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REVIEW

Adverse Drug Reactions of Acetylcholinesterase Inhibitors in Older People Living with Dementia: A Comprehensive Literature Review

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Abstract: The rising of global geriatric population has contributed to increased prevalence of dementia. Dementia is a neurodegenerative disease, which is characterized by progressive deterioration of cognitive functions, such as judgment, language, memory, attention and visuospatial ability. Dementia not only has profoundly devastating physical and psychological health outcomes, but it also poses a considerable healthcare expenditure and burdens. Acetylcholinesterase inhibitors (AChEIs), or so-called anti-dementia medications, have been developed to delay the progression of neurocognitive disorders and to decrease healthcare needs. AChEIs have been widely prescribed in clinical practice for the treatment of Alzheimer's disease, which account for 70% of dementia. The rising use of AChEIs results in increased adverse drug reactions (ADRs) such as cardiovascular and gastrointestinal adverse effects, resulting from overstimulation of peripheral cholinergic activity and muscarinic receptor activation. Changes in pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics (PGx), and occurrence of drug interactions are said to be major risk factors of ADRs of AChEIs in this population. To date, comprehensive reviews in ADRs of AChEIs have so far been scarcely studied. Therefore, we aimed to recapitulate and update the diverse aspects of AChEIs, including the mechanisms of action, characteristics and risk factors of ADRs, and preventive strategies of their ADRs. The collation of this knowledge is essential to facilitate efforts to reduce ADRs of AChEIs.

Keywords: older adults, dementia, acetylcholinesterase inhibitors, adverse drug reactions, drug–drug interactions

Introduction

Globally, the number of older population aged 60 years or over was 962 million in 2017 and will almost double to reach 2.1 billion by 2050.[1,2] The rising geriatric population results in an exponential increase in incidence of neurodegenerative disorders such as dementia.[3,4] Worldwide, the population of people living with dementia was estimated at 50 million in 2017 and is predicted to increase to 131.5 million by 2050.[5,6] Dementia is described as symptoms related to a cluster of major neurocognitive disorders or conditions which are usually manifested as slowly progressive decline of multiple cortical functions including orientation, comprehension, memory, language, learning skills and problem-solving ability.[7] The most common type of dementia is AD (50–75%), followed by vascular dementia (20%), dementia with Lewy bodies (5%) and finally frontotemporal lobar dementia (5%).[8–10] In AD, the progressive loss of

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cholinergic neurons in the basal forebrain leads to a decrease in acetylcholine (ACh) which is essential in cognition and neuroprotection.[11] Dementia has a devastating impact on healthcare infrastructures in economic and medical aspects. This neurodegenerative disease is one of the leading causes of death and contributors to premature disability and dependency burdens.[5,12,13] With increased disability, dementia could be overwhelming for caregivers and families, leading to increased healthcare needs.[3,12,14–17] Appropriate management, including non-pharmacological and pharmacological therapies, are necessary to delay worsening of symptoms and to reduce healthcare burdens.[18] Anti-dementia medications are being used worldwide, especially in Alzheimer's disease (AD), which is the most common type of dementia.[19] One-fourth of older people with dementia are prescribed anti-dementia medications which are classified into two classes: Acetylcholinesterase inhibitors (AChEIs) and N-Methyl-D-aspartate (NMDA) receptor antagonists.[20,21] AChEIs were the first pharmacological treatment approved by the US Food and Drug Administration (FDA) for AD and have been reported to be used in 10–20% of dementia patients.[22–25]

The aging population usually have multiple other chronic diseases as well as behavioral and psychological symptoms of dementia (BPSD),[12,22,26–35] resulting in the concurrent use of five or more medications or polypharmacy.[26] The exposure of 82–98% of people with dementia to polypharmacy was reported in previous studies.[36–38] This can lead to a greater risk of undesirable or harmful reactions to medications or adverse drug reactions (ADRs).[39–41] The alterations in pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics (PGx) of AChEIs also result in higher risk of AChEIs' ADR.[42–47] Over the last decades, there has been an increase in the reports of AChEI-induced ADRs with 70% being severe and up to 2.3% being fatal ADRs.[48–50]

Therefore, the significance of the paper is to facilitate effort to address the issue of AChEI-induced ADRs among older patients with dementia. We aim to review and update the diverse aspects of AChEIs such as the mechanisms of action, characteristics and risk factors of ADRs, and preventive strategies of their ADRs.

Search Strategy

PubMed, Scopus and Web of Science databases were searched for relevant articles published in English from January 1, 1976 until March 31, 2021. The search terms were "donepezil", "galantamine", "rivastigmine", "acetylcholinesterase inhibitors", "dementia", "Alzheimer's disease", "older adults", "mechanism", "pharmacokinetics", "pharmacodynamics", "pharmacogenetics", "adverse drug reactions", "drug-drug interactions", "prevention". Google Scholar was searched using main keywords for any additional studies.

Acetylcholinesterase Inhibitors

Mechanism of Acetylcholinesterase Inhibitors

ACh is mostly hydrolyzed by acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).[51] Both enzymes are responsible for rapid hydrolysis of ACh in synaptic clefts, producing the products: Choline and acetate. AChE predominates in the human brain whereas BuChE is widely distributed in peripheral nervous system (PNS) and other organs such as intestine, heart and liver.[52–54] In the brain, AChE levels are usually high in synapses while BuChE is distributed in glial cells.[53] In AD patients, BuChE has progressively increased activity in particular part of the brain such as hippocampal area and has raised accumulation of Aβ-aggregation and neurofibrillary tangles, resulting in the reduction of ACh.[52,55–61] Therefore, a class of AChEIs is developed to block both AChE and BuChE in the synaptic clefts to reduce the degradation of Ach.[19] Furthermore, one AChEI has a pharmacological property for modulation of muscarinic or nicotinic receptors, contributing to enhancement of cholinergic activity.[62] AChEIs increase cholinergic activities to improve and sustain cognitive functions and ADLs as well as to make better psycho-behavioral symptoms in dementia patients.[22] However, AChEIs also inhibit rapid hydrolysis of ACh in PNS including sympathetic autonomic nervous system, and parasympathetic and preganglionic sympathetic neurons. This leads to peripheral adverse outcomes, such as diarrhea, nausea and vomiting, dizziness, and muscle cramping.[63]

The first-generation of AChEIs such as tacrine, velnacrine, and physostigmine were removed from the market because of high incidence rates of potential drug interactions and serious side effects.[64] Three second-generation AChEIs were rapidly developed to replace the first-generation AChEIs. Donepezil, galantamine and rivastigmine have been approved by the FDA for the treatment of AD. Donepezil (58.4%) is the most frequently

prescribed AChEIs, followed by rivastigmine (13.6%) and galantamine (12.4%).[22,65–67] Donepezil in oral form and rivastigmine transdermal patches have received regulatory approval for the treatment of all stages of AD ranging from mild to severe.[19,22,68–80] There is no significant difference between the efficacy of these AChEIs in terms of improving psychometric and cognitive scales.[81] However, three AChEIs differ in both PK and PD properties,[82–84] as shown in Supplementary Table 1.

