the metabolism of drugs (including the aforementioned AEDs). On the other hand, in COVID infected patients CYPs are downregulated by elevation of IL-6 (as well as other cytokines). By reducing hepatic metabolism (CYP-mediated), and RMD may augment the plasmatic concentration of co-administered medication.

Tocilizumab (TCZ) is an IL-6 receptor monoclonal antibody, with no inhibitory or inducing effects on CYPs. Inhibition of IL-6 signalling may restore CYP450 activities to higher levels, leading to increased metabolism of drugs that are CYP450 substrates, and subsequently reducing plasmatic concentrations of other previous co-treatments [83].

Levetiracetam (LEV), gabapentin (GBP) and pregabalin (PGL) do not cause interactions with any drugs, including medications tested in SARS-CoV-2 infection. Possible interactions between AEDs with some potentially antiviral agents are summarized in Table I.

Clinically relevant pharmacokinetic drug interactions might occur between AEDs and second-generation antidepressants (fluoxetine, paroxetine, fluvoxamine, which undergo extensive hepatic degradation mediated by CYP450 isoenzymes, and metabolically compete with some AEDs). Taking into account a 0.1% risk of *de novo*-seizures induced by the new antidepressants, it is recommended to avoid the aforementioned associations [71].

Positive diagnosis in LOE may be challenging because the elderly already presents a variety of concomitant complex medical issues (cerebrovascular disease, cognitive impairment and frailty [29, 33].

Pharmacotherapeutic strategies for LOE and under-lying mechanisms

The structural and functional physiological changes in geriatric patients are characterized by two main biological hallmarks: reduced serum albumin synthesis and renal clearance. Age-related physiological decline affects drug pharmacokinetics and pharmacodynamics of AEDs [22, 84].

AEDs with high protein binding rates (i.e., CBZ, PHT and VPA) may have higher serum levels of anti-seizure medication. Renally excreted ones (i.e., GBP, TPM and LEV) have also increased blood concentrations, due to reduced glomerular filtration rate [38].

Treatment for symptomatic seizures should address the root cause, using monotherapy (ideally new AEDs as front-line drugs), whenever possible [7, 28, 29, 38, 68, 85].

The elderly usually responds to first-line anti-seizure medication (96.3%), require fewer AEDs [28, 38], and have better tolerability for conventional anti-convulsant medication. Most seizures are controlled with monotherapy in small, gradually titrated/ increased doses [10, 13, 21, 38, 42, 43, 86, 87].

LTG, GBP, and CBZ are indicated in patients with partial seizures, secondary to brain insults [38]. A slow-release AEDs (carbamazepine retard or sodium valproate chrono) at the lowest possible dosage could be indicated, and their blood levels should be monitored.

Table I

Regular antiepileptic drugs (AEDs) used in seizures / LOE in elderly [8, 29, 73, 92, 95, 96]

Drug	Advantages	Disadvantages	Potential Cognitive AEs	Potential effect on mood	Specific AEs in elderly	Common Drug-Drug interactions	AEDs – anti COVID drugs interactions
CBZ	"gold standard" for partial seizures low cost studied in elderly	neurotoxicity hyponatremia allergic reactions	more marked in elderly	mood stabilizer	greater risk for osteoporosis dizziness can lead to falls	-enzyme induction: high propensity for drug-drug interactions -reduces levels of Ca^{++} channel blockers	a) should not be co-administered with ATV; RDV; CLQ; HCLQ (marked decrease in antiviral efficacy) b) no effect on FAVI, RBV c) no significant effect on IFN-β-1a (potential interaction, requiring dose adjustment/ close monitoring)
PHT	management of generalized tonic-clonic and complex partial seizures low cost once daily	sedation allergic reactions narrow therapeutic window negative effects on lipid metabolism and cardiac markers	can be associated with adverse effects on cognition	(sometimes) adverse effects on mood	great risk for osteoporosis dizziness can result in falls	-enzyme induction: extensive drug-drug interactions - impairs efficacy of: • apixaban corticosteroids, • Ca^{++}channel blockers, • tricycle antidepressants - levels raised by: • H2 antagonists, • fluoxetine, • VPA	a) should not be co-administered with ATV RDV; CLQ; HCLQ (marked decrease in antiviral efficacy) b) no effect on FAVI, RBV c) no significant effect on IFN-β-1a (potential interaction, requiring dose adjustment/ close monitoring)
VPA	"gold standard" for generalized seizures relatively cheap	thrombocytopenia, weight gain,	can affect cognition hyperammonaemia encephalopathy	mood stabilizer	tremor at higher doses	few interactions -increases levels of: • LTG, • diazepam, • tricycle antidepressants (amitryptiline)	a) + ATV - no significant interactions - no significant effect on COVID drug b) + LPV/r -potential interaction (may require VPA dose adjustment, or close monitoring). - Potential very high exposure of COVID drug c) IFN-β-1a - potential interaction, requiring VPA dose adjustment/ close monitoring) - no significant effect of COVID drug
PB	broad spectrum once daily the cheapest	sedation	cognitive impairment	behavioural problems		-increases levels of acetaminophen, (paracetamol) -reduces levels of Ca^{++} channel blockers -impairs efficacy of: • apixaban, • warfarin	a) should not be co-administered with ATV; RDV; CLQ; HCLQ (marked decrease in antiviral efficacy) b) no effect on FAVI, RBV c) no significant effect on IFN-β-1a (potential interaction, requiring dose adjustment/ close monitoring)

