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Review

Pharmacokinetic considerations about antiseizure medications in the elderly

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Abstract

Introduction: Epilepsy represents the third most common neurological disorder in the elderly. Antiseizure medications (ASMs) are often used not only to treat epilepsy but also other disorders in this age group. Many physio-pathological changes occur in body composition and organ or system functions with aging. Furthermore, drug-drug interactions (DDIs) represent a major risk considering the prevalence of polytherapy in the elderly.

Areas covered: Relevant studies on pharmacokinetics of ASMs in the elderly were identified through a literature search. We have reviewed all available data on known alterations in pharmacokinetic parameters of ASMs in elderly also considering pathophysiological alterations such as renal function impairment. Finally, we have highlighted the potential risk of DDIs with some drug classes.

Expert opinion: Large interindividual variability also due to co-morbidities and related co-therapies, make elderly patients a not homogeneous group. Overall, a reduction in loading and maintenance doses of almost all ASMs should be considered to avoid adverse events (AEs) as well as a slow titration, following the rule "*start low and go slow*". Therapeutic drug monitoring should be performed to apply the "*individual therapeutic concentration"* and implemented to overcome the age-related differences between dose and plasma concentrations, to monitor DDIs and guide dosage adjustments.

Keywords: Metabolism; Renal function; Plasma Proteins; Antiseizure medications; Antiepileptic Drugs; Drug-drug interactions; Distribution

Article highlights

- Antiseizure medications (ASMs) are often used in the elderly, not only to treat epilepsy but also other diseases.
- Age-related physiological and pathological changes occur in body composition and organ or system functions with a substantial inter- and intra-individual variability, affecting all pharmacokinetic (PK) processes.
- Clearance of almost all ASMs (with the exception of brivaracetam, eslicarbazepine, perampanel, tiagabine and zonisamide) is reduced by about 20–50% in elderly patients; other PK modifications include a reduction in plasma protein binding and a subsequent increase in unbound fraction.
- A reduction in loading and maintenance doses as well as a slow titration of almost all ASMs should be considered in order to avoid adverse events; therapeutic drug monitoring should be implemented.
- ASMs can act as inducers or inhibitors of drug-metabolizing enzymes, leading to a high potential risk of drug-drug interactions (DDIs) with other medications used to treat common comorbidities (e.g. antihypertensive drugs, anticoagulants, statins, antibiotics, antidepressants and anti-inflammatory drugs).
- Second and third-generation ASMs seem to be well tolerated with low potential of DDIs although more specific studies are needed and safety concerns should be considered.

1. Introduction

After stroke and dementia, epilepsy represents the third most common neurological disorder in the elderly, increasing in incidence with aging, up to 180 per 100,000 in the over 85 age-group [1]. Most common etiologies include cerebrovascular diseases, brain tumors and traumas, whereas the remaining 25-40 % are unknown. In the recent decades, the incidence of epilepsy is increasing due to the aging of population and partly because of the increasing prevalence of stroke and brain tumors [1]. There are many antiseizure medications (ASMs) commonly used for the management of epilepsy and other pathologies (e.g. neuropathic pain) in the elderly [2], and management can be challenging according to associated age-related physiological changes, affecting pharmacokinetics and pharmacodynamics and therefore requiring adjustments in drug dosage [3]. Furthermore, the high incidence of comorbidities in the elderly, such as cardiovascular diseases, diabetes, mild cognitive impairment and dementia, leading to polytherapy further raises the risk of drug interactions, adverse events (AEs) and poor medication adherence.

Drug-drug interactions (DDIs) are particularly important in patients with epilepsy, since optimal seizure control is often achieved only after repeated treatment attempts or using ASMs different combinations [4]. The pharmacokinetic properties of ASMs are variable and complex, many of them are metabolized by hepatic cytochrome P-450 system increasing the DDIs risk. Newer generation ASMs are less likely to be associated with potent enzyme-inducing activity or only at higher doses, therefore they seem to have numerous advantages over older generation medications, such as more favorable pharmacokinetic profiles and fewer interactions [5]. However, newer generation ASMs undoubtedly need to be further evaluated in order to definitively ascertain their therapeutic profile.

This article reviews some of the general principles of treatment in elderly patients with epilepsy focusing on the effects of aging on pharmacokinetic features of ASMs.

2. Methods

Relevant studies on pharmacokinetics of ASMs in the elderly and on DDIs due to polytherapy were identified through a literature search on PubMed and the Cochrane databases up to June 2020 using the following search terms: “antiseizure medications” OR “antiepileptic drugs” AND “elderly”; “antiseizure medications” OR “antiepileptic drugs” AND “elderly” AND “pharmacokinetics”. Furthermore, the searches combined the generic names of each ASMs with the term “pharmacokinetics” AND “elderly”, and the terms “antiseizure medications” OR “antiepileptic drugs” AND “drug-drug interactions” OR “DDIs”. Additional articles were found by a manual search of the reference lists of identified articles. Only papers in English were included in the search.

3. Results

3.1 Pathophysiological modifications in the elderly

Although there is no exhaustive definition of aging, it can be defined as the gradual decline and deterioration of biological functions, resulting from the lifelong accumulation of molecular and cellular damage [6]. Several age cut-offs to define elderly population have been proposed and used in literature, making challenging to compare results from different studies. Furthermore, older people cannot be considered as an homogeneous group, due to large differences between age ranges and clinical conditions. In this light, elderly can be subdivided into the “young old” (65-74 years of age), “middle old” or “old,” (75–84 years), and the “old old” (≥85 years), considering for each age range that people can be healthy, have medical problems, or be frail [7].

Age-related physiological and pathological changes occur in body composition and organ or system function [6], albeit with a substantial inter- and intra-individual variability. These pathophysiological modifications can affect all pharmacokinetic processes, as synthetically discussed below and summarized in table 1.