Donepezil

Donepezil was the first AChEI approved by the FDA for AD treatment in 1996. It is a piperidine-based reversible inhibitor of AChE.[82,85] Donepezil is 500-fold selective for AChE inhibition in comparison with BuChE.[86,87] The oral bioavailability is 100% and time to peak plasma concentration (T_{max}) approximates 3–5 hours following a single-dose administration.[88,89] Plasma albumin binding is 75% and volume of distribution (Vd) is 12 L/kg.[88–90] Donepezil readily transports across the blood brain barrier (BBB), resulting in 7-fold higher concentration in the brain compared with plasma. Cytochrome P450 2D6 (CYP2D6) is accounted for the major Phase I metabolism (90%) and the rest by Cytochrome P450 3A4 (CYP3A4).[89,91] 6-O-desmethyl donepezil (6DD) is the end product of Phase II metabolism which is excreted via kidney route.[88,92] The average apparent plasma clearance is approximately 0.13–0.19 L/h/kg. According to its elimination half-life (70 hours), it takes around 15 days to reach the steady state. Then, it is conveniently administered as once daily.[88,89] Both 5 mg and 10 mg once daily administration for 24 weeks could improve cognitive and quality of life scales in mild to moderate AD patients.[93–95] The initial dose should be administered initially with 5 mg/day, followed by slow-dose titration every 4–6 weeks along with the clinical status monitoring until reaching the maximum dose of 10 mg for mild to moderate AD.[64,95] For severe AD, the maximum daily dose of donepezil is 23 mg once daily.[76]

Rivastigmine

Rivastigmine was approved by the FDA to be marketed in 1997. Rivastigmine is classified as a carbamate substance.[81,82,85] Its mechanism of action is a slow reversible or pseudo-irreversible inhibition of both AChE and BuChE.[85,96,97] The oral bioavailability is poor, approximate 40% with T_{max} ranging from 0.5 to 2 hours following oral single-dose administration.[88,98] Plasma protein binding is 40% and Vd is 1.8–2.7 L/kg.[88,99,100] Rivastigmine easily passes through the BBB to exert activity in the brain.[101,102] Intestinal esterase is the major enzyme responsible for first pass metabolism and the rest is minimally metabolized by liver cytochrome P450.[88] The main metabolite is NAP 226–90 which is rapidly excreted by renal system.[88] The plasma clearance of rivastigmine is estimated to be 1.5 L/h/kg. Its half-life is short, nearly 1.5 hours. Therefore, twice-daily dosing is recommended in clinical practice.[88,100] Several double-blind controlled studies showed significant improvement in cognitive and global functions with 6 month-treatment.[103,104] Clinical studies pointed out the effective doses of rivastigmine to be 6 to 12 mg per day.[64,105] Rivastigmine is recommended to start at the dose of 1.5 mg twice-daily as capsules or liquid formulations and slowly titrate up to 6 mg twice-daily at intervals of every 2 to 4 weeks.[81,103] In terms of other efficacy of rivastigmine, the improvement of peripheral insulin resistance has not been reported.[106] Transdermal patch is another preparation which delivers rivastigmine constantly into the blood circulation without level fluctuation.[71,97,107] The therapeutic dose of transdermal patch delivering rivastigmine is 4.6 mg per 24 hours to 13.3 mg per 24 hours in clinical practice.[107,108] Rivastigmine patch is suggested to be started at 4.6 mg per 24 hours for at least for 4 weeks and then to be increased to 9.5 mg per 24 hours. After a minimum of 6 months a dose of 9.5 mg per 24 hours, 13.3 mg per 24 hours is recommended for well-tolerated patients with progressive cognitive decline.[109]

Galantamine

Galantamine was approved by the FDA in 2000 for the treatment of AD.[110] This agent is a tertiary alkaloid-based compound that acts as both rapidly reversible-competitive inhibitor of AChE and a positive allosteric modulator of nicotinic acetylcholine receptors.[62,85,110] The oral bioavailability of galantamine ranges from 85 to 100% with rapid absorption.[88,111] The T_{max} is approximately 52 minutes following a single oral administration. Unlike donepezil, protein binding of galantamine is less than 50% and the mean Vd is 2.64 L/kg.[88,111] This medication is demethylated and oxidized by CYP2D6 and CYP3A4. The active metabolite of galantamine is sanguinine or O-desmethyl galantamine.[88,112] Galantamine goes through glucuronidation forming a water-soluble metabolite which is excreted via the renal route.[88,111,112] The total plasma clearance of galantamine is 0.34 L/h/kg.[113] Due to its short half-life of

6–8 hours, twice-daily dosing is recommended.[88,111,113] The formulation of galantamine consists of both immediate-release tablets and extended-release capsules. The efficacy of both extended and immediate release tablets of galantamine was studied in a randomized, double-blind, placebo-controlled trails, using doses titrating up to 16 or 24 mg per day for 6 months duration of treatment in patients with mild to moderate AD.[104,114,115] These studies demonstrated a significant improvement in cognitive and neuropsychiatric scales.[114] The recommended therapeutic dose of galantamine is 8 mg per day and gradually escalates every 4 weeks up to a maximum daily dose of 24 mg.[116]

Therefore, the safety and effectiveness of AChEIs should be evaluated in older population in whom adverse reactions may be serious.[117] In terms of efficacy and effectiveness assessment of AChEIs, the common tools for cognitive evaluation includes Mini-Mental-State Examination (MMSE),[118] Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog),[119] and Severe Impairment Battery (SIB).[120] Other tests are used to measures functional status and psycho-behavioral symptoms are the Basic and Instrumental Activity of Daily Living[121–123] and Neuropsychiatric inventory (NPI),[124] respectively. According to previous clinical practice guideline based on systematic reviews,[104,125,126] AChEIs treatment for dementia contributed to marginally significant improvement of cognitive function, functional and global status, and psycho-behavioural symptoms.[117,125,127] In mild to moderate AD patients, meta-analyses on AChEIs have revealed the results with cognitive improvements on 1.5 points in MMSE and 2.5 points in ADAS-cog, comparing to the placebo.[19] The Pooled data presented an improvement of 0.1 standard deviations of ADLs[104,125] and 2 of 144 points in NPI.[128] Besides cognitive and behavioural improvement, AChEIs have positive effects on balance and gait function without orthostatic hypotension.[129] However, there is limited evidence of AChEI efficacy and effectiveness in severe dementia, advanced age and long-term treatment.[19,130,131]