Drug	Advantages	Disadvantages	Potential Cognitive AEs	Potential effect on mood	Specific AEs in elderly	Common Drug-Drug interactions	AEDs – anti COVID drugs interactions
LTG	broad spectrum good tolerability studied in elderly	dose related rash (1: 30)	usually cognitive neutral	mood stabilizer	insomnia, vivid dreams, night-mares possible tremor	few interactions -may enhance the depressant effect of sublingual zolpidem	
LVT	few allergic reactions		usually, cognitive neutral	can have adverse effects on mood (irritability, anxiety, low mood)	behaviou ral problems	no interactions	
PGL*	no allergic reactions frequently used in chronic pain	few data in LOE weight gain ankle oedema	usually, cognitive neutral	anxiolytic and benefit mood	dizziness increased risk of falls in elderly	no interactions	no significant interaction (RDV; FAV; CLQ; HCLQ; RBV; TCZ; IFN-β-1a)
GBP*	no allergic reactions studied in elderly	sedation weight gain			dizziness could result in falls	no interactions	no significant interaction (RDV; FAV; CLQ; HCLQ; RBV; TCZ; IFN-β-1a)
OXC	good tolerability	neurotoxicity hyponatremia allergic reactions (rush)	confusion	probably no substantial adverse effect on mood	apathy lethargy dizziness, risk of falls	-enzyme induction	
LCS		electrocardiogram check prolongation of PR interval (all patients)	usually, cognitive neutral benign psychological profile	(occasionally) adverse effects on mood	possibility of palpitatio ns; rarely atrial fibrillation and atrial flutter		
TPM	broad spectrum	slow titration nephrolithiasis weight loss	cognitive impairment (world-finding difficulty, in particular)	(could have) adverse effects on mood	few data on elderly	-may decrease the serum level of • digoxin • glibenclamide -may enhance toxicity of • carbonic anhydrase inhibitors (i.e., acetazolamide) • metformin	
ZNS	better tolerated than TPM broad spectrum	nephrolithiasis	cognitive impairment (world-finding difficulty, in particular)	(could have) adverse effects on mood	few data on elderly	no interactions	

Legend: AEs = adverse-effects; CAEs = cognitive adverse-effects. The drugs with cognitive adverse effects are described in the grey, shaded area of the table. CBZ = carbamazepine, PHT = phenytoin; VPA = valproate; PB = phenobarbital; LTG = lamotrigine, LVT = levetiracetam; PGL = pregabalina; GBP = gabapentin; OXC = oxcarbazepine; LCS = Lacosamide; TPM= topiramate; ZNS = zonisamide; (*) = adjunctive therapy associated with another AED drug; * Antiviral agents against SARS-CoV-2: ATV = atazanavir; CLQ = chloroquine; HCLQ = hydroxy-chloroquine; FAVI = favipiravir; LPV/r = lopinavir/ritonavir; RBV = ribavirin; RDV = remdesivir; TCZ = tocilizumab (anti-IL6R); IFN-β-1a = interferon β-1a

Some AEDs have potential cognitive adverse effects that may worsen dementia and exacerbate the difficulties in daily life activities of patients with Alzheimer's disease [88, 89]. The cognitive tolerability of the currently available AEDs is one of the main therapeutic objectives. Cognitive-behavioural evaluation/ screening in elderly patients with *de novo* seizures is mandatory before treatment [37]. AEDs with fewer

adverse effects including cognitive ones, and less significant pharmacokinetic drug interactions are indicated [5, 7, 29, 54].

There are two main groups of AEDs, with and without (or minimal) cognitive known adverse effects [88, 90, 91].

LEV has no significant affinity to GABAergic and glutamatergic receptors, regulates calcium-dependent neurotransmitter release, exerts neuroprotective effects, has fewer adverse events than other AEDs [25, 85, 88], and is better tolerated than CBZ in patients with late poststroke seizures [13, 48]. LEV was found superior to controlled-release CBZ [87]. Due to its broad-spectrum, safe profile with a lack of drug-drug interactions, high tolerability and advantageous pharmacokinetics, LEV is preferred in most cases of LOE in the elderly [7, 25, 38, 85, 89, 92]. By reducing neuronal hyperexcitability, LEV manifests a favourable neuropsychological profile and improves cognitive performances, specifically attention level and oral fluency [25, 93]. Given its unique cellular site of action, favourable pharmacological profiles and low potential for drug interactions, LEV has advantages for seizures control in older people with associated medical complications [22, 38].

LEV was the most prescribed AED among the overall population, while valproate was most frequently used in children [93, 94]. SANAD study in the UK indicated LEV as first-choice AED in monotherapy for focal epilepsy, while in many other countries CBZ is the initial monotherapy indicated for LOE [22, 71].

Comparing the effectiveness of monotherapy (levetiracetam, valproate and carbamazepine) in elderly with newly diagnosed seizures, the AEDs performed similarly, but LEV had fewer adverse effects and a lower withdrawal rate compared to CBZ [22].

