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An update on the utility and safety of cholinesterase inhibitors for the treatment of Alzheimer's disease

Andrea Haake[1], Kevin Nguyen[1], Lauren Friedman[2], Binu Chakkamparambil[1] and George T Grossberg[1]

[1]Saint Louis University School of Medicine, Department of Psychiatry and Behavioral Neuroscience, Saint Louis, Missouri, USA
[2]University of Missouri School of Medicine, Columbia, Missouri, USA

Corresponding author:
George Grossberg,
Department of Geriatric Psychiatry, SSM Health Saint Louis University, 1438 South Grand Blvd., Saint Louis, MO 63104, USA
Tel.: +1 (314)-977-4800
Fax: +1 (314)-977-4878
Email: george.grossberg@health.slu.edu

Abstract

Introduction: Alzheimer's disease (AD) is the most common cause of major neurocognitive disorders with a prevalence in the US of about 5.7 million in 2018. With the disease burden projected to increase dramatically in the coming years, it is imperative to review the current available treatment regimens for their safety and utility. The cholinesterase inhibitors (ChEIs) have continued to play a pivotal role in managing the symptoms and possibly slowing the rate of progression of AD since 1993. Owing to their being a mainstay in the treatment of AD, the safety and efficacy of prescribing these drugs needs to be reviewed often, especially with the approval of new formulations and doses.

Areas covered: The three ChEIs currently approved by the FDA are donepezil, rivastigmine and galantamine. This article will review the safety and tolerability of these ChEIs and analyze the potential disease modifying properties of these drugs. The authors have reviewed all recent literature including review articles, meta-analyses, clinical trials and more.

Expert opinion: These ChEIs differ subtly in their mechanisms of action, in their tolerability and safety and FDA-approved indications. All are considered first-line, symptomatic treatments of the various phases of AD and may even have potentially disease-modifying effects.

Key words: Alzheimer's disease treatment, cholinesterase inhibitors, safety of cholinesterase inhibitors, side effects, adverse effects, donepezil, galantamine, rivastigmine, symptomatic treatment for Alzheimer's disease

Article highlights

- The ChEIs are still considered the mainstay of treatment which target the cholinergic hypothesis of AD.
- Among the 3 FDA approved ChEIs, donepezil at a dose of 23mg/day and rivastigmine transdermal patch of 13.3mg/24hr can be used in severe AD.
- GI side effects are the most common adverse events and it can be minimized by slow titration of the dose.
- Introducing the ChEIs early on in the disease stage, helps to minimize the behavioral problems associated with later stages of AD.
- Even though there have been case reports of cardiac side effects with donepezil, the studies done so far have not shown any major arrhythmogenic, hypotensive, or negative chronotropic effects.
- The higher proportion of adverse events due to rivastigmine is due to improper application of the patch, especially applying a new patch without removing the old patch.
- In a large randomized controlled trial, galantamine showed lower mortality rate when compared to placebo, thus establishing its safety.

1.Introduction

The first mention of dementia in the Diagnostic and Statistical Manual of Mental Disorders (DSM) was in the DSM-II [1] in 1975 as senile or presenile dementia under the heading “psychosis associated with Organic Brain Syndrome (OBS)” [2,3]. DSM-5 replaced the term “dementia” from DSM-III, with major neurocognitive disorder - a neurodegenerative disorder with a focus on decline rather than deficits in cognition and function. [4]

The most common cause of major neurocognitive disorder is Alzheimer’s disease (AD) – a clinical syndrome first described by Aloysius Alzheimer in 1907 in his 51 year old patient. He also described the neuritic plaques, neurofibrillary tangles, and amyloid angiopathy – the hallmarks of AD in her brain at autopsy. [2] The prevalence of AD in the US was about 5.7 million in 2018 and is projected to increase by about 30% to 7.1 million, by 2025 and to 13.8 million by 2050. According to the Center for Disease Control (CDC), AD is the 6th leading cause of age adjusted deaths in the United States. [5]