Adverse Drug Reactions of Acetylcholinesterase Inhibitors

The prevalence of AChEI-induced ADRs tends upward significantly in older population with dementia.[48] In a 16-year period study, the number of AChEI-induced ADRs increased from 1924 ADRs in 1998 to 2961 ADRs in 2013.[48] Most reported cases are serious ADRs (50–70%) of which 2.3% are fatal ADRs.[48–50] AChEIs have a dose-related toxicity and a narrow therapeutic index. Therefore, the prevalence of ADRs has an upward trend with an increasing dose.[48] Most ADRs of AChEIs are described as type A reactions which are associated with dose and altered PK and PD. However, most type A reactions are potentially preventable In a recent study, preventable ADRs from prescription and administration errors were presented in 2.0% of all serious cases.[48] According to the mechanism of AChEI action, overstimulation of central and peripheral muscarinic and nicotinic receptors may contribute to diarrhea, nausea, vomiting, vagotonic effects (bradycardia, heart block, syncope), tremor, insomnia, urinary incontinence, and seizure.[63,132–135] Common ADRs induced by AChEIs are principally neuropsychiatric (17%), gastrointestinal (16.2%), and cardiovascular (11.2%) in nature[49] as a result of overstimulation of peripheral cholinergic activity and muscarinic receptor activation, as revealed in Supplementary Table 2.[48,72,83,132,133]

Gastrointestinal Adverse Effects

Oral administration of AChEIs increases gastric acid secretion of hydrochloric acid and internal propulsion which lead to the increase of gastrointestinal adverse effects, namely gastrointestinal ulceration and bleeding, especially for the concomitant use of AChEI and NSAIDs.[136,137] Commonly reported gastrointestinal adverse effects are abdominal pain, nausea, vomiting, diarrhea, and poor appetite.[72,133,138–141] The increase of gastrointestinal side effects is associated with the rapid escalation of AChEI dose.[142]

Cardiovascular Adverse Effects

Both conduction and sinus node function gradually deteriorate with advanced age. Moreover, AChEI increases the availability of choline in the heart and vagotonic effects via muscarinic receptors.[143,144] Cardiovascular side effects are some of the most common peripheral adverse cholinergic effects. Therefore, older adults treated with AChEIs are at greater risk of life-threatening conduction dysfunction such as sinoatrial and atrioventricular block,[140,145,146] severe sinus bradycardia[147] and QT interval prolongation with torsades de pointes (TdP).[148–150] Wandering atrial pacemaker (WAP) is another uncommon cardiac side effect in patients treated with donepezil. This condition is an atrial arrhythmia which presents with at least three distinctly different P wave morphologies.[151] Negative chronotropic effects contribute to detrimental

health outcomes including syncope, pacemaker insertion, falls, fractures, hospitalization.[147,152–154] However, there is controversy that AChEIs result in negative chronotropic effects.[155–158] Therefore, older people receiving AChEIs should be routinely asked regarding syncope histories and be evaluated for arrhythmia or bradycardia by physical examination and electrocardiogram.[159] Concomitant use of AChEIs and drug-induced QT prolongation such as beta-blockers, antiarrhythmic drugs and antipsychotics should be closely monitored by physicians and pharmacists.[159] In contrast, AChEIs treatment may be correlated with lower risk of cardiovascular events.[158]

Neurological and Psychological Adverse Effects

Neurological side effects mainly result from excessive activation of nicotinic receptors. Common neurological adverse effects are dizziness, dyskinesia, convulsion, muscle cramps, insomnia, and vivid dream. The epileptic seizure is a very rare neurological adverse effects induced by AChEIs.[160,161] From previous report, patient with mild AD treated with 10 mg donepezil once daily for 3 weeks presented convulsions during the treatment.[160] Moreover, AChEI-induced seizures may result from nutritional and metabolic disorders such as hyponatremia.[161] The vivid dream results from the disorder of brainstem cholinergic systems in processing rapid eye movement sleep. One characteristic of the vivid dream is extremely realistic. Vivid dreams usually appear in patients treated with donepezil in the evening owing to peak plasma concentration at night.[63,162] Psychiatric adverse outcomes in older adults treated with AChEIs may include worsening of hallucination, anxiety, aggression, and confusion.[163,164] Psychiatric problems are usually presented in dementia patients treated with high doses of AChEIs.

Respiratory Adverse Effects

Bronchospasm was presented as a pulmonary side effect after AChEI administration.[165] Therefore, patients with a history of bronchoconstriction should be closely monitored during treatment.[165] Furthermore, nasal problems could be presented among patients treated with AChEI.[165] There is no report of respiratory failure from AChEIs for dementia treatment.

Genitourinary Adverse Effects

Urinary incontinence may occur after treatment with AChEIs, in particular for galantamine.[166] The mechanism is related to nicotinic Ach receptor stimulation at the neuromuscular junction, resulting in an increased peripheral ACh.

Dermatological Adverse Effects

Rivastigmine could be used in the form of a skin patch. The most common skin adverse reaction is irritant contact dermatitis as a local skin reaction which is not associated with an immunological process. Its manifestation is localized erythema and itching.[167,168] These symptoms usually resolve within 48 hours after patch removal. As a rare dermatological adverse reaction, allergic contact dermatitis is delayed type-IV immunologic reaction and manifests as erythema, vesicles and edema appearing more than 48 hours after rivastigmine patch removal. The life-threatening skin adverse reaction called Stevens-Johnson Syndrome (SJS) can occur in patients treated with oral or dermal administration and was reported in patients treated with galantamine.[138,167–169]

Uncommon Adverse Effects

According to post-marketing surveillance, a rare dystonic reaction called Pisa syndrome has been reported in patients receiving AChEIs. This syndrome is described as tonic flexion of the head and trunk one side accompanied by slight axial rotation.[170] The pathophysiology of the syndrome results from dopaminergic-cholinergic imbalance. Pisa syndrome was reported in a patients receiving 9 mg per day rivastigmine for 2 years.[171,172] However, this abnormal syndrome disappeared when the drug dose was decreased.[171] Rhabdomyolysis and neuroleptic malignant syndromes are uncommon side effects which have been reported in older adults receiving donepezil.[173–175] Furthermore, hemolytic anemia, syndrome of inappropriate antidiuretic hormone (SIADH),[161] and severe hepatitis[176] also present as uncommon adverse effects in clinical practice.