A systematic review and meta-analysis (including five randomized trials with 1425 patients) evaluated the efficacy and safety of AEDs in monotherapy for LOE (new-onset epilepsy at old age). VPA had the highest probability of being the best-tolerated option *versus* CBZ-IR (immediate-release), CBZ-CR (controlled-release), and GBP. The highest rank of probability to achieving seizure freedom was quoted for lacosamide (LCM), LEV and lamotrigine (LTG) [85].

LTG is a mood stabilizer that could relieve depression and has a favourable cognitive profile, besides controlling the number and severity of seizures. Although it could have caused some difficulty in finding words, LTG improved several areas of knowledge. Recently published meta-analyses have demonstrated that LTG was better tolerated than CBZ, but was associated with a lower probability of seizure freedom compared to LEV [5, 22, 86].

LEV and LTG have a disease-modifying effect and are considered good choices for treating LOE in patients with Alzheimer [63, 92]. Featuring a broad antiepileptic spectrum, monotherapy with LTG or

LEV represents front-line drugs in elderly with new-onset focal epilepsy [38].

The rate of AEDs indicated in neuropathic pain gabapentin (GBP) and pregabalin (PGL) has increased more than 10-fold in the elderly, with four times the higher prevalence among older patients, compared to the younger ones [13, 104]. GBP and PGL do not interact with any anti-seizure medications, and are indicated as adjunctive therapy associated with another AED, in partial seizures with or without secondary generalization [45]. Therapeutic guidelines recommend new-AEDs (LEV, LTG, GBP) for the elderly group.

Topiramate (TPM) and zonisamide (ZNS), used as monotherapy and/or adjuvant therapy in the treatment of partial seizures with or without secondary generalization, have cognitive adverse effects. Although non-inferiority of ZNS compared to controlled-release CBZ has been shown for newly diagnosed partial epilepsy, cognitive impairments and mood adverse effects limited ZNS use in LOE.

Some of the new AEDs – such as topiramate (TPM), perampanel (PER), levetiracetam (LEV), can induce unpredictable psychiatric behavioural adverse reactions (drowsiness, agitation, irritability, aggressivity and depression) in some elderly patients, mainly in those with mental health disorders [38, 84, 89].

Lacosamide (LCS) is usually cognitively neutral and has a benign psychological profile, but can induce severe cardiac side-effects and should be used with caution in the elderly.

Phenobarbital (PB) is a common and inexpensive AED, but can cause persistent cognitive adverse effects in patients with dementia and epilepsy.

The pros and cons of the most appropriate AEDs indicated in the treatment of LOE, the potential drug-drug interactions and their risks for cognitive and mood side effects are summarized in Table I.

Management of seizures in COVID-infected elderly
In the actual pandemic recrudescence, tailoring pharmacological management of seizures in elderly infected with SARS-CoV-2 should take into consideration potential pharmacokinetic and pharmacodynamic interactions of AEDs with medication used in SARS-CoV-2 (summarized in Table I) [95, 96].

Certain associations are not recommended or require supplementary attention to prevent severe adverse effects. LEV may be of interest due to its particularity of not interacting with any other AED and/or COVID medication [97]. Most seizures can be therapeutically controlled with appropriate AEDs, tailored to the underlying pathophysiological mechanisms [98].

The long-term prognosis of LOE in people aged ≥ 60 years is favourable when using appropriate AED treatment [29], and approximately one-half of patients achieve prolonged seizure remission [98, 99], but up to a third of patients suffer from recurrent seizures despite therapeutic advances (including modern AEDs,

surgery, neuromodulation and genomic advances) [100, 101].

Seizures in old persons are possible life-threatening issues, mainly because of the falling risk, and a high potential for severe injuries [103]. Epilepsy-related high rate of premature mortality is linked to accidents, burns, falls and is favoured by the elderly`s frailty, presbyopia, impairment in the domains of psycho-motor speed, decreased muscle mass, impaired peripheral nerves and cognitive impairment [12, 21, 102, 103]. Comorbidities, generalized tonic-clonic, nocturnal seizures and drug refractory epilepsy may predispose to a high rate of sudden and unexplained epilepsy-related mortality (SUDEP), in the vulnerable elderly heterogeneous groups, mainly with comorbid psychiatric illness and low socioeconomic status [21, 99, 102]. Although SUDEP is responsible for less than half of all epilepsy-related deaths, it comes immediately after stroke, as the second leading cause of total neurologic deaths. AEDs can significantly reduce seizure frequency and SUDEP risk [102].

Advances in the treatment of pharmacoresistant epilepsy using new antiseizure medications over the past 30 years were quite disappointing, regarding seizure freedom (the most important determinant biological and psychosocial aspect of the quality of life), albeit some of the newer-generation AEDs (e.g., LTG and LEV) showed superior tolerability [29, 105]. New technological methods including neurostimulation techniques, callosotomy and palliative surgical resections to remove the epileptogenic lesion did not provide superior efficacy in achieving seizure freedom [71, 105, 106]. Temporal lobe epilepsy surgery in older patients was followed by a post-operative decline of cognitive parameters (verbal memory, naming, and subjective ratings) [30]. It was estimated at a maximum of 2% of patients who might benefit from surgical techniques [71].

There are actually no randomized data informing the timing of the AEDs withdrawal in LOE at old age, as well as in adult's epilepsy [107]. There are gaps in our knowledge concerning the safe, gradual withdrawal of anti-seizure medications.