3.1.1. Absorption

A decreased gastric acid secretion is observed in older adults, which may be due to the high prevalence of gastric mucosal atrophy and also to the common use of some medications such as proton pump inhibitors (e.g. omeprazole, lansoprazole) and histamine-2 receptor antagonists (e.g. ranitidine) [8], rather than to

the age-related modifications [9]. The resulting increase in gastric pH, according to a reduced dissolution, may reduce absorption of weakly basic drugs such as diazepam; conversely, it may enhance absorption of weakly acid ones (e.g. phenytoin, valproate, phenobarbital) [10,11]. Furthermore, delayed gastric emptying and reduced peristalsis, as well as lower gastrointestinal blood flow and mucosal surface area, may delay and/or decrease drugs' absorption and therefore their bioavailability [12]. On the other hand, decreases in mucosal absorption and in liver mass and perfusion may increase the oral bioavailability of drugs which undergo extensive first-pass metabolism [13]. Moreover, albeit with no direct effect on absorption, pathophysiological factors (e.g. impaired oral protective reflexes, xerostomia, delayed esophageal emptying) may complicate oral administration of some medications [14].
Overall, co-morbidities, rather than physiological modifications, are more likely responsible for changes in drugs' absorption [15]. Actually, age-related modifications do not significantly affect the absorption of most drugs, with passive diffusion being undoubtedly unchanged. The active transport mechanisms [mainly P-glycoprotein (P-gp) activity] seem to be impaired in older adults, but the effect of aging has not been completely clarified yet [10]. Focusing on ASMs, absorption processes have not been so far systematically investigated, therefore clinically relevant alterations cannot be excluded [15].

3.1.2. Distribution

Aging-related modifications include significant changes in body tissue composition, with a decrease of total body water and lean body mass, accompanied by an increase of body fat. The latter is higher in women than men with the same body mass index (BMI) [16]. As a consequence, lipophilic drugs as diazepam may have an increased volume of distribution (V_d) with a prolongation of half-life, whereas the V_d of hydrophilic drugs (e.g. midazolam, which shows both lipophilic and hydrophilic properties) may decrease; moreover, peak concentrations after a bolus or rapid infusion may be increased [13]. Accordingly, a decrease up to 20% in parenteral loading doses of water-soluble drugs has been recommended [17]. Furthermore, plasma albumin concentration decreases of approximatively 10-15% with aging, and liver or renal diseases decreasing by a variable extent its concentration. Whereas, α1-acid glycoprotein concentrations can be increased, mainly by acute illness and chronic inflammatory disease states, or decreased by severe liver disease, which are more likely to occur in the elderly [10]. These modifications should be considered bearing in mind differences in protein binding among drugs, notably among ASMs. Indeed, ASMs such as clobazam, clonazepam, perampanel, retigabine, stiripentol, tiagabine, and valproic acid are highly protein bound (≥88%), whereas gabapentin and pregabalin are not bound [18]. However, changes in plasma proteins binding are not considered of clinical relevance, except for highly protein bound drugs, with small V_d and narrow therapeutic window (e.g. warfarin) [9]. Generally, the higher unbound drug fraction, responsible for therapeutic and toxic effects, is rapidly compensated by increased elimination.

3.1.3. Metabolism

Old age is associated with a reduction in liver size and hepatic blood flow (by up to 40% and 50%, respectively), as well as a decreased hepatic and biliary uptake and transport. These alterations may affect drugs elimination, mainly of those with high hepatic extraction or clearance (flow-limited clearance), as morphine, propranolol or verapamil [19].
When assessed in vitro, the activity of phase I reactions enzymes was not affected by aging [20] as well as in some in vivo studies, suggesting no impairment or no significant effects on specific isoforms activity, such as cytochrome P450 (CYP)1A2, 2D6, 3A4, 2C19 [20]. Conversely, other studies show a decreased activity of many CYP450 isoforms, including CYP3A family [21].
Overall, hepatic drug clearance can be reduced by up to 30%. Among drugs with low hepatic extraction or clearance (capacity-limited clearance), a decrease in clearance has been observed mainly for those with low protein binding; however, a clearance reduction ranging between 20-60% has been also reported for highly protein bound drugs such as valproic acid [22,23].
Furthermore, it has been shown that chronic renal disease can impact on drug disposition and hepatic metabolism through downregulation of transporter proteins and enzymes [24]. In recent studies, clearance of organic anion transporting polypeptide (OATP), CYP2D6 and 2C8 substrates decreases as renal function declines, whereas CYP3A4/5, 1A2, 2C9, and 2C19 activity seem to be less affected by renal impairment [25].

Phase II reactions (e.g. glucuronidation, acetylation or sulfatation), are generally preserved in elderly, albeit a decrease in clearance has been observed in some drugs metabolized through glucuronidation (e.g. lamotrigine and monohydroxycarbazepine) [3]. However, the impact of frailty as a confounding factor on PK in elderly should to be considered [19].

3.1.4. Elimination

Kidneys undergo anatomical and functional modifications with aging [26], including a decrease in renal mass and in functioning nephrons (reduced by up to 30%), and a decline in glomerular filtration rate (GFR) by more than 50% (due to decreases in blood flow, vascular compliance and lean mass). These changes occur between the age of 30 and 80 years, although with a significant inter- and intra-individual variability. Indeed, cross-sectional and cohort studies assessing creatinine clearance have shown an average decline of renal function in the elderly, but also a clearance rate not reduced or increased in some subjects [27]. In a study including 83 patients with epilepsy aged 60 years or older, creatinine clearance resulted positively associated with the substantial intrapatient variability (ranged from 2-79%) observed in serial gabapentin serum concentrations (coefficient=0.5, p=0.03) [28]. Finally, kidney function might be affected by confounding factors such as hypertension, chronic heart diseases, diabetes, and chronic exposure to nephrotoxic drugs [9]. A declined renal function leads to accumulation of drugs mainly excreted by kidneys and requires dosage adjustments according to GFR estimates.