AChEI-induced adverse effects may provide chance for prescribing cascades. AChEIs activate muscarinic receptors in urinary tract, leading to strong contraction of detrusor muscle and urinary incontinence. Therefore, bladder anticholinergic agents such as oxybutynin, tolterodine, trospium and solifenacin are usually used to relieve urge incontinence which called AChEI-induced urinary incontinence prescribing cascade.[177] Another common

prescribing cascade is AChEI-induced rhinorrhea which is concomitant use of rhinorrhea medications to relieve side effects of AChEIs. The rhinorrhea medications consist of antihistamine, nasal anticholinergics and nasal glucocorticoids.[178] These co-medications may contribute to negative side effects. Therefore, physicians should consider dose reduction of AChEIs instead of adding other medications to treat adverse effects of AChEIs.[179]

Factors Associated with Adverse Drug Reactions of Acetylcholinesterase Inhibitors in Older Adults with Dementia

In geriatric patients with dementia, changes in PK and PD are major risk factors of ADRs. In terms of PK, hepatic and renal functions usually decline in these patients, resulting in decreased drug elimination. Older patients are vulnerable to get an uneventful ADRs from these medications according to their sensitivity to the pharmacodynamic effects.[180] Additionally, patients with AD are prone to be sensitive to ADRs as a result of increased BBB permeability and decreased P-gp activity in the brain.[43,101,102,181,182] Polypharmacy is common in aging populations and is an important risk factor for drug-related problems (DRPs) such as potentially inappropriate medications (PIMs), drug–drug interactions (DDIs), ADRs and poor compliance.[183,184] ADRs derived from DDIs, PIMs or poor compliance are often reported in older patients with dementia.[183,184] ADRs are major causes of hospitalization, morbidity and mortality in older people with dementia.[185,186]

Changes in Pharmacokinetics

PK is what an individual's body does to a medication after its administration, and refers to absorption, distribution, metabolism and excretion.[42–47] In geriatric population, the alteration of absorption does not lead to major adverse effects whereas changes in distribution, metabolism and excretion play important roles in clinical outcomes. The alterations of PK and PD of AChEIs among older people living with dementia were presented in Tables 1 and 2.

Absorption

Age-related gastrointestinal tract changes often affect the oral absorption. Hypochlorhydria in older adults alleviate the degree of absorption of weakly basic drugs. Furthermore, reduced splanchnic blood flow and gastrointestinal motility as well as delayed gastric emptying time result in longer staying of drug in the gastrointestinal tract and delaying absorption of the drug. Older adults treated with donepezil presented a significant increase in mean T_{max} but not in plasma level concentration contributing to slower donepezil's absorption.[86,90] In contrast, the bioavailability and absorption of rivastigmine have no significant change with advancing age.[187] Concomitant administration of galantamine with food delays T_{max} by 1.5 hours and slows its absorption rate but does not affect the extent of absorption.[74] A moderate food effect was found in previous studies of rivastigmine.[54] Food slows the absorption of rivastigmine and reduces T_{max} by 30%.[54,188] Therefore, the coadministration of food and galantamine or rivastigmine is indicated to reduce cholinergic adverse effects such as nausea and vomiting. Conversely, food intake has no significant effect on the absorption of donepezil.[54,189]

Rivastigmine could also be administered via a skin patch. Age-related changes in skin includes atrophy of epidermis and dermis and decreased blood perfusion, leading to reduced drug absorption via the skin.[190] Nevertheless, age-related changes to drug absorption have minimal effects on the pharmacotherapy of dermal medications.

Distribution

Many factors affect volume of distribution. Patients with dementia are more likely to experience malnutrition and frailty as a result of inability to feed by themselves, changes in feeding behaviours, and difficulty with swallowing.[191] Changes in the body composition of older adults with dementia also occur including, 10–15% reduction in total body water, 25–30% reduction in muscle mass, and a 25–30% relative increase in body fat.[192,193] The aging and frailty processes in this group of patients also contributes to a 10–20% reduction in serum albumin concentration which plays a major role in plasma protein binding.[193–196] Medication that predominately binds albumin such as donepezil (75% bind to albumin), a reduction in albumin binding may contribute to the rising of unbound fraction being pharmacologically active, resulting in greater potency and toxicity.[88,90] Furthermore, donepezil may displace other high-protein binding medications such as warfarin, benzodiazepine and valproate, leading to an increased unbound form of these medications and serious adverse effects. Due to age-related changes, the Vd throughout the whole body of donepezil is substantially

Table 1 The Changes in Pharmacokinetics of Acetylcholinesterase Inhibitors Among Older Adults Living with Dementia

Physiologic Changes	Causes of PK Changes			PK Consequences
	Aging Process	Frailty	Dementia	
Reduction in GI mobility[86,90]	✓✓	✓✓		Increased in mean T_{max} of donepezil
Reduction in splanchnic blood flow[86,90]	✓✓			Increased in mean T_{max} of donepezil
Reduction in tissue blood perfusion[190]	✓✓			Reduction in rivastigmine's absorption via skin
Atrophy of epidermis and dermis[190]	✓✓			Reduction in rivastigmine's absorption via skin
Reduction in serum albumin[88,90,193–196]	✓✓	✓✓	✓✓	Increased free fraction in plasma of high-protein binding AChEI (donepezil)
Reduction in hepatic mass and size[88,89,91,111,112,201–205]	✓✓			Reduced first-pass metabolism (phase I) and hepatic clearance of donepezil, galantamine and rivastigmine
Increased of inflammatory process[198–200]		✓✓ Reduced phase II metabolism		Downregulation in metabolism and transporter pathway of donepezil, galantamine and rivastigmine

Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; AChEI, acetylcholinesterase inhibitor; GI, gastrointestinal; $T_{max,}$ Time to maximum serum concentration.

increased by approximately 40%, resulting in a prolonged half-life.[90,197]