Recommendation's state: "Antiepileptic treatment might be discontinued after a period of minimum 2 years of seizure freedom; shorter seizure-free period should be discouraged because of a higher risk of relapse." [108].

The association of two or more clinical factors (i.e., older age at the onset of the disease, abnormal neurological examination, partial seizures) and bio-electrical abnormalities (epileptiform EEG grafo-elements) are arguments that argue for continued treatment with AEDs [8, 13, 42, 70, 73, 74, 108].

The clinician's experience, a careful follow-up of the evolutionary cruise and observation of AEDs' adverse effects are essential in making the decision of revoking therapy in older patients with LOE [22, 107].

Conclusions

Unique metabolic, pharmacokinetics and pharmaco-dynamics changes occur by ageing. The development of epilepsy is common in the elderly, and late-onset epilepsy (LOE) has become a worldwide public health problem, with negative repercussions on the elderly`s quality of life.

Structural epilepsy is prevalent in epileptogenesis at old age, ischemic stroke being the leading cause. An aetiology-based approach is the major therapeutic desideratum in LOE. In half of the situations, there is no obvious reason why an older person starts having seizures. LOE management is challenging owing to its atypical presentation, frequent occurrence of complex medical issues (cognitive impairment, cardio-cerebro-vascular diseases or other comorbidities) and poly-therapy.

For patient`s safety, it is important to avoid poly-pharmacy with AEDs, antipsychotic and/or antidepressant drugs, due to the potential risks of drug-drug interactions and toxicity.

Treatment for symptomatic seizures should address the root cause, using monotherapy (ideally new AEDs as front-line drugs − whenever possible). The choice of AEDs should be focused on cognitively safe drugs, with fewer side effects and fewer drug-drug interactions. In cognitively impaired elderly epileptic patients, the first-line AEDs choices are LEV or LTG.

The pharmacological approach of seizures in the elderly infected with COVID is challenging and requires multidisciplinary management and coordination between primary care physicians and specialists. AEDs for LOE must be carefully chosen and closely monitored by a multi-/interdisciplinary team, including the general practitioner, internist, and neurologist [109].

The goals of anticonvulsant treatment should be the psychosocial benefits of seizure absence and the quality of life. Socio-economic support for the patient and caregiver is essential for a good outcome.

Conflict of interest

The authors declare no conflict of interest.

References

1. World Population Ageing 2015. United Nations Department of Economic and Social Affairs - Population Division WPA2015_Report.pdf https://www.un.org/en/development/desa/population/publications/pdf/ageing.
2. European Commission, The 2012 Ageing Report: Economic and budgetary projections for the 27 EU Member States (2010-2060), European Economy 2, 2012, http://ec.europa.eu/economy_finance/publications/european_economy/2012/pdf/ee-2012-2_en.pdf.
3. GBD 2016 Epilepsy Collaborators, Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.

Lancet Neurol., 2019; 18(4): 357-375. *Erratum* in: *Lancet Neurol.*, 2019; 18(5): e4.

4. Epilepsy Foundation - https://health.usnews.com/wellness/articles/2017-03-29/5-surprising-facts-about-seizures.

5. Lee SK, Epilepsy in the elderly: treatment and consideration of comorbid diseases. *J Epilepsy Res.*, 2019; 9(1): 27-35.

6. WHO, Epilepsy: a public health imperative https://www.who.int/mental_health/neurology/epilepsy/report_2019/en/ 2019

7. Ferlazzo E, Sueri C, Gasparini S, Aguglia U, Challenges in the pharmacological management of epilepsy and its causes in the elderly. *Pharmacol Res.*, 2016; 106: 21-26.

8. Sarma AK, Khandker N, Kurczewski L, Brophy GM, Medical management of epileptic seizures: challenges and solutions. *Neuropsychiatr Dis Treat.*, 2016; 12: 467-485.

9. GBD 2015 Neurological Disorders Collaborator Group, Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.*, 2017; 16(11): 877-897.

10. Sillanpää M, Gissler M, Schmidt D, Efforts in epilepsy prevention in the last 40 years: Lessons from a large nationwide study. *JAMA Neurol.*, 2016; 73(4): 390-395.

11. Sadr SS, Javanbakht J, Javidan AN, Ghaffarpour M, Khamse Sm Naghshband Z, Descriptive epidemiology: prevalence, incidence, sociodemographic factors, socioeconomic domains, and quality of life of epilepsy: an update and systematic review. *Arch Med Sci.*, 2018; 14(4): 717-724.

12. Wang G, Jia H, Chen C, Lang S, Liu X, Xia C, Sun Y, Zhang J, Analysis of risk factors for first seizure after stroke in Chinese patients. *BioMed Res Int.*, 2013; 2013: 702871: 1-9.

13. Huang C, Feng L, Li YH, Wang Y, Chi XS, Wang W, Hao NY, Zhou D, Chen L, Clinical features and prognosis of epilepsy in the elderly in western China. *Seizure*, 2016; 38: 26-31.

14. Sillanpää M, Lastunen S, Helenius H, Schmidt D, Regional differences and secular trends in the incidence of epilepsy in Finland: a nationwide 23-year registry study. *Epilepsia*, 2011; 52(10): 1857-1867.

15. Lee SY, Jung KY, Lee IK, Yi SD, Cho YW, Kim DW, Hwang SS, Kim S, Prevalence of treated epilepsy in Korea based on National Health Insurance Data. *J Korean Med Sci.*, 2012; 27(3): 285-290.