Though various hypotheses have been proposed to explain the pathophysiology and symptoms of AD, including the amyloid hypothesis, hyperphosphorylated tau protein hypothesis, cholinergic deficit hypothesis, neuro-inflammation and others, current FDA-approved pharmacotherapy mostly targets the cholinergic hypothesis. [6,7]. Cholinergic neurotransmitters play a very significant role in memory, learning, attention and behavior. Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) are 2 main enzymes that hydrolyze Ach in the brain. [7] The cholinergic hypothesis suggests that reduced brain acetylcholine (ACh) levels due to the atrophy of cholinergic neurons, primarily in the nucleus basalis of Meynert are the cause of cognitive decline in AD [8]. In AD, there are changes in AChE and BChE activity, which are the targets for the action of the ChEIs. Other treatment approaches targeting the amyloid and the tau hypotheses have to date not been productive including immunotherapy-based approaches, which have failed in phase II or III clinical trials [9]. With repeated failures in developing preventative and disease-modifying therapies, the Cholinesterase inhibitors (ChEIs) continue to play a pivotal role in managing the symptoms and possibly slowing the rate of progression of AD.

This article reviews the safety and efficacy of the various ChEIs in the treatment of major neurocognitive disorder of the Alzheimer's type.

The first FDA approved drug for AD was Tacrine, followed by Donepezil, Rivastigmine and Galantamine.

2.Tacrine

The first drug to be introduced to the US market for managing Alzheimer's disease was Tacrine (tetrahydroaminoacridine; Cognex-Warner-Lambert) [10]. The drug inhibits the acetylcholinesterase (ACheE) and butyrylcholinesterase (BChE)enzymes (dual inhibitor),

thereby preventing the metabolism of acetylcholine leading to its increased availability for binding to muscarinic receptors. In AD, it has been found that with disease progression, AChE levels decrease and the levels of BChE levels are the same or increased, which could account for the greater efficacy of using dual cholinesterase inhibitors. [7] Clinical trials with Tacrine have shown mixed results with regards to efficacy. [11,12] Though some studies had shown a statistically significant decrease in cognitive decline, which led to its FDA approval in 1993 [13], the drug was discontinued in 2013 due to its significant adverse effects, the most common being gastrointestinal and less commonly hepatotoxicity (elevated transaminase), potentially leading to death [14,15] The need to take Tacrine three times daily, often leading to poor adherence, and the need to monitor liver enzymes, also contributed to the demise of Tacrine.

3.0. Donepezil

Donepezil was the second FDA-approved cholinesterase inhibitor to be marketed (Aricept-Eisai/Pfizer). The initial formulations, 5 and 10 mg, received FDA approval in 1996 for mild to moderate AD and a 23 mg dose received approval in 2010 for the treatment of moderate to severe AD [16]. Donepezil functions as a highly selective, centrally acting, reversible inhibitor of acetylcholinesterase- thereby increasing the amount of acetylcholine present in the synaptic cleft [17]. This mechanism of action draws upon the cholinergic hypothesis of Alzheimer's disease (AD), whereby neuronal

function is improved by increasing the concentration of acetylcholine [18]. Donepezil is administered orally and is available as film-coated (5, 10, 23 mg/day) or orally-disintegrating tablets (5, 10 mg/day) [19]. The drug has a half-life of 60-90 hours, making it convenient for once daily dosing [20]. It reaches maximum plasma concentration in 3-5 hours, and steady state in 14-21 days with routine dosing [21]. Donepezil is largely metabolized by the liver (hepatic enzymes CYP2D6 and CYP3A4), with the majority of the unchanged drug and its metabolites then being excreted via the kidneys.

In a 2017 meta-analysis by Blanco-Silvente et al., donepezil was noted to be more efficacious than galantamine or rivastigmine in improving global AD symptomatology [22]. The main documented adverse effects (AEs) following donepezil administration reflect its mechanism of action of increasing cholinergic activity. The neurocognitive effects and AEs following donepezil administration are highlighted in (Table 1). GI side effects including nausea, vomiting, diarrhea and abdominal cramping have been commonly reported [17-20]. Sleep disturbances [23-24] and rarer cardiac AEs including bradycardia and QTc prolongation [24-28] have also been documented.