3.2 Pharmacokinetic modifications of antiseizure medications in the elderly

3.2.1. First-generation antiseizure medications

First generation ASMs (*e.g.* carbamazepine, phenytoin, phenobarbital and valproate) have been recently considered either third-line or usually inappropriate in the treatment of genetically mediated epilepsy or focal epilepsy in older adults [29] and the prescription of newer ASMs has been encouraged in elderly patients with newly diagnosed epilepsy. Nevertheless, older ASMs are still largely used [30].

Carbamazepine absorption in the elderly is highly variable and seems to be increased by delayed gastrointestinal transit [31]. A modest increase in carbamazepine free fraction has been reported in patients older than 65 years compared with younger (16-64 years) (26.7% *vs* 31.1%, respectively) with a significant contribute of α1-acid glycoprotein concentrations to the interindividual variability [32]. Population pharmacokinetic studies, as well as studies based on therapeutic drug monitoring (TDM) data, have shown a decrease by 25-40% of apparent carbamazepine clearance in patients aged 65 years and older compared with younger adults; notably, factors other than age contribute to the observed variability (i.e. different doses of carbamazepine, co-medication with enzyme inducers, body weight) [33]. However, no age-related changes in pharmacokinetic parameters have been observed in other studies [31,34]. Finally, in a population pharmacokinetic study on community-dwelling subjects aged 60 years and older, age seems not to be implicated *per se* in carbamazepine clearance, although no comparative analysis has been performed with a control group (*i.e.* younger than 60 years) [35].

A single-dose study has shown that **clobazam** absorption is not affected by age, whereas V_d and unbound fraction (ranging between 8.6-15.0%) tend to increase in the elderly. Furthermore, total clearance has been significantly reduced and half-life prolonged (48 h vs 17 h) in older men (60-69 years) compared with younger adults (20-37 years); similar but not significant differences have been observed comparing elderly with young women [36]. Consistent results have been reported in multiple-dose study, with significant differences only in the elderly men group (60-69 years). In this latter, clobazam showed delayed rates of accumulation and washout (as well as its metabolite desmethylclobazam), increased steady-state plasma concentrations, and reduced steady-state clearance [37].

Studies evaluating the pharmacokinetics of **primidone** in elderly observed a slight decrease in renal clearance of primidone and also of its major metabolites phenobarbital and phenylethylmalonamide, which had statistical but not clinical significance only for phenylethylmalonamide [38]. A study specifically conducted on phenobarbital reported a decrease of apparent clearance by about 20% ($p < 0.0001$) in patients aged 65 years and older compared with younger (20-50 years) adults [39]. In a previous trial, a halved phenobarbital clearance was shown in subjects aged >40 years [40].

Phenytoin displays a more variable absorption in the elderly, although significant differences in bioavailability have not been reported between younger and older patients [31]. Furthermore, a broad daily intraindividual variability in serum concentrations has been observed among elderly nursing home residents [41]. Phenytoin is highly bound to plasma proteins (~90%), a reduction in protein binding and a subsequent increase in unbound fraction have been reported with aging [42]. Patterson and colleagues (1982) found a slight but significant increase in phenytoin free fraction between older and younger patients (12.8% *vs* 11.1%, respectively); however, this was not considered clinically relevant [42]. Conflicting results have been reported evaluating phenytoin kinetics in elderly patients. In some studies age had no effects on phenytoin clearance, V_d or half-life [43,44]. However, half-life was prolonged compared with the value reported in the product label (~40 h *vs* 22 h, respectively) and more variable in older patients [31,43]. Conversely, other studies showed an age-related decline in the maximum rate of metabolism (V_{max}) and a reduction in phenytoin clearance by about 25%, which may be greater for unbound fraction clearance [45]. Furthermore, phenytoin apparent clearance was reduced approximately of 20% in patients aged 65 years and older, although statistical significance was not reached [46]. Finally, in a population pharmacokinetic analysis, age was a significant covariate for phenytoin clearance also after administration of its prodrug fosphenytoin [47].

In healthy volunteers studies, unbound **valproic acid/valproate** concentrations in elderly were approximatively 50% higher than in young subjects, albeit no differences have been shown in total plasma concentrations between these two age groups [48]

No differences in total valproic acid clearance have been observed among elderly patients (≥65 years) and younger controls (20-50 years), and also among elderly age groups (65–74, 75–84, ≥85 years) [49]. However, a reduction of at least 40% in the clearance of the unbound valproic acid has been reported in older adults [48]. Furthermore, a significant increase in valproic acid's V_d (0.19 *vs* 0.13 l) and a prolonged half-life (14.9 *vs* 7.2 h) have been shown in elderly (75-85 years) compared with younger subjects (20-35 years) [50].

Ethosuximide is rarely used in the elderly [51]. Studies evaluating the effect of age on the relationship between ethosuximide oral dose and plasma concentrations have been conducted only on patients up to 40 years, showing contrasting results [52,53].

3.2.2. Second-generation antiseizure medications

Clearance of **gabapentin**, **pregabalin** and **vigabatrin**, mainly eliminated unchanged in the urine, declines with aging according to the physiological reduction in GFR and disease-related decreases in renal function [54]. Indeed, the estimated gabapentin's V_d may increase (63%), with a proportional decrease in clearance by 32-46%. Furthermore, an approximately twofold higher gabapentin half-life has been observed in the elderly (13.3h), compared with the reported half-lives of 5 and 7 h in younger subjects [55]. Likewise, vigabatrin's peak concentration (C_{max}) and half-life are significantly increased and area under the concentration–time curve (AUC) may be 5-times greater than that in young adults [56]. The few available data on pregabalin pharmacokinetics in the elderly have shown an apparent oral clearance (Cl/F) 50% lower than younger subjects as well as an increased concentration–dose ratio (CDR) by approximately 25% in adults aged 50 years and older [57].

Several pharmacokinetic studies on **lamotrigine** compared older and younger adults, showing a reduction in lamotrigine clearance by 22-37% and a mean 6.3h prolongation in lamotrigine half-life, approximately 31.2 h in the elderly *vs* 24.9 h in the younger subjects [58]. The pharmacokinetic variability of lamotrigine was more pronounced (clearance ±70%) when receiving both enzyme inducers and inhibitors [59].