16. Amudhan S, Gururaj G, Satishchandra P, Epilepsy in India I: Epidemiology and public health. *Ann Indian Acad Neurol.*, 2015; 18(3): 263-277.

17. Santhosh NS, Sinha S, Satishchandra P, Epilepsy: Indian perspective. *Ann Indian Acad Neurol.*, 2014; 17(Suppl 1): S3-S11.

18. Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu VK, Thomas P, Chawla J, Kumar R, Prandi P, Ray D, Golla S, Surya N, Yang H, Martinez S, Ozgen MH, Codrington J, González EMJ, Toosi M, Hariya Mohan N, Menon KV, Chahidi A, Mederer Hengstl S, Chronic Neurology in COVID-19 Era: Clinical Considerations and Recommendations From the REPROGRAM Consortium. *Front Neurol.*, 2020; 11: 664: 1-13.

19. Beghi E, Hesdorffer D, Prevalence of epilepsy - An unknown quantity. *Epilepsia*, 2014; 55(7): 963-967.

20. Tang DH, Malone DC, Warholak TL, Chong J, Armstrong EP, Slack MK, Hsu CH, Labiner DM, Prevalence and incidence of epilepsy in an elderly and low-income population in the United States. *J Clin Neurol.*, 2015; 11(3): 252-261.

21. Busnatu S, Munteanu C, Cellular and Molecular Targets for Non-Invasive Non-Pharmacological Therapeutic/Rehabilitative Interventions in Acute Ischemic Stroke. *Int J Mol Sci.*, 2022; 23(2): 907: 1-37.

22. Pohlmann-Eden B, Marson AG, Noack-Rink M, Ramirez F, Tofighy A, Werhahn KJ, Wild I, Trinka E, Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. *BMC Neurol.*, 2016; 16: 149: 1-12.

23. International League Against Epilepsy (ILAE). The 2014 Definition of Epilepsy: A perspective for patients and caregivers, www.ilae.org/guidelines/definition-and-classification/the-2014-definition-of-epilepsy-a-perspective-for-patients-and-caregivers.

24. Shield KD, Parry C, Rehm J, Chronic diseases and conditions related to alcohol use. *Alcohol Res.*, 2013; 35(2): 155-173.

25. Jesse S, Bråthen G, Ferrara M, Keindl M, Ben-Menachem E, Tanasescu R, Brodtkorb E, Hillbom M, Leone MA, Ludolph AC, Alcohol withdrawal syndrome: mechanisms, manifestations, and management. *Acta Neurol Scand.*, 2017; 135(1): 4-16.

26. Tai XY, Koepp M, Duncan JS, Fox N, Thompson P, Baxendale S, Liu JYW, Reeves C, Michalak Z, Thom M, Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: A study of temporal lobe resections. *Brain*, 2016; 139: 2441-2455.

27. Motika PV, Spencer DC, Treatment of epilepsy in the elderly. *Curr Neurol Neurosci Rep.*, 2016; 16(11): 96.

28. Tanaka A, Akamatsu N, Tsuji S, Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. *Seizure*, 2013; 22(9): 772-775.

29. Vu LC, Piccenna L, Kwan P, O'Brien TJ, New-onset epilepsy in the elderly. *Br J Clin Pharmacol.*, 2018; 84(10): 2208-2217.

30. Thompson PJ, Baxendale SA, McEvoy AW, Duncan JS, Cognitive outcomes of temporal lobe epilepsy surgery in older patients. *Seizure*, 2015; 29: 41-45.

31. Liu S, Yu W, Lu Y, The causes of new-onset epilepsy and seizures in the elderly. *Neuropsychiatr Dis Treat.*, 2016; 12: 1425-1434.

32. Bruscky IS, Amorim Leite RA, da Cunha Correia C, Ferreira MLB, Characterization of epilepsy with onset after 60 years of age. *Rev Bras Geriatr Gerontol.*, 2016; 19(2): 343-347.

33. Lezaic N, Roussy J, Masson H, Jetté N, Keezer MR, Epilepsy in the elderly: Unique challenges in an increasingly prevalent population. *Epilepsy Behav.*, 2020; 102: 106724: 1-12.

34. Wolfson C, Fereshtehnejad SM, Pasquet R, Postuma R, Keezer MR, The high burden of neurological disease in the older general population: Results from the Canadian Longitudinal Study on Aging. *Eur J Neurol.*, 2019; 26(2): 356-362.

35. Bălăceanu A, Omer S, Marinescu SA, Pițuru SM, Dumitrache S, Popa DE, Gheorghe AA, Popescu S, Bejinariu C, Ginghină O, Giuglea C, New approaches of the hyponatremia treatment in the elderly - An update. *Farmacia*, 2020; 68(3): 406-418.

36. Pennisi M, Bramanti A, Cantone M, Pennisi G, Bella R, Lanza G, Neurophysiology of the "Celiac Brain": Disentangling Gut-Brain Connections. *Front Neurosci.*, 2017; 11: 498: 1-13.

37. Witt JA, Werhahn KJ, Kramer G, Ruckes C, Trinka E, Helmstaedter C, Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. *Acta Neurol Scand.*, 2014; 130(3): 172-177.