3.1. Safety of 5 mg/day and 10 mg/day of donepezil

Both the 5 and 10 mg formulations of donepezil are indicated for mild to moderate AD [19]. The 23 mg formulation can be used for moderate to severe AD. Broad ranges in AEs, from 9.3% to 96% of participants affected, have been reported following donepezil administration in studies examining the drug. Participants have reported AEs in a dose-dependent manner following administration of 5 or 10 mg/day of donepezil [23]. In controlled clinical trials, the most commonly cited adverse events (AEs) leading to donepezil 5 and 10 mg/day discontinuation were gastrointestinal AEs and urinary tract infection [19]. These effects were usually transient and mild in nature, but were reported more frequently with higher doses of the drug [23]. Slow titration, starting with donepezil 2.5 mg and titrating to 5 mg over the course of 6 weeks, can be helpful in patients who are sensitive to cholinergic side effects [20]. After 4-6 weeks of the 5 mg dose, patients can then start the 10 mg formulation and after 3 months may be transitioned to the 23 mg dose [19].

In addition to GI side-effects, other commonly reported side effects include: agitation, fatigue, dizziness, headache, influenza-like symptoms and sleep disturbances (Table 1). When compared to placebo, insomnia and vivid dreams are more often cited following donepezil administration, particularly with nighttime dosing [24]. It has been hypothesized that these nighttime symptoms are related to the drug's mechanism of increasing cholinergic activity, as the REM-induction region within the medial pontine reticular formation is activated by cholinergic transmission [24, 31]. Advising patients to take their medication in the morning and spacing out doses immediately before titrating to a higher dose may help alleviate sleep disturbances.

3.2. Safety of 23 mg/day of donepezil

The higher-dose formulation of donepezil was approved for the treatment of moderate to severe AD following its established efficacy in large clinical studies. A randomized, double-blinded safety analysis of 1,434 patients found that the 23 mg/day dose provided improved cognitive benefits (as measured by the Severe Impairment Battery) in patients at 24 weeks, as compared to the 10 mg/day formulation [29] (Table 1). There were no significant differences in functional measures or MMSE scores between the groups.

As with the increase in donepezil dosing from 5 mg/day to 10 mg/day, AEs in this study were more commonly reported in those taking the 23 mg/day formulation (73.7%) compared to the 10 mg/day dose (63.7%) [29]. The majority of reported AEs comprised GI **side-** effects (nausea, vomiting, diarrhea and anorexia). Weight loss was more frequently reported in those receiving 23 mg of donepezil, as 8.4% of participants receiving the 23 mg formulation of donepezil had their weight decrease by greater than 7% by the end of the study, versus 4.9% of participants receiving the 10 mg dose [29]. The 23 mg dose was also associated with higher rates of GI bleeding (1.1% vs. 0.6%) and bradycardia (2.8% vs. 0.6%). Both groups had similar reported incidences of agitation, hallucinations and falls (Table 1). A 2019 meta-analysis supported this finding, indicating that donepezil may even be associated with a lower fall risk compared to placebo [32].

Discontinuation rates due to AEs also increased with higher doses of donepezil. In a controlled clinical trial of donepezil 23 mg/day, over 18% of participants

discontinued the medication due to GI side-effects (nausea, vomiting, diarrhea) and dizziness compared to 7.9% of participants receiving the 10 mg/day dose [19]. The majority of participants who discontinued the medication did so within the first month of beginning treatment with the 23 mg/day dose of donepezil.