Since about 70% of **levetiracetam** administered is excreted unchanged renally, elimination is expected to be reduced in parallel with aging-related decrease in renal function. Compared with adults, levetiracetam clearance has been shown to be decreased by 20-52% in patients over 55, with a more pronounced pharmacokinetic variability in presence of polypharmacy, especially enzyme-inducing drugs [59,60]. Likewise, the half-life of levetiracetam has been reported to be longer in the elderly (10-11h) than in younger subjects (6-8h) [61].

The influence of aging on **oxcarbazepine** pharmacokinetic has been assessed in several clinical trials. Compared with younger adults, a decrease by 35% in oxcarbazepine clearance has been shown in patients over 65. After single and multiple doses of oxcarbazepine, the C_{max} of monohydroxycarbazepine (MHD),

the active metabolite, were found to be approximately 50% higher in elderly men and 33% higher in elderly women than in the younger men and women, respectively [62]. Concomitant therapy with enzyme inducers is associated with a remarkable increase in oxcarbazepine Cl/F (75%) [59].
Aging *per se* does not appear to alter the clearance of **topiramate** [63]. However, topiramate is cleared primarily by renal elimination, and only 20% of a dose administered is removed by hepatic elimination [3]. So, any age-related changes in renal function may affect drug clearance. A single-dose study published in abstract form, compared a group of older adults with compromised renal function, with younger subjects, showing a decrease in drug clearance by about 20%, an increase of C_{max} and AUC respectively of 23% and 25%, and a prolonged half-life (13%) [64].
After single dose of **zonisamide** (300mg), adults aged 65–71 years had a higher C_{max} and shorter elimination half-life than those aged 21–40 years, probably as a result of the smaller V_d in the older population (1.19 L/kg) compared with the non-elderly group (1.44 L/kg). No significant age-related differences have been found for Cl/F, AUC, renal clearance [65]. However, the pharmacokinetic variability was more pronounced in patients co-medicated with enzyme-inducing drugs.
A multiple-doses pharmacokinetic study compared healthy young volunteers and two small groups of elderly individuals (healthy volunteers and patients with epilepsy co-medicated with one or more enzyme-inducing ASMs), showing no differences in the pharmacokinetic parameters of **tiagabine** between young and elderly volunteers, with the exception of AUC which was slightly but significantly smaller in 20% in the elderly patients co-administered with enzyme-inducing ASMs [66]. Finally, **felbamate** is rarely prescribed due to the high risk of aplastic anemia and liver toxicity and only exceptionally used in older patients. In a single dose pharmacokinetics study comparing elderly (66-78 years) and younger (18-45 years) healthy volunteers, a decrease in felbamate clearance by about 20% has been observed in the older group. Furthermore, a prolongation in half-life (18.6 h *vs* 21 h) as well as an increase in mean AUC and C_{max} values have been shown in the elderly [67].

3.2.3. Third- generation antiseizure medications
The pharmacokinetic of **lacosamide** in elderly people with epilepsy has been poorly studied. In a study published in abstract form only, plasma lacosamide concentrations at steady state, after normalization for differences in body weight, were about 10-35% higher in subjects aged over 65 years than in non-elderly adults [68]. Furthermore, Svendsen and colleagues, evaluating the pharmacokinetic variability of lacosamide in a real-life setting, using therapeutic drug monitoring, demonstrated that lacosamide concentration dose ratio was 28% higher in older adults (> 65 years) than younger adults (< 65 years) [69].
Brivaracetam showed similar pharmacokinetic profile as in healthy young controls when studied in elderly individuals with mild renal impairment (creatinine clearance 53–98 mL/min/1.73 m^2) and in adults with severe renal impairment but not in dialysis (creatinine clearance 8.5–26 mL/min/1.73 m^2); only a moderate increase (mean ratio, 1.21; 90% confidence interval, 1.01-1.45) in AUC for severe renal impairment was observed. Furthermore, in a population pharmacokinetic analysis of samples obtained from phase II and phase III placebo-controlled add-on studies, it has been demonstrated that brivaracetam Cl/F remains unchanged with increasing age [70]. An open-label trial on patients with liver dysfunction revealed that the plasmatic half-life of brivaracetam may increase up to 17.4 h, depending on the severity of the hepatic disease. Nevertheless, the exposure to brivaracetam increases by 50-60% in patients with hepatic impairment, (irrespective of severity classified by Child–Pugh score) [71,72]. However, the data supporting these clinical evidence is still limited [44].
In a pharmacokinetic study conducted in 16 healthy elderly volunteers (65-76 years) treated with **perampanel**, mean clearance was comparable to those for younger adults, suggesting that clearance is not influenced by age [73]. Similarly, the pharmacokinetic profile of **eslicarbazepine acetate** is not age-related but similar in parameters such as C_{max}, time to reach C_{max} (t_{max}), AUC over the dosing interval (AUC_{0-24}), and AUC from time 0 to infinity ($AUC_{0-\infty}$), both in young and elderly subjects [74]. However, a non-significant increase (15%) of the CDR was observed in the elderly after eslicarbazepine administration [75]. Usually, age and co-medication represent factors that influence ASMs pharmacokinetic variability, especially in elderly that show a reduced drug elimination [76,77], but more recently, Svendsen and colleagues demonstrated that age is not a significant aspect in the pharmacokinetic eslicarbazepine profile [75].

Rufinamide, **stiripentol** are among the latest third-generation of ASMs, whose pharmacokinetic profile is established but limited data are available about their kinetics in the elderly. So far, C_{max}, AUC and half-life seems to be not significantly different in the elderly in comparison to young adults.
There is no data on **cenobamate** and **cannabidiol** pharmacokinetics in the elderly people with epilepsy, therefore it is impossible to determine how the changes in pharmacokinetic factors associated with increasing age (decreased lean body mass, reduction of renal and hepatic clearance and loss of ability to maintain homeostasis) can influence their administration. About **everolimus**, limited data are available in the elderly such as that the dose adjustment in the adult (≥ 65 years) is not necessary even in elderly with renal diseases [78]. However, more appropriated studies are needed to determine the dosage and drug-drug interaction in the elderly.
A summary of pharmacokinetic modifications for each ASM in the elderly is reported in table 2.