38. Hanaya R, Arita K, The new antiepileptic drugs: their neuropharmacology and clinical indications. *Neurol Med Chir.*, 2016; 56(5): 205-220.

39. Zamudio SR, Pichardo-Macías LA, Díaz-Villegas V, Flores-Navarrete IL, Guzmán-Velázquez S, Subchronic cerebrolysin treatment alleviates cognitive impairments and dendritic arborization alterations of granular neurons in the hippocampal dentate gyrus of rats with temporal lobe epilepsy. *Epilepsy Behav.*, 2019; 97: 96-104.

40. Hanby MF, Al-Bachari S, Makin F, Vidyasagar R, Parkes LM, Emsley HCA, Structural and physiological MRI correlates of occult cerebrovascular disease in late-onset epilepsy. *Neuroimage Clin.*, 2015; 9: 128-133.

41. Hassani M, Cooray G, Sveinsson O, Cooray C, Post-stroke epilepsy in an ischemic stroke cohort - Incidence and diagnosis. *Acta Neurol Scand.*, 2020; 141(2): 141-147.

42. Xu MY, Poststroke seizure: optimising its management. *Stroke Vasc Neurol.*, 2018; 4(1): 48-56.

43. Hesdorffer DC, Comorbidity between neurological illness and psychiatric disorders. *CNS Spectr.*, 2016; 21(3): 230-238.

44. Nicastro N, Assal F, Seeck M, From here to epilepsy: the risk of seizure in patients with Alzheimer's disease. *Epileptic Disord.*, 2016; 18(1): 1-12.

45. Honarmand A, Safavi M, Zare M, Gabapentin: An update of its pharmacological properties and therapeutic use in epilepsy. *J Res Med Sci.*, 2011; 16(8): 1062-1069.

46. Owolabi MO, Arulogun O, Melikam S, Adeoye AM, Akarolo-Anthony S, Akinyemi R, Arnett D, Tiwari H, Gebregziabher M, Jenkins C, Lackland D, Ovbiagele B, Akpalu A, Sagoe K, Sarfo FS, Obiako R, Owolabi L, The burden of stroke in Africa: a glance at the present and a glimpse into the future. *Cardiovasc J Afr.*, 2015; 26(2 Suppl 1): S27-S38.

47. Zhao Y, Li X, Zhang K, Tong T, Cui R, The progress of epilepsy after stroke. *Curr Neuropharmacol.*, 2018; 16(1): 71-78.

48. Sarecka-Hujar B, Kopyta I, Poststroke epilepsy: current perspectives on diagnosis and treatment. *Neuropsychiatr Dis Treat.*, 2018; 15: 95-103.

49. Cleary P, Shorvon S, Tallis R, Late-onset seizures as a predictor of subsequent stroke. *Lancet*, 2004; 363: 1184-1186.

50. Farrokh S, Tahsili-Fahadan P, Ritzl EK, Lewin JJ 3rd, Mirski MA, Antiepileptic drugs in critically ill patients. *Crit Care*, 2018; 22(1): 153.

51. Huang YH, Chi NF, Kuan YC, Chan L, Hu CJ, Chiou HY, Chien LN, Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan. *Eur J Neurol.*, 2015; 22(11): 1459-1468.

52. Anghelescu A, Elderly epilepsy, "Carol Davila" Publishing House, Bucharest, Romania, 2020, (available in Romanian).

53. Imfeld P, Bodmer M, Schuerch M, Jick S, Meier C, Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. *Epilepsia*, 2013; 54: 700-707.

54. Pandis D, Scarmeas N, Seizures in Alzheimer disease: clinical and epidemiological data. *Epilepsy Curr.*, 2012; 12: 184-187.

55. Sánchez MP, García-Cabrero AM, Sánchez-Elexpuru G, Burgos DF, Serratosa JM, Tau-induced pathology in epilepsy and dementia: notions from patients and animal models. *Int J Mol Sci.*, 2018; 19(4): 1092: 1-20.

56. Irizarry MC, Jin S, He F, Emond JA, Raman R, Thomas RG, Sano M, Quinn JF, Tariot PN, Galasko DR, Ishihara LS, Weil JG, Aisen PS, Incidence of new-onset seizures in mild to moderate Alzheimer disease. *Arch Neurol.*, 2012; 69(3): 368-372.

57. Voglein J, Noachtar S, McDade E, Quaid KA, Salloway S, Ghetti B, Noble J, Berman S, Chhatwal J, Mori H, Fox N, Allegri R, Masters CL, Buckles V, Ringman JM, Rossor M, Schofield PR, Sperling R, Jucker M, Laske C, Paumier K, Morris JC, Bateman RJ, Levin J, Danek A, Seizures as an early symptom of autosomal dominant Alzheimer's disease. *Neurobiol Aging*, 2019; 76: 18-23.

58. Kitchigina VF, Alterations of Coherent Theta and Gamma Network Oscillations as an Early Biomarker of Temporal Lobe Epilepsy and Alzheimer's Disease. *Front Integr Neurosci.*, 2018; 12: 36: 1-15.

59. Najm R, Jones EA, Huang Y, Apolipoprotein E4, inhibitory network dysfunction, and Alzheimer's disease. *Mol Neurodegener.*, 2019; 14(1): 24: 1-13.