Metabolism

Liver CYP enzymes system plays a major role in drug metabolism and may be affected by increasing age. CYP2C19 functions are reduced with age while other isoenzymes show minimal reduction or no change.[45] In contrast, there is no significant change in phase II metabolism, especially conjugation in older adults. However, phase II metabolism and downregulation of the transporter pathway of AChEIs are decreased in frail older adults, leading to a greater risk of drug toxicity.[198–200] The decrease of drug metabolism in the geriatric population, especially in phase I metabolism, results from a 30% and 40% reduction in liver mass and in hepatic blood flow, respectively.[201–205] The reduction in drug metabolism may account for decreased hepatic clearance, prolonged half-life and increased dose-dependent ADRs. In terms of AChEIs, there are diverse pharmacological properties and differences of clinical outcomes. Data from clinical trials of geriatric patients with AD reveal that the steady-state concentrations of galantamine are 40% higher than those in a healthy younger population as a result of reduced galantamine's metabolism.[88,111,112,138] Based on a population pharmacokinetic analysis, the hepatic clearance of donepezil and of rivastigmine has a tendency to decrease with increasing age.[88,89,91,187] Apart from age-related changes in metabolism, most older adults with dementia have multiple chronic diseases including hepatic diseases or cirrhosis, which may lead to decreased hepatic function and drug metabolism. The clearance of both galantamine and rivastigmine was reduced by 25% and 65%, respectively in patients with moderate hepatic impairment (Child-Pugh score of 7–9).[88,111,121] Hence, dose adjustment is recommended for these populations. The use of galantamine for such patients should be initiated with a low dose (4 mg per day) and slowly titrated to a maximum daily dose (16 mg per day).[88,111,138] However, no data is available on the use of galantamine or rivastigmine in patients with severe hepatic impairment (Child-Pugh score of 10–15).[88,111,112,138] Consequently, the use of galantamine or rivastigmine in patients with severe hepatic impairment is contraindicated in clinical practice.[138] A recent study showed a 20% reduction in the clearance of donepezil in dementia patients with cirrhosis.[206] However, there is no clinically significant alteration in the PK of donepezil in AD

patients with moderate or severe hepatic impairment.[206,207] This may explain why dose modification of donepezil is not required.

Excretion

After metabolism, most substances are transformed to products that are readily excreted via the kidneys. As a results of age-related physiological changes, the reduction in renal blood flow (50%), renal mass and size (20–30%), and number of nephrons (60%), lead to a decline in drug excretion and drug half-life prolongation.[208] Apart from metabolism changes, dosage adjustment should be done based on renal function which is calculated from laboratory measurement (serum creatinine) by using a mathematical equation including the Cockcroft-Gault (CG) formula to ensure proper drug dose for older adults.[45,46,209] However, serum creatinine level in older frail individuals may not accurately present renal function because of decreased muscle mass.[209] Older AD patients presented a 30% reduction in renal clearance of galantamine, compared with healthy individuals.[210] As a consequence of increasing age and frailty, the clearance rate of galantamine, rivastigmine and donepezil in older patients with AD is reduced, compared to healthy individuals.[138,210] The clearance of galantamine and rivastigmine is decreased by 25% and 64%, respectively in AD patients with moderate renal impairment.[138] This PK alteration may necessitate dose modification and close monitoring to avoid adverse outcomes.[138] A total daily dose of galantamine should not exceed 16 mg in patients with moderate renal decline or creatinine clearance 9–59 mL/min[138] whereas specific-dose adjustment of rivastigmine is not indicated.[211] Nevertheless, the use of galantamine is not recommended given the insufficient data for patients with severe renal impairment or creatinine clearance less than 9 mL/min.[138] On the contrary, donepezil disposition is not affected by renal dysfunction. The renal clearance of donepezil in patients with moderate to severe renal impairment has no difference to sex- and age-matched healthy population despite donepezil and its metabolites are mostly excreted by kidneys. In a population pharmacokinetic study of AD patients with moderate to severe renal impairment, there is no clinically significant change of PK or PD parameters of donepezil, compared with healthy population. Therefore, dose adjustments are not necessary in AD patients with renal impairment.[64,207]

As a result of decreased elimination of rivastigmine, dose adjustments with close monitoring should be done. Nevertheless, no study has been reported for rivastigmine transdermal patches in AD patients with renal or hepatic impairment. Therefore, rivastigmine transdermal patches should be avoided in AD patients with severe renal or hepatic impairment.[107,108]

Changes in the Blood-Brain Barrier

The BBB is a highly selective semipermeable layer of endothelial cells which limits the access of water-soluble and large molecules transporting from blood circulation into the brain parenchyma. Older adults with dementia have changes in the permeability and integrity of the BBB, as presented in Table 2. BBB mechanism includes reabsorption of CSF and efflux pumps for molecules such as p-glycoprotein (P-gp) which assists the maintenance of hemostasis in the brain and in the clearance of beta-amyloid.[43,101,102] P-gp is a phosphorylated protein encoded by multidrug resistance gene 1 (MDR1) and belongs to the family of ATP-binding cassette (ABC) membrane transporters.[102,212] It is located on the apical surface of endothelial cells and is involved in limiting the transfer of small molecules into the brain.[213,214] With aging process and dementia, levels and activity of P-gp have a tendency to decline.[101,102,181,215] Furthermore, micro-disruption of the BBB is found in patients with dementia, contributing to increased allowance of some medications across BBB around the disruption areas.[181] These changes may lead to increased permission of AChEIs to the brain as a predisposing factor of AChEI-induced ADRs in this population.[43]

Changes in Pharmacodynamics

By definition, PD is described as what medication does to the body such as receptor binding and chemical interaction.[42–47] The changes of PD are difficult to predict and evaluate in individuals. In the aging process, the sensitive affinity of receptors for particular medications may change. Moreover, the number of receptor sites may alter and may impact on the efficacy of many medications. The geriatric population is more susceptible to certain central nervous system (CNS) adverse outcomes of AChEIs due to increased permeability of the BBB and decreased P-gp activity.[101,102,181,182,215] Furthermore, high sensitivity to cholinergic receptors in the brain and the reduction in homeostasis are found in the older adult population.[45,46,216] These alterations result in an elevated responses to AChEIs and contribute to PNS and CNS cholinergic ADRs, as presented in Table 2. However,

Table 2 The Changes in Pharmacokinetics and Pharmacodynamics of Acetylcholinesterase Inhibitors Among Older Adults Living with Dementia

Physiologic Changes	Causes of PK or PD Changes			PK Consequences
	Aging Process	Frailty	Dementia	
Reduction in hepatic blood flow[88,89,91,111,112,201–205]	✓✓			Increased half-life of donepezil, galantamine and rivastigmine
Reduction in renal blood flow[138,208,210,211]	✓✓			Reduced renal clearance of donepezil, galantamine and rivastigmine
Reduction in number of nephron[138,208,210,211]	✓✓			Increased half-life of donepezil, galantamine and rivastigmine
Reduction in glomerular infiltration rate[138,208,210,211]	✓✓	✓✓		Increased half-life of donepezil, galantamine and rivastigmine
Physiologic changes				**PD consequences**
Micro-disruption of BBB[43,101,102,181,182,215]	✓✓		✓✓	Increased permeability of donepezil, galantamine and rivastigmine across BBB
Reduction in P-gp activity[43,101,102,181,182,215]	✓✓		✓✓	Increased permeability of donepezil, galantamine and rivastigmine across BBB
High sensitivity to cholinergic receptor[45,46,216]	✓✓			Increased response to donepezil, galantamine and rivastigmine

Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; BBB, blood-brain barrier; P-gp, P-glycoprotein.

changes in the PD of AChEIs in older patients with dementia have not been extensively explored.