3.3 Considerations on potential drug-drug interactions with antiseizure medications in the elderly

ASMs have a high potential risk of interactions with several medications commonly used in older adults, above all considering the high rate of polytherapy in this population [79,80]. The ASM choice in these patients should consider not only seizure type but also comorbidities, adverse effects and their DDIs [81]. The majority of clinically important interactions result from the induction or inhibition of drug-metabolizing enzymes.
First-generation ASMs (*e.g*. phenobarbital, phenytoin, carbamazepine and primidone) acting as strong inducers of several enzymes such as CYP3A4, 1A2, 2C9 and 2C19, but also of uridine 5'-diphospho-glucuronosyltransferases (UGTs) and epoxide hydrolase, are more likely to significantly reduce the pharmacological effect of drugs substrate of these enzymes (including cardiovascular drugs, psychotropic medications and anti-depressants, cancer therapy, antibiotics and anticoagulants). Furthermore, carbamazepine besides being a potent inducer of its metabolism and of other several drugs, also undergoes heteroinduction by phenytoin and barbiturates [82]. Instead, second and third generation ASMs are less likely to be associated with potent enzyme-inducing activity or probably only at higher doses. Valproate acts as an inhibitor of CYP2C9, and, to a lesser extent of CYP3A4, 2C19, UGT1A4 and 2B7, whereas it does not inhibit CYP2D6, 1A2, and 2E1 [83]. The activity of CYP3A4 and/or some UGT isoenzymes may be induced by perampanel (doses ≥8 mg/day), eslicarbazepine acetate, felbamate, oxcarbazepine (doses ≥1,200 mg/ day), topiramate, levetiracetam and rufinamide (doses ≥400 mg/day) that seem to have weaker enzyme-inducing properties. Furthermore, a weak inhibitory activity on CYP2C19 is exerted by oxcarbazepine, eslicarbazepine, felbamate, and topiramate [83]. Brivaracetam did not significantly inhibit or induce CYP3A [84]. In vitro, everolimus seems a competitive inhibitor of CYP3A4 and an inhibitor of CYP2D6 [85], whereas cannabidiol has a strong influence, mainly inhibiting, on several CYPs such as 2C19 and 3A4 [86,87]. However, the definition of cannabidiol interactions is rapidly growing and future studies will determine the full spectrum of interactions and their clinical significance [88,89]. Early results from phase I studies, showed that cenobamate significantly increases phenytoin and phenobarbital exposure via inhibition of CYP2C19 [90].
Stiripentol strongly inhibits several CYP isoforms (*i.e.* CYP3A4, 2D6, 2C19, and 1A2) [91]. An inhibitory activity of zonisamide on CYP2A6, 2C9, 2C19 and 2E1, but not on CYP3A4, 1A2, and 2D6 has also been highlighted [83]. Lacosamide, at therapeutic doses, in vitro does not inhibit or induce the activities of CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 and CYP3A4/5. Ethosuximide, gabapentin, pregabalin, and vigabatrin apparently do not have any effect on human CYP or UGT isoenzymes [83].

3.4 Specific drug-drug interactions

Common co-prescribed drugs in older adults with epilepsy are represented by antihypertensive drugs, antiplatelets, anticoagulants, statins, antibiotics, antidiabetics, antidepressants and antipsychotics, analgesics and anti-inflammatory drugs. Many of these medications used in the elderly may exhibit interactions with ASMs leading to adverse events [92]. As an example, carbamazepine, phenobarbital, phenytoin, and primidone, being potent inducers of hepatic drug metabolizing enzymes, are the most common ASMs involved in interactions with other drugs. These ASMs cause a significant decrease plasma concentration of oral anticoagulants, calcium antagonists, steroids, antimicrobial and antineoplastic drugs

resulting in a reduced efficacy [5]. Some examples of principal DDIs between ASMs and common co-administered drugs in the elderly are summarized below.

3.4.1 Antiseizure medications and cardiovascular drugs

Interactions between ASMs and drugs used for the treatment of cardiovascular diseases have been recently reviewed [93,94]. Summarizing, verapamil and many dihydropyridine calcium-channel blockers (CCBs) are extensively metabolized by CYP3A4 and 3A5 and may be subject to enzyme induction (increased metabolism) if co-administered with first generation ASMs leading to a reduction in their concentration. On the other hand, some CCBs (e.g. nicardipine and amlodipine) may alter the exposure to and the effect of several ASMs by inhibiting CYP3A4 pathway and/or P-gp [93]. Many data documented that older generation ASMs stimulating the metabolism of warfarin and other coumarin drugs, via cytochrome, increase the risk of "*lack of efficacy*" with consequent dosage adjustments required. Phenytoin's interactions with warfarin results complex and unpredictable, causing an initial decrease in anticoagulant effect, followed by an increase in warfarin concentration [95]. Valproic acid may increase serum warfarin concentrations either through the effects on the hepatic enzymes or through the displacement from protein binding sites with consequent risk of massive bleeding [96]. Furthermore, intravenous loading with valproic acid could cause transient international normalized ratio (INR) fluctuations by displacing warfarin from protein binding sites [97]. Eslicarbazepine acetate, at a dose of 1200 mg/day, significantly reduces serum S-warfarin concentrations without changing R-warfarin pharmacokinetics or INR values [98].

Regarding the newest oral anticoagulants (direct oral anticoagulants, DOACs) such as dabigatran, rivaroxaban or apixaban, there are few case reports and limited evidence on their interaction with ASMs; however, pharmacokinetics considerations suggest that phenytoin, carbamazepine and phenobarbital might reduce significantly DOACs efficacy. Furthermore, for oxcarbazepine and valproate, there are some data demonstrating a reduction of rivaroxaban efficacy [94].