60. Hithersay R, Startin CM, Hamburg S, Mok KY, Hardy J, Fisher EMC, Tybulewicz VLJ, Nizetic D, Strydom A, Association of dementia with mortality among adults with Down syndrome older than 35 years. *JAMA Neurol.*, 2019; 76(2): 152-160.

61. Assis TR, Bacellar A, Costa G, Nascimento OJM, Etiological prevalence of epilepsy and epileptic seizures in hospitalized elderly in a Brazilian tertiary center-Salvador-Brazil. *Arq Neuropsiquiatr.*, 2015; 73: 83-89.

62. Born HA, Seizures in Alzheimer's disease. *Neuroscience*, 2015; 286: 251-263.

63. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TLS, Marcus DS, Fagan AM, Goate A, Fox NC, Cairns NJ, Holtzman DM, Buckles V, Ghetti B, McDade E, Martins RN, Saykin AJ, Masters CL, Ringman JM, Ryan NS, Forster S, Laske C, Schofield PR, Sperling RA, Salloway S, Correia S, Clifford JJ, Weiner M, Bateman RJ, Morris JC, Mayeux R, Brickman AM, White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. *Ann Neurol.*, 2016; 79: 929-939.

64. Sen A, Capelli V, Husain M, Cognition and dementia in older patients with epilepsy. *Brain*, 2018; 141(6): 1592-1608.

65. Pottoo FH, Javed MN, Barkat MA, Alam MS, Nowshehri JA, Alshayban DM, Ansari MA, Estrogen and Serotonin: complexity of interactions and implications for epileptic seizures and epileptogenesis. *Curr Neuropharmacol.*, 2019; 17(3): 214-231.

66. Dalic L, Cook MJ, Managing drug-resistant epilepsy: challenges and solutions. *Neuropsychiatr Dis Treat.*, 2016; 12: 2605-2616.

67. Subota A, Pham T, Jette N, Sauro K, Lorenzetti D, Holroyd-Leduc J, The association between dementia and epilepsy: a systematic review and meta-analysis. *Epilepsia*, 2017; 58: 962-972.

68. Acharya JN, Acharya VJ, Epilepsy in the elderly: Special considerations and challenges. *Ann Indian Acad Neurol.*, 2014; 17(Suppl 1): S18-S26

69. Sculier C, Gaínza-Lein M, Sánchez Fernández I, Loddenkemper T, Long-term outcomes of status epilepticus: A critical assessment. *Epilepsia*, 2018; 59(Suppl 2): 155-169.

70. Marawar R, Basha M, Mahulikar A, Desai A, Suchdev Km Shah A, Updates in Refractory Status Epilepticus. *Crit Care Res Pract.*, 2018; 2018: 9768949: 1-19.

71. Manford M, Recent advances in epilepsy. *J Neurol.*, 2017; 264(8): 1811-1824.

72. Najjar S, Najjar A, Chong DJ, Pramanik BK, Kirsch C, Kuzniecky RI, Pacia SV, Azhar S, Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. *J Neuroinflammation*, 2020; 17: 231: 1-14.

73. Grönheit W, Popkirov S, Wehner T, Schlegel U, Wellmer J, Practical management of epileptic seizures and status epilepticus in adult palliative care patients. *Front. Neurol.*, 2018; 9: 595: 1-8.

74. Azabou E, Magalhaes E, Braconnier A, Yahiaoui L, Moneger G, Heming N, Annane D, Mantz J, Chrétien F, Durand MC, Lofaso F, Porcher R, Sharshar T, Early standard electroencephalogram abnormalities predict mortality in septic intensive care unit patients. *PLoS One*, 2015; 10(10): e0139969:1-18.

75. Pennisi M, Lanza G, Falzone L, Fisicaro F, Ferri R, Bella R, SARS-CoV-2 and the Nervous System: from clinical features to molecular mechanisms. *Int J Mol Sci.*, 2020; 21(15): 5475: 1-21.

76. Emami A, Fadakar N, Akbari A, Lotfi M, Farazdaghi M, Javanmardi F, Rezaei T, Asadi-Pooya AA, Seizure in patients with COVID-19. *Neurol Sci.*, 2020; 41(11): 3057-3061.

77. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, Pringsheim T, Lorenzetti DL, Jetté N, Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*, 2017; 88(3): 296-303.

78. Niazkar HR, Zibaee B, Nasimi A, Bahri N, The neurological manifestations of COVID-19: a review article. *Neurol Sci.*, 2020; 41(7): 1667-1671.

79. Asadi-Pooya AA, Attar A, Moghadami M, Karimzadeh I, Management of COVID-19 in people with epilepsy: drug considerations. *Neurol Sci.,* 2020; 41(8): 2005-2011.

80. Pinna P, Grewal P, Hall JP, Tavarez T, Dafer, RM, Garg R, Osteraas ND, Pellack DR, Asthana A, Fegan K, Patel V, Conners JJ, John S, Silva ID, Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. *J Neurol Sci.*, 2020; 415: 116969: 1-4.

81. Asadi-Pooya AA, Seizures associated with coronavirus infections. *Seizure*, 2020; 79: 49-52.

82. Banerjee D, Viswanath B, Neuropsychiatric manifestations of COVID-19 and possible pathogenic mechanisms: Insights from other coronaviruses. *Asian J Psychiatr.*, 2020; 54: 102350.

83. https: //www.covid19-druginteractions.org.