Changes in Pharmacogenetics

Pharmacogenetics is defined as genetic variations in individuals which contribute to different responses to medications. PGx plays a major role in ADRs and therapeutic failures (TFs). Polymorphism of CYP enzymes for AChEIs results in PK and PD difference.[84,217] In terms of AChEIs, PGx of encoded gene on P-gp, CYP2D6, and CYP3A4 plays an important role in PK of donepezil and galantamine.[218] Interesting studies presented genetic variations of single nucleotide polymorphisms (SNP) in cholinergic markers on AChE and BuChE which have effects on clinical responses to AChEIs as well.[82,219] Moreover, polymorphism in the gene encoding choline acetyltransferase (ChAT), acetylcholine biosynthetic enzyme, and a genetic variation of paraoxonase-1 (PON-1) 192Q/R (rs662) which influences the activity of this arylesterase, are involved as the prognostic indicators of response to AChEIs.[220,221] Pharmacogenetic considerations for AChEIs should be heeded because they could help predict drug toxicity and efficacy in individuals. In recent decades, genetic polymorphism on CYP2D6 genotype was increasingly studied in various populations.[222–225] CYP2D6 phenotypes are categorized into four types of metabolizers: Poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs). PMs have functional deficiency of CYP2D6 due to mutated allele of CYP2D6. EMs have normal functions of CYP2D6 while UMs have a very low concentration of AChEI owing to multiple copies of CYP2D6 gene. IMs metabolize medications with a rate between PMs and EMs.[222,223,225] According to PGx of CYP2D6 (PGX-CYP2D6), approximately 30% of older AD patients have poor metabolite of galantamine and donepezil.[226] This situation can be explained by the phenotypic profile of CYP2D6 genotypes being associated with the presence of the APOE-4 allele.[227–229] Furthermore, the prevalence of each CYP2D6 polymorphism differs according to race and ethnicity.[84,230] In Caucasian populations, PMs, IMs, EMs and UMs account for approximately 5–10%, 10–17%, 70–80% and 3–5% of individuals, respectively.[231,232] Asians, Africans and African Americans have a greater percentage of reduced-function of CYP2D6 (50%), compared with Caucasians (26%).[233] CYP3A4 polymorphism is not responsible for the variation in metabolism of donepezil and galantamine. The effect of genetic variation in ATP-binding cassette sub-family

B member 1 (ABCB1) on membrane transporter P-gp plays an important role in donepezil transporters across the BBB and in the clearance of amyloid β (Aβ) peptide related to APOE, ABCB1 gene polymorphisms which have an impact on distribution, excretion, and absorption of donepezil.[102,212,234,235]

Drug–Drug Interactions

DDI is defined as the pharmacological activities of one drug changed by the concomitant administration of another medication.[236] Generally, drug interactions are responsible for 20% to 30% of ADRs. Over 30% of reported ADRs caused by AChEIs result from DDIs.[237] The major risk factors for DDIs are polypharmacy and age-related PK and PD changes.[238,239] DDIs are classified into two types: PK and PD drug interactions. By definition, PK drug interaction involves one medication altering the absorption, distribution, transport, metabolism or excretion of another medication.[240] PD drug interaction is defined as one medication changing the response to another medication.[240] CYP enzymes-mediated and transporter-mediated PK drug interactions as well as synergistic or antagonistic PD drug interactions are common DDIs among dementia patients treated with AChEIs.[241–243] Inducers and inhibitors of CYP2D6 and CYP3A4 enzyme play important roles in the mechanism of PK drug interactions of donepezil and galantamine.[226,244] P-gp inducers and inhibitors are involved in transporter-mediated PK drug interactions of donepezil, which is considered a weak P-gp substrate.[245]

Potent CYP2D6 and CYP3A4 inhibitors such as antidepressants (paroxetine, fluoxetine), and antifungal drugs (ketoconazole) contribute to increased plasma concentration of donepezil and galantamine, as shown in Table 3.[138,242,246–249] The adverse outcomes may be hypercholinergic effects of AChEIs, such as bradycardia, diarrhea and hypersalivation. However, there is no significant CYP2D6 and CYP3A4 inducers of donepezil and galantamine. In terms of transporter-mediated PK drug interactions, PK of donepezil is affected by P-gp inhibitors and inducers. Most medications, which are transported by P-gp, are also metabolized by CYP3A4.[214,245,250] Many P-gp inhibitors and inducers are also inhibitors and inducers of CYP3A4. Therefore, many DDIs are associated with inhibition or induction of both CYP3A4 and P-gp.[250] The most common P-gp inhibitors in patients with dementia are antibiotics (azithromycin, clarithromycin, erythromycin), cardiovascular medications (carvedilol, verapamil) and antiplatelets (cilostazol, ticagrelor), resulting in the rising of donepezil plasma concentration.[250–252] There was the clinical report of cardiotoxicity owing to coadministration of donepezil and cilostazol.[252] Due to P-gp interaction with cilostazol, the concentration of donepezil in the heart tissue was increased, leading QT prolongation.[252] In the case of P-gp inducers, the plasma concentration of donepezil is decreased by carbamazepine, phenobarbital, phenytoin and rifampicin,[250–252] as presented in Table 4.

Pharmacoepidemiological studies in people with dementia have revealed that anticholinergics, antidepressants, antipsychotics, non-steroidal anti-inflammatory

Table 3 Common CYP Enzymes-Mediated Pharmacokinetic Drug Interactions of Acetylcholinesterase Inhibitors in Older Adults Living with Dementia

PK Drug Interactions	CYP2D6	CYP3A4	Outcomes
Strong Inhibitors[138,242,246–249]	**Antidepressants** Bupropion Duloxetine Fluoxetine Paroxetine Sertraline **Antiarrhythmic drugs** Amiodarone **Antipsychotics** Aripiprazole Haloperidol	**Antibiotics** Erythromycin **Antifungal drugs** Fluconazole Ketoconazole **Antiarrhythmic drugs** Amiodarone **Antipsychotics** Haloperidol **Antidepressants** Sertraline	Increased plasma concentration of donepezil and galantamine **Hypercholinergic outcomes** Hypersalivation, abdominal pain, diarrhea, nausea, vomiting

Abbreviations: PK, pharmacokinetics; CYP, cytochrome P450; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4.