A 12-week multi-center, randomized trial was completed to determine whether dose-titration method had an effect on donepezil safety and tolerability, particularly within the first four weeks of treatment [42]. Two distinct titration methods were compared to a direct escalation method (with no titration) to the 23 mg/day dosing of donepezil. The participants in the 2 titration method were titrated to dose of 23mg /day in 4 weeks (group 1 received 15mg for 4weeks and then increased to 23mg, whereas group 2 received the 10mg and 23mg on alternate days for 4weeks before increasing to 23mg). Participants in the direct escalation group with no titration had significantly increased incidences of dizziness and nausea, when compared to the titration groups. The authors of the study conclude that titration to the 23 mg/day dose, particularly within the first four weeks of treatment, may be helpful in improving safety and tolerability of the drug. And although not statistically significant, the second titration method (alternating between 10 and 23 mg/day pills for 4 weeks) had the highest dropout rates due to AEs. In general however, donepezil is well tolerated due to its selectivity for central inhibition of acetylcholinesterase and its limited interaction with other drugs [30].

3.3. Cardiovascular safety

Reported cardiac effects constitute rare but serious AEs following donepezil administration. Cholinergic innervation to pacemaker cells of the heart results in vagotonic effects- and bradycardia and heart block are cited as potential AEs following donepezil use [19]. First degree AV block was infrequently observed in 0.1-1 % of patients during the AD trials [19]. Although physicians are encouraged to exercise caution with patients who have known arrhythmias or who are on medications that reduce heart rate (beta-blockers, nondihydropyridine calcium channel blockers) prior to initiating donepezil, large trials have failed to show any increase in cardiac AEs in patients taking said medications concomitantly with donepezil [24].

Other cardiac conduction abnormalities have also been infrequently observed following donepezil administration. Case reports illustrate examples of potential adverse cardiac effects which can occur with donepezil dosing. Tanaka, Koga and Hiramatsu (2009) describe the findings of bradycardia and QTc prolongation in two elderly patients receiving routine dosing of donepezil, with these cardiac findings correcting after discontinuation of the drug. Case reports of QTc prolongation have also been described in the setting of donepezil overdose in an elderly patient [27] and with routine dosing in a 26-year-old patient post-TBI [26]. To determine the extent of donepezil's cardiac effects, a study [25] of 52 participants with AD evaluated their baseline ECG parameters and blood pressure and then reevaluated these parameters at each donepezil dose adjustment (5 and 10 mg) (Table 1). This small study concluded that donepezil had no major arrhythmogenic, hypotensive, or negative chronotropic effects.

3.4. Disease-modifying effects of donepezil

The current FDA-approved treatment options for Alzheimer's disease are considered symptomatic therapies. There are no disease-modifying drugs currently shown to help stop the underlying pathogenesis of AD [34]. Various studies of donepezil have shown some promising, potential disease-modifying effects of the drug compared to placebo. Donepezil's potential disease-modifying effects are highlighted in (Table 2). A 2014 randomized control trial of 216 subjects with mild cognitive impairment (MCI) used magnetic resonance imaging to determine whether donepezil 10 mg/day slowed the rate of hippocampal atrophy after one year compared to placebo [35]. The rate of hippocampal atrophy was significantly reduced in the donepezil treatment group (annual percentage change = -1.89%) compared to placebo (-3.47; $p < 0.001$). Despite this structural benefit, there were no significant differences between treatment groups on neuropsychological test outcomes.

A larger study of 769 subjects with MCI showed no effect of either donepezil 10 mg/day or vitamin E supplementation (2000 IU QD) on the progression to AD over the course of three years [36]. In this study, donepezil seemed to have an effect of slowing cognitive decline in the first 6 to 18 months, but thereafter cognitive function declined at the same rate as placebo (Table 2). The study also examined donepezil's benefit in

individuals who were carriers of APOE □4 alleles- the presence of which is predictive of progression to AD in patients with MCI. In these individuals, donepezil had a significant effect of reducing the risk of AD progression after three years.□