84. Sen A, Jette N, Husain M, Sander J, Epilepsy in older people. *Lancet*, 2020; 395(10225): P735-P748.

85. Lattanzi S, Trinka E, Del Giovane C, Nardone R, Silvestrini M, Brigo F, Antiepileptic drug monotherapy for epilepsy in the elderly: a systematic review and network meta-analysis. *Epilepsia*, 2019; 60(11): 2245-2254.

86. Cheng S, Non-convulsive status epilepticus in the elderly. *Epileptic Disord.*, 2014; 16: 385-394.

87. Werhahn KJ, Trinka E, Dobesberger J, Unterberger I, Baum P, Deckert-Schmitz M, Kniess T, Schmitz B, Bernedo V, Ruckes C, Ehrich A, Kramer G, A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*, 2015; 56(3): 450-459.

88. Lezaic N, Gore G, Josephson CB, Wiebe S, Jette N, Keezer MR, The medical treatment of epilepsy in the elderly: a systematic review and meta-analysis. *Epilepsia*, 2019; 60: 1325-1340.

89. Hansen CC, Ljung H, Brodtkorb E, Reimers A, Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on Topiramate, Levetiracetam and Perampanel. *Behav Neurol.*, 2018; 2018: 2064027: 1-18.

90. Cretin B, Pharmacotherapeutic strategies for treating epilepsy in patients with Alzheimer's disease. *Expert Opin. Pharmacother.*, 2018; 19(11): 1201-1209.

91. Giorgi FS, Guida M, Vergallo A, Bonuccelli U, Zaccara G, Treatment of epilepsy in patients with Alzheimer's disease. *Expert Rev Neurother.*, 2017; 17(3): 309-318.

92. Werhahn KJ, Klimpe S, Balkaya S, Trinka E, Kramer G, The safety and efficacy of add-on levetiracetam in elderly patients with focal epilepsy: a one-year observational study. *Seizure*, 2011; 20: 305-311.

93. El Sabaa RM, Hamdi E, Hamdy NA, Sarhan HA, Effects of Levetiracetam Compared to Valproate on Cognitive Functions of Patients with Epilepsy. *Neuropsychiatr Dis Treat.*, 2020; 16: 1945-1953.

94. Alkharfy KM, Rehman MU, Ahmad A, Nitric oxide pathway as a potential therapeutic target in COVID-19. *Farmacia*, 2020; 68(6): 966-969.

95. Liverpool COVID-19 Interactions. www.covid19-druginteractions.org.

96. The Italian League Against Epilepsy - www.lice.it/pdf/ Antiepileptic_drugs_interactions_in_covid-19.pdf.

97. Kuroda N, Epilepsy and COVID-19: Associations and important considerations. *Epilepsy Behav.*, 2020; 108: 107122: 1-4.

98. Farrukh MJ, Makmor-Bakry M, Hatah E, Tan HJ, Use of complementary and alternative medicine and adherence to antiepileptic drug therapy among epilepsy patients: a systematic review. *Patient Prefer Adherence*, 2018; 12: 2111-2121.

99. Beghi E, The epidemiology of epilepsy. *Neuroepidemiology*, 2020; 54(2): 185-191.

100. Ichikawa N, Fujimoto A, Okanishi T, Sato K, Enoki H, Efficacy and safety of epilepsy surgery for older adult patients with refractory epilepsy. *Ther Clin Risk Manag.*, 2020; 16: 195-199.

101. Santoshi B, Orrin DO, Kim KW, Why we urgently need improved epilepsy therapies for adult patients. *Neuropharmacology*, 2020; 170: 107855.

102. Devinsky O, Spruill T, Thurman D, Friedman D, Recognizing and preventing epilepsy-related mortality. A call for action. *Neurology*, 2016; 86(8): 779-786.

103. Anghelescu A, Clinical and pathophysiological considerations of gait limitations and high prevalence of falls, in the elderly with most common, disabling neurological diseases. *Int J Neurorehabil.*, 2017; 4: 2: 1-4.

104. Bilgener E, Gümüş B, Pregabalin consumption in Turkey: Was it an abuse?. *Farmacia*, 2021; 69(6): 1189-1194.

105. French JA, Wechsler RT, Have new antiseizure medications improved clinical care over the past 30 years?. *Lancet Neurol.*, 2020; 19(6): 476-478.

106. Anghelescu A, Deaconu V, Axente C, Onose G, Therapeutic difficulties in recurrent, multidrug-resistant epilepsy and vagal nerve stimulation, with recent traumatic brain complications needing iterative neurosurgical interventions. *Balneo Res J.*, 2019; 10(4): 530-534.

107. Terman SW, Lamberink HJ, Braun KPJ, Deprescribing in epilepsy: Do no harm. *JAMA Neurol.*, 2020; 77(6): 673-674.

108. Beghi E, Giussani G, Grosso S, Iudice A, Neve AL, Pisani F, Specchio LM, Verrotti A, Capovilla G, Michelucci R, Zaccara G, Withdrawal of antiepileptic drugs: guidelines of the Italian League Against Epilepsy. *Epilepsia*, 2013; 54(Suppl 7): 2-12.

109. Ghosh S, Jehi LE, New-onset epilepsy in the elderly: challenges for the internist. *Clevel Clin J Med.*, 2014; 81(8): 490-498.