Finally, several case reports seem to show that cannabinoids may inhibit warfarin metabolism via CYP2C9 interactions, with consequent increased plasma concentrations of the anticoagulant drug [99].

To date, there are only few data available on the interaction between statins and ASMs; for example it has been reported that the co-administration of carbamazepine with simvastatin lead to a 75-82% decrease in the AUC of the latter, possibly by induction of CYP 3A4 [100]. Similarly, eslicarbazepine acetate decreases the AUC of both simvastatin and rosuvastatin requiring dose adjustments; on the other hand, eslicarbazepine acetate may reduce low-density lipoprotein (LDL) cholesterol [101]. There is also one case report of loss of efficacy when phenytoin was co-prescribed with atorvastatin and simvastatin [102].

Accordingly, growing evidence reported that ASMs (e.g. carbamazepine, phenytoin, and phenobarbital) increase blood cholesterol levels probably via cytochrome P450 system [103].

3.4.2 Antiseizure medications and psychotropic drugs

An increase in plasma amitriptyline and nortriptyline concentrations in patients taking valproic acid has been observed probably by inhibition of metabolism leading to a risk of toxicity [104]. Regarding SSRIs, a decrease in plasma levels of paroxetine by about 25% by phenobarbital, phenytoin and carbamazepine has been reported [105]. Carbamazepine and phenytoin, by induction of CYP3A4, determine a decrease of mirtazapine concentrations [106]. A case report described two patients with low serum concentrations of reboxetine during carbamazepine or phenobarbital treatment probably mediated by CYP3A4 induction [107]. Phenytoin and carbamazepine strongly inhibit metabolism of sertraline and reduce citalopram effect [108]. Fluoxetine and fluvoxamine are relevant inhibitors of phenytoin and valproic acid. Furthermore, valproic acid may be an inhibitor and/or inducer of clozapine and olanzapine, an inhibitor of paliperidone, and a weak inducer of aripiprazole [109]. Regarding antipsychotics, carbamazepine reduces the serum concentrations of both the older typical and newer atypical drugs, including risperidone, clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, haloperidol, chlorpromazine as a result of induced microsomal liver enzymes. Conflicting data exist about the effect of valproic acid on clozapine concentrations [110]. Chlorpromazine inhibiting the metabolism of phenytoin, phenobarbital and valproic acid increases their plasmatic concentration [111]. Phenobarbital decreases clozapine, haloperidol and chlorpromazine concentrations. Phenytoin decreases quetiapine, clozapine and haloperidol concentrations [111]. Coadministration of strong enzyme-inducers as carbamazepine, phenobarbital, phenytoin and

primidone decreases alprazolam, clobazam, clonazepam, desmethyldiazepam, diazepam, midazolam plasma concentrations [96]. Moreover, cannabidiol, due to CYP2C19 strong inhibition, interferes with clobazam metabolism with consequent accumulation of N-desmethylclobazam, these data were confirmed by a phase III trial [112].

3.4.3 Antiseizure medications and antibiotics

Several studies, both in elderly and non-elderly patients, have shown that concomitant administration of valproic acid and carbapenem antibiotics leads to an interaction with consequent rapid decrease in valproic acid plasma concentrations [113]. Regarding interaction between carbamazepine and different macrolides, some clinical studies concluded that the co-administration of macrolides leads to an increase in carbamazepine serum concentrations giving rise to potential serious toxicity [114,115]. Two studies focused on the effects of trimethoprim/sulfamethoxazole on phenytoin pharmacokinetics showing that trimethoprim/sulfamethoxazole increases phenytoin toxicity [116,117].

3.4.4 Antiseizure medications and corticosteroids

Coadministration of phenytoin with dexamethasone [118] and prednisolone [119] enhances steroids clearance, as well as phenytoin and phenobarbital increase methylprednisolone clearance or carbamazepine with dexamethasone and other glucocorticosteroids [120]. On the other hand, dexamethasone may induce the metabolism of phenytoin [121]. Notably, interleukine (IL)-6 as well as other cytokines in inflammatory states may lead to a reduced CYP metabolic activity which can be normalized by drugs reducing inflammation such as corticosteroids but also drugs acting on IL-6 such as tocilizumab leading therefore to an increased metabolic activity and a reduction in the concentrations of all other concomitantly administered drugs [122,123].

n this way, enzyme- inducing drugs can enhance the clearance of steroids; such effects have been shown on coadministration of phenytoin with dexamethasone (Brophy et al., 1983; Chalk et al., 1984) and prednisolone (Frey & Frey, 1984), phenytoin and phenobarbital with methylprednisolone (Stjernholm & Katz, 1975), or carbamazepine with dexamethasone and other glucocorticosteroids (Spina et al., 1996). Conversely, and, although beyond the scope of this article, dexamethasone may induce the metabolism of phenytoin with a risk of higher seizure frequency. When dexamethasone is discontinued, phenytoin concentrations can easily rise to toxic levels (Lackner, 1991). In addition, dexamethasone may lead to unpredictable interactions, including both enzyme-inducing and enzyme-inhibiting effects, thus emphasizing the importance of therapeutic drug monitoring. In this way, enzyme-inducing drugs can enhance the clearance of steroids; such effects have been shown on coadministration of phenytoin with dexamethasone (Brophy et al., 1983; Chalk et al., 1984) and prednisolone (Frey & Frey, 1984), phenytoin and phenobarbital with methylprednisolone (Stjernholm & Katz, 1975), or carbamazepine with dexamethasone and other glucocorticosteroids (Spina et al., 1996). Conversely, and, although beyond the scope of this article, dexamethasone may induce the metabolism of phenytoin with a risk of higher seizure frequency. When dexamethasone is discontinued, phenytoin concentrations can easily rise to toxic levels (Lackner, 1991). In addition, dexamethasone may lead to unpredictable interactions, including both enzyme-inducing and enzyme-inhibiting effects, thus emphasizing the importance of therapeutic drug monitoring.