Table 4 Common Transporter-Mediated Pharmacokinetic Drug Interactions of Acetylcholinesterase Inhibitors in Older Adults Living with Dementia

Transporter-Mediated PK Drug Interactions	Medications	Outcomes
P-gp inhibitors[250–252]	**Antibiotics** Erythromycin Azithromycin Clarithromycin **Antifungal drugs** Itraconazole Ketoconazole **Cardiovascular drugs** Verapamil Carvedilol **Antiplatelet** Cilostazol Ticagrelor	Increased plasma concentration of Donepezil as P-gp substrate **Hypercholinergic outcomes** hypersalivation, QT prolongation, diarrhea, nausea, vomiting
P-gp inducers[250–252]	**Anticonvulsants** Carbamazepine Phenytoin Phenobarbital **Antituberculosis drugs** Rifampicin	Decreased plasma concentration of Donepezil as P-gp substrate

Abbreviations: PK, pharmacokinetics; P-gp, P-glycoprotein.

drugs (NSAIDs), and cardiovascular drugs are common co-medications with AChEIs, resulting in PD drug interactions.[237,243,253,254] Synergistic PD drug interactions of AChEIs with cholinomimetics or cholinergic agonists have additional cholinergic effects such as hypersalivation, diarrhea, nausea, and vomiting, as presented in Table 5.[255–257] Many antagonistic PD drug interactions of AChEIs are related to changes in PD from advancing age and to dementia processes. In the aging process, a reduction in the number of cholinergic and dopaminergic neurons and dopamine D_2 receptors are reported. Therefore, the uses of anticholinergics and antipsychotics which affect cholinergic and dopaminergic neurotransmitters, potentially interfere with the activity of cholinesterase inhibitors and can cause adverse clinical outcomes.[253,254,258,259] The clinical report described rigidity, parkinsonism and immobilization in AD patients treated with donepezil and risperidone which these adverse symptoms resolved after risperidone was discontinued.[260] Furthermore, concomitant use of beta-blockers, calcium channel blockers or antiarrhythmics in older patients with dementia treated with AChEIs may result in adverse cardiovascular effects such as bradyarrhythmia, heart block, syncope and QT prolongation,[63,243,261] as presented in Table 5.

Principles for Prescribing Acetylcholinesterase Inhibitors

Recommendations for Prescribing Acetylcholinesterase Inhibitors

AChEI should be initiated at a low efficient dose and titrated slowly upward. The starting dose of donepezil is 5 mg once daily. Donepezil dosage should not be adjusted too quickly because the time to reach the steady state is within 15 days. Therefore, donepezil should be slowly titrated after the first dose is started over 4–6 weeks. Older adults with moderate to severe AD could slowly titrate the donepezil dose to 23 mg per day,[262] as presented in Supplementary Table 1. However, gastrointestinal complaints and poor appetite may be reported in patients receiving high donepezil doses.[75,139,262,263] Among patients with mild to moderate hepatic insufficiency, a low dose (5 mg daily) consumption

Table 5 Pharmacodynamic Interactions in Older Adults with Dementia

PD Drug Interactions	Interactions	Mechanism Effects	Adverse Outcomes
Anticholinergics + AChEIs[138,243,253,254]	Antagonistic	Decreased acetylcholine in CNS	Constipation, delirium, cognitive impairment, urinary retention Antagonized the effects of AChEIs
Cholinomimetics or cholinergic agonists + AChEIs[255–257]	Synergistic	Increased acetylcholine in PNS	Hypersalivation, abdominal pain, diarrhea, nausea, vomiting,
Beta blockers + AChEIs[63,243,261]	Synergistic	Decreased sympathetic Increased vagotonic effects	Bradyarrhythmia, heart block, prolonged QT, torsades de pointes syncope
Calcium channel blockers + AChEIs[63,243,261]	Synergistic	Decreased sympathetic Increased vagotonic effects	Bradyarrhythmia, heart block, prolonged QT, torsades de pointes, syncope
Antiarrhythmic drugs + AChEIs[63,243,261]	Synergistic	Decreased sympathetic Increased vagotonic effects	Bradyarrhythmia, heart block, torsades de pointes, syncope
Antipsychotics + AChEIs[242,243,258,259]	Antagonistic	Decreased dopamine in striatum	Rigidity, parkinsonism, worsening of extrapyramidal effects
NSAIDs + AChEIs[136,137,237,243]	Synergistic	Increased gastric acid secretion	Gastrointestinal ulcer

Abbreviations: PD, pharmacodynamics; AChEIs, acetylcholinesterase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; CNS, central nervous system; PNS, peripheral nervous system.

of donepezil is safe and the use of its doubling dose should be monitored.[264] Galantamine is a daily oral medication ranging from 8 to 24 mg per day,[116] as shown in Supplementary Table 1. Galantamine doses must be adjusted for people with moderate hepatic impairment. Furthermore, galantamine should not be recommended to patients with severe liver and kidney dysfunction. Rivastigmine may be a good choice for older demented patients exposed to polypharmacy to reduce the incidence of PK drug interactions related to CYP enzymes. Rivastigmine prescriptions start at 1.5 mg and could be gradually increased to 6 mg twice a day,[64,81,103,105] as shown in Supplementary Table 1. Rivastigmine transdermal patches are usually recommended for dementia patients with severe gastrointestinal side effects from oral administration. Transdermal patches have a long half-life and are easily applied only once a day. The dose of rivastigmine in a patch can be titrated from 4.6 mg per 24 hours to 13.3 mg per 24 hours.[107–109] However, some patients treated with a transdermal patch may develop dermatological side effects such as pruritus or an allergic reaction. Therefore, patients should be examined for adverse skin reactions during treatment.[108]

Contraindication and Caution in the Prescribing of Acetylcholinesterase Inhibitors

Allergic reaction to the medication itself and chemicals in the same structural group is an absolute contraindication. Donepezil is a piperidine-based compound.[81,82,85] Rivastigmine is derived from carbamate compound whereas galantamine is belonged to alkaloid substance.[62,81,82,85] Rivastigmine patches are contraindicated for patients with suggestive allergic contact dermatitis.[107–109] Galantamine is also contraindicated for patients with severe hepatic and renal dysfunction.[212] Additionally, patients with sick sinus syndrome (SSS) and second or third heart block should avoid using AChEIs.[138,140,141] AChEIs should be used with cautions in people with severe hepatic impairment, severe obstructive pulmonary disease, active gastrointestinal ulcers or bleeding, seizure and significant conduction abnormalities such as supraventricular conduction problems, and arrhythmias.[138,140,141] However, older patients treated with AChEIs rarely develop cholinergic crisis in the clinical practice.