4. Conclusions

ASMs are widely prescribed in the elderly, often in polytherapy and with multiple comorbid conditions. However, age-related pharmacokinetic changes make the management challenging requiring often adjustments in drug dosage and accurate changes in therapy whether necessary.

Nowadays, there are few available data on the pharmacokinetic variability of ASMs in the elderly, especially about newer ASMs and their potential interactions.

The inter-individual pharmacokinetic variability in elderly is due and not limited to the physiological changes related to aging, but also to the impact of comorbidities and DDIs. Available data showed that the clearance of almost all ASMs (with the exception of brivaracetam, eslicarbazepine, perampanel, tiagabine and zonisamide) is reduced on average by about 20–50% in elderly patients compared with non-elderly

adults. Therefore, both loading and maintenance doses in the elderly should be 20-50% lower than in young adults.
Nowadays, although first-generation ASMs have been considered either third-line or usually inappropriate to treat epilepsy in the elderly, phenytoin, carbamazepine and valproate still represent treatments of choice based on clinical experience. However, carbamazepine is associated with clinically relevant pharmacokinetic interactions with other concomitantly administered drugs, whereas valproic acid and oxcarbazepine exhibit a minimal risk of DDIs.
Among ASMs, lamotrigine, levetiracetam, and lacosamide (second and third-generation drugs) seem to be well tolerated with low potential of DDIs; therefore, newer generation ASMs should be considered as initial monotherapy in old patients although more specific studies are needed and safety concerns should be kept in mind.

5. Expert opinion

Drugs' pharmacokinetic substantially changes during the lifespan, with significative differences generally appearing at the extreme ages, but not exclusively. Several age cut-offs to define elderly population have been defined during the years without a shared consensus. However, chronological age is one of the most utilized parameters in clinical practice leading to treatment choice and diagnostic procedures. Large interindividual variability and/or pathological modifications due to co-morbidities, as well as subsequent co-therapies, make age-matched patients not homogenous and often substantially different.
The effect of age on pharmacokinetic features of ASMs has been largely demonstrated, although no specific pharmacokinetic studies have been performed for all the ASMs in the elderly.
Drugs' elimination generally decreases with aging, due to a reduction in drug-metabolizing activity, renal function, or both. Therefore, for ASMs extensively cleared by oxidation (such as carbamazepine, phenytoin, and valproic acid) lower or less frequent doses compared with younger patients may be required. Starting and maintenance doses should be reduced by a variable extent (up to 50%) to avoid dose-dependent AEs and a slow titration is recommended, following the rule "*start low and go slow*" [17].
For ASMs mainly eliminated by renal excretion (e.g. ethosuximide, gabapentin, pregabalin, vigabatrin levetiracetam, and topiramate), dosage must be adjusted according to the most reliable formulas for predicting renal function in the elderly (*i.e.* Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] and the Cockcroft and Gault formula). Indeed, serum creatinine alone is considered a suboptimal indicator of renal function in old age, due to several factors including the reduced lean mass, and the influence of protein intake and hydration [26].
ASMs extensively bound to plasma proteins (such as phenytoin and valproic acid) may displace or be displaced by other highly protein bound drugs. Moreover, protein binding reduction due to age or diseases (e.g. hypoalbuminemia, renal or hepatic disease) may lead to toxic effects at total serum drug levels lower than usual. Therefore, total plasma concentrations of these drugs should be interpreted with caution, correcting for serum albumin values; monitoring the free fraction could be more useful to establish dosage adjustments.
Nowadays, limited or no data have been provided on age-related pharmacokinetic changes of newer ASMs, as well as for some medications belonging to the first generation (*i.e.* clonazepam, ethosuximide). For these drugs, we can only speculate according to the pharmacokinetic features available. For example, since clonazepam undergoes extensive hepatic metabolism, liver disease as well as age is likely to impair its elimination. On the other hand, older patients can receive the usual doses of zonisamide recommended for younger adults.
Bearing in mind the large prescription of ASMs in the elderly, also in diseases other than epilepsy (e.g. mood disorders and neuropathic pain), specific studies appositely designed to evaluate aging effects on pharmacokinetic are mandatory. Population pharmacokinetic studies will also help to clarify which clinical factors should be accounted to establish dosage changes. Indeed, age is one of the major contributors to the substantial inter- and intra-individual variability in ASMs' pharmacokinetic, but several others factors could be involved, including genetic factors, frailty, comorbidities, body weight and DDIs [77]. ASMs can act as inducers or inhibitors of drug-metabolizing enzymes, leading to a high potential risk of interactions with other medications. Therefore, studies are required to provide details on enzyme induction in the elderly,

which has shown contrasting results. Moreover, recent data on a possible pharmacokinetic interaction between valproic acid and perampanel suggest to better characterize metabolic pathways of newer ASMs to predict DDIs and improve polytherapy [124]. In addition, the influence of renal function on the pharmacokinetic of ASMs metabolized through CYP3A4 should be further clarified to help the management of patients with moderate-to-severe renal impairment treated with topiramate, clobazam, or perampanel.
The potential interactions among ASMs and supplements or herbal medicines but also with laxatives might be investigated in the next years, due to the widespread use of these products in the last decade. For example, further information is needed on a decrease by about one third in serum carbamazepine concentrations in elderly nursing home residents taking iron supplements [125]. This potential interaction has been observed applying a nonlinear mixed effect model in which confounding factors cannot be excluded [126]. In this light, several products may modify gastrointestinal (e.g. pH, motility) or hepatic metabolic (e.g. CYP induction or inhibition) functions leading to altered absorption or elimination.
Once the starting dose has been established based on pharmacokinetic modelling, TDM should be performed to determine and apply the "*individual therapeutic concentration*" [127]. It may be implemented to overcome the large age-related differences in the relationship between drug dose and plasma concentrations, to monitor DDIs and guide dosage adjustments, minimizing the risk of AEs. Finally, dosing should be individualized according to clinical response and plasmatic concentrations.

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**An update on the TDM in ASMs.