Table 6 Prevention Strategies for Adverse Drug Reactions of Acetylcholinesterase Inhibitors

Medication Problems	Management
DDIs[47,238,272–275,277,280,281]	Evaluate drug interactions via application (Micromedex) Evaluate drug-disease interactions by Beers Criteria
Poor compliance[47,272–275,282–288]	Easily understandable drug labels Use simplest regimens Encourage memory techniques (alarm clock, calendar) Evaluate health literacy (language, education, dementia)
Polypharmacy[47,272–275]	Comprehensive medication review Minimize number of physicians and hospital visits Prescribe only necessary medications
The discontinuation of AChEIs[268]	Weighting the risks and the benefits of continuous AChEIs use Consider deprescribing AChEIs in patients with lack of treatment response, severe cognitive function, significantly impaired functional status
PIMs[47,272–275,278,279]	Comprehensive medication review Evaluate potentially inappropriate medication for older adults with dementia following Beers Criteria
Miscommunication[272–275,286–288]	Evaluate health literacy (language, education, dementia) Ensure the plan with patients and caregivers or family members Encourage technology and technique for older patients to make proper pharmacological plan and management
Age-related physiological changes[47,270,272–275]	Check physiological problems related to drug administration such as cognitive impairment, visual and auditory problems, and bone-joint deformity
Age-related changes in PK[47,270,272–275]	Evaluate weight and nutritional status, refers to protein levels Evaluate patients' hepatic and renal function
Age-related changes in PD[47,270,272–275]	Start low and slowly titrate AChEIs due to be highly sensitive drug-induced action on cholinergic receptors

Abbreviations: DDIs, drug–drug interactions; PIMs, potentially inappropriate medications; PK, pharmacokinetics; PD, pharmacodynamics; AChEIs, acetylcholinesterase inhibitors.

Recommendations for Discontinuation of Acetylcholinesterase Inhibitors

The continuous use of AChEIs should be often weighted the risks and the benefits. According to the Food and Drug Administration Adverse Event Reporting System database, serious ADRs related to AChEIs were reported, especially in long-term treatment.[135,136,179,213,265,266] Advanced dementia patients may be offered unnecessary treatment that may not provide positive effects, resulting in increased adverse outcomes.[267] Therefore, many studies offered recommendations to discontinue AChEI treatment in particular conditions to optimize medication prescribing.[268] The common reason for deprescribing AChEIs were lack of response, significantly impaired functional status, severe cognitive impairment (MMSE score < 10), and side effects.[268] Besides minimized medication prescribing, the benefits of AChEI discontinuation are improved medication non-adherence, and reduced DDI, medication management burden and cost of medications.[269]

The discontinuation of AChEIs should be slowly tapered the dose by halving the previous dose and stepping down to the lowest available dose.[269] The abrupt cessation should be done in patients with experiencing ADRs. After discontinuation, physicians should closely monitor the withdrawal symptoms and the changes of cognitive function, psycho-behavioral symptoms and functional status.[269]

Strategies to Prevent Adverse Drug Reactions of Acetylcholinesterase Inhibitors

Many strategies have been developed and implemented to prevent ADRs in patients using AChEIs, as shown in Table 6. Minimizing effective dose is required to reduce the occurrence of adverse outcomes. The "start low go slow" strategy is widely recommended as the lowest initial dose, slow-dose titration and close monitoring.[270,271] The dose adjustment of AChEIs is recommended according to

the alteration of PK or PD.[47,270,272–275] Furthermore, older patients usually have comorbidities for which multiple medications are taken, resulting in DRPs including potential DDIs, drug–disease interactions, inappropriate medications and medication non-adherence.[270,272–274,276] Thus, comprehensive medication reviews and optimizing medications prescribing are necessary to address DRPs.[275] Another potential strategy could be using tools such as the Micromedex Drug Interaction Database[277] and the 2019 American Geriatrics Society Beers criteria[278] to evaluate DDIs and PIMs, respectively.[238,279] The discontinuation of AChEIs in older adults with particular circumstances including lack of treatment response, severe cognitive function, significantly impaired functional status, could have reduced DDIs and PIMs.[268] Moreover, computerized alert systems for screening prescriptions and flagging DDIs and PIMs could also prevent ADRs.[275,280,281] Medication non-adherence is another major DRP in older adults, resulting from language barriers, complex regimens and physiological changes including cognitive impairment, visual and auditory problems and bone-joint deformities.[282–286] Many techniques could provide benefits to people with medication non-adherence; for example, readily openable containers, clearly written instructions in large print, the simple possible dosage regimens and supporting technology (alarm clock and drug calendar).[287,288]

Conclusions

AChEIs have been widely prescribed to delay worsening of cognitive functions and psycho-behavioral problems in older people living with dementia. In the aging population, age-related PK and PD changes, and multiple comorbidities lead to altered pharmacological responses and increased ADRs. Furthermore, geriatric people are more likely to be sensitive to pharmacological toxicity. The most common negative effects of AChEIs are adverse neuropsychiatric, gastrointestinal, and cardiovascular outcomes. Thus, prescribing of AChEIs for dementia treatment should carefully consider both risks and benefits. The discontinuation of AChEIs in older people with particular circumstances such as lack of treatment response, severe cognitive impairment and side effects, could reduce DRPs. Many strategies have been developed to prevent adverse effects. The "start low go slow" strategy as well as comprehensive medication review are highly recommended to address ADRs.

Abbreviation

ABCB1, ATP-binding cassette sub-family B member 1; Aβ, amyloid β; Ach, acetylcholine; AChE, acetylcholinesterase; AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; ADRs, adverse drug reactions; AGS Beers Criteria, American Geriatrics Society Beers Criteria; BBB, blood brain barrier; BPSD, behavioral and psychological symptoms; BuChE, butyrylcholinesterase; CG, Cockcroft-Gault; ChAT, choline acetyltransferase; CNS, central nervous system; CSF, cerebrospinal fluid; CYP, cytochrome P450; CYP2D6, cytochrome P450 2D6; CYP3A4, cytochrome P450 3A4; DDIs, drug–drug interactions; DRPs, Drug-related problems; Ems, extensive metabolisers; FDA, Food and Drug Administration; GI, gastrointestinal; IMs, intermediate metabolisers; MDR1, multidrug resistance gene 1; nAChRs, nicotinic acetylcholine receptors; NMDA, N-Methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs; PD, pharmacodynamics; P-gp, p-glycoprotein; PIMs, potentially inappropriate medications; PGx, pharmacogenetics; PGx-CYP2D6, pharmacogenetics of CYP2D6; PK, pharmacokinetics; PMs, poor metabolisers; PNS, peripheral nervous system; PON-1, paraoxonase-1; SIADH, syndrome of inappropriate antidiuretic hormone; SJS, Stevens-Johnson Syndrome; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome; TdP, torsades de pointes; TFs, therapeutic failures; $T_{max,}$ time to peak plasma concentration; Ums, ultra-rapid metabolisers; Vd, volume of distribution; WAP, wandering atrial pacemaker; 6DD, 6-O-desmethyl donepezil.

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