Table 1. The most relevant age-related physiological changes which affect drug disposition

Pharmacokinetic parameter	Physiological effect	Pharmacokinetic consequences	Clinical significance
Absorption	↓ Gastric secretion ↑ Gastric pH	Potential reduced/increased absorption	Might be of clinical significance only for weakly basic poorly water-soluble, highly permeable drugs (e.g. ketoconazole, itraconazole, indinavir), which require sufficient gastric acidity for adequate dissolution and absorption [11]
	↓ Gastric emptying ↓ GI motility	Time of onset of action may be delayed	Rarely of clinical significance
Permeability	Passive diffusion unchanged	No change in bioavailability for most drugs	
	Possible decrease in active transport	Increased bioavailability for some drugs	Rarely of clinical significance
	Possible decrease or increase in the P-gp activity	Unclear	
Distribution	↓ total body water	Altered V_d with increased active plasma concentrations of hydrophilic drugs	A decrease up to 20% in parenteral loading doses has been recommended [17]
	↑ body fat	Altered V_d with prolonged half-life of lipophilic drugs	Lower or less frequent doses should be required according to plasma concentrations
	↓ muscle mass		
	↓ albumin	Increased free concentration of acidic drugs (e.g. phenytoin, valproic acid)	
	↑ α-1-acid-glycoprotein		Total plasma concentrations of highly bound drugs should be interpreted with caution; Monitoring the free fraction could be more useful to establish dosage adjustments.

		Decreased free concentration of alkaline drugs	When warfarin is coadministered with valproic acid or phenytoin, INR should also be monitored closely.
Metabolism	↓ Enzyme induction ↓ Hepatic mass ↓ Hepatic blood flow ↓ Activity in mixed function oxydase system ↓ first-pass metabolism	Reduced clearance for drugs with high hepatic extraction ratios Reduction in metabolism of drugs that undergo Phase I metabolism Increased potential for drug interactions Increased concentrations of the active drug	Lower or less frequent doses compared with younger patients may be required. For ASMs such as carbamazepine, phenytoin, and valproic acid, a reduction by up to 50% of loading and maintenance doses should be considered. Can be clinically significant in drugs with high first-pass metabolism TDM should be considered to adjust dosage
Elimination	Possible decrease of renal clearance ↓ kidney size	Reduced clearance for drugs mainly excreted by the kidneys	Dosage adjustments according to CKD-EPI or the Cockcroft and Gault formula are needed for ASMs mainly eliminated by renal excretion (e.g. ethosuximide, gabapentin, pregabalin, vigabatrin levetiracetam, and topiramate)

ASMs, antiseizure medications; CKD-EPI, chronic kidney disease epidemiology collaboration; INR, international normalized ratio; P-gp, P-glycoprotein; V_d, volume of distribution; TDM, therapeutic drug monitoring.

Table 2. Pharmacokinetic modifications for ASMs in the elderly

	Pharmacokinetic modifications	**Reference**	**Notes**
Brivaracetam	Cl not influenced by age	[70]	Moderate ↑ AUC with severe renal impairment; ↑ half-life and doubled exposure with hepatic impairment [71,72]

Table 2. Pharmacokinetic modifications for ASMs in the elderly

	Pharmacokinetic modifications	Reference	Notes
Carbamazepine	↑ variability in absorption and FF Cl ↓ 25-40%	[31,33]	No age-related modifications in other studies [31,34]
Clobazam	Cl ↓~40% half-life ↑ about threefold	[36,37]	Significant differences in men
Eslicarbazepine	No age-related modifications	[74]	No significant ↑ CDR (15%) [75]
Felbamate	Cl ↓~20% ↑half-life, AUC, C_{max}	[67]	
Gabapentin	V_d ↑ 63% Cl ↓ 32-46% half-life ↑ about twofold	[55]	
Lacosamide	Plasma concentrations ↑10-35% CDR ↑ 28%	[68,69]	
Lamotrigine	Cl ↓ 22-37% half-life ↑ mean 6.3h	[58]	
Levetiracetam	Cl ↓ 20-52% half-life ↑ about twofold	[60,61]	Patients >55 years involved
Oxcarbazepine	Cl ↓ 35% MHD C_{max}, ↑ 50% in elderly men and ↑ 33% in elderly women	[62]	
Perampanel	Cl not influenced by age	[73]	
Phenobarbital	Cl ↓~20-50%	[39,40]	Patients >40 years involved [40]
Phenytoin	↑ variability in absorption ↑FF (not considered clinically relevant) ↓V_{max} Cl ↓~25% (may be greater for FF clearance)	[45]	No age-related modifications in other studies [43]
Pregabalin	Cl ↓ 50% CDR ↑ ~25% (in adults aged 50 years and older)	[57]	
Primidone	Slight ↓renal Cl	[38]	Statistical significance only for PEMA
Tiagabine	AUC ↓ 20%	[66]	With co-administered enzyme-inducing ASMs

Table 2. Pharmacokinetic modifications for ASMs in the elderly

	Pharmacokinetic modifications	Reference	Notes
Topiramate	Cl not influenced by age	[63]	In patients with compromised renal function: Cl ↓ ~20% C_{max} ↑ 23% AUC ↑ 25% half-life ↑13% [64]
Valproic acid	FF ↑ 50% FF Cl ↓~40% half-life ↑ about twofold	[48,50]	
Vigabatrin	↑ C_{max} and half-life AUC ↑ up to 5-times	[56]	
Zonisamide	↑ C_{max} ↓half-life	[65]	No significant age-related differences for Cl, AUC
Everolimus, rufinamide, stiripentol	Limited data suggest no effect	[78]	
Cannabidiol, cenobamate, clonazepam, ethosuximide	No data in the elderly		

ASMs, antiseizure medications; AUC, area under the concentration–time curve; CDR, concentration–dose ratio; Cl, clearance; C_{max}, peak concentration; FF, free fraction; MHD, monohydroxycarbazepine; PEMA, phenylethylmalonamide; V_d, volume of distribution; V_{max} maximum rate of metabolism.