Combination disease-modifying therapies are another AD treatment option being studied. A selection of these combination therapies can be found in (Table 2). These therapies target the amyloid, tau, and inflammation pathways that are involved in the development of AD [37]. 5-HT_6 antagonists, idalopirdine and intepirdine, have been studied as adjunct AD treatment options when combined with donepezil. Phase 2 trials and animal models have suggested that these drugs may improve cognition in AD [38]. In a 2018 study, three randomized clinical trials with a combined 2,525 patients were evaluated to determine whether the addition of idalopirdine (10, 30, or 60 mg/day) to ChEI therapy improved cognition after 24 weeks. Cognitive performance, as measured by the Alzheimer's Disease Assessment Scale (ADAS-Cog), was not significantly different between groups compared to placebo. Results of the phase 3 MINDSET study of intepirdine 35 mg/day addition to ChEI therapy had similar discouraging outcomes. The addition of intepirdine did not improve cognitive or functional outcomes in AD patients after 24 weeks [39].□

New disease-modifying additive therapies continue to be explored (Table 2). The effects of the anti-seizure medication, levetiracetam, is being studied in a phase II clinical trial of 36 participants who are stable on their current AD treatment medication (donepezil, galantamine, rivastigmine or memantine) [40]. The study is estimated to be completed in December of 2019. Another phase II RCT anticipated to be complete in November of 2020 is evaluating the added benefits of Riluzole to current AD therapies [41]. Riluzole is a glutamate modulator which is hypothesized to have positive effects on the glutamate-mediated excitotoxicity involved in AD pathogenesis.□ Forty eight individuals with mild AD who have received at least two months of ChEI therapy will be included in the trial. These studies represent an important shift in the treatment direction of AD; combination therapies are being utilized to treat multiple pathways involved in AD onset and progression.

4.0. Rivastigmine

Oral rivastigmine (Exelon-Novartis Pharmaceuticals Corporation) was FDA-approved in 2000 for the treatment of mild-to-moderate Alzheimer dementia and later (2006) for the treatment of mild-moderate Parkinson's dementia, with an optimal therapeutic dose of 6-12mg/day[43]. At the time, it was only available as a capsule (1.5mg, 3mg, 4.5mg, and 6mg doses) and as an oral solution (2mg/mL). A transdermal patch formulation was introduced in 2007[44].

Rivastigmine is a slowly-reversible dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)[45]. The involvement of the latter in subcortical structures associated with executive tasks and concentration suggests a potential added benefit of dual inhibition[46]. Rivastigmine also remains unmetabolized by the CYP-450 system, reducing the potential for drug-drug interactions[47, 48]. Donepezil, on the other hand, is selective for only AChE inhibition and is metabolized by CYP-450. But despite these benefits of rivastigmine, in its oral form, it has been associated with the highest rate of adverse events and poorer outcome on all-cause discontinuation when compared with other cholinesterase inhibitors[22, 49-51].

Focus has shifted away from rivastigmine as a disease-modifying therapy for Alzheimer's disease (AD), being used as a symptomatic treatment[52]. However, there may be a suggested neuroprotective effect as rivastigmine has been shown to alter the ratio of AChE-R and -S isoforms and increase nicotinic receptor expression, which are associated with improved cognition in AD patients[53]. Also, secondary analyses of the InDDEx study, which initially failed to demonstrate a benefit of rivastigmine from preventing the progression of mild cognitive impairment to AD, found a significant difference after controlling for age, education, and baseline cognitive function[54, 55]. This effect was especially prominent in women with the BChE wild-type genotype[56, 57]. Regardless, the outcomes from randomized controlled trials have not proven a disease-modifying effect[58].

4.1. Safety of rivastigmine capsule

In terms of gastrointestinal side effects, a meta-analysis showed rivastigmine at doses of 1-4mg/day and 6-12mg/day was associated with higher rates of nausea, vomiting, diarrhea, weight loss, anorexia, and decreased appetite when compared to placebo[59]. These side effects may be due to increased cholinergic neurotransmission

from the drug's dual cholinesterase inhibition, as well as direct stimulation of muscarinic receptors of the chemoreceptor trigger zone of the area postrema[60]. Moreover, adverse symptoms of rivastigmine tend to be more common during the titration phase of treatment and decrease with the maintenance phase[43, 46]. To reduce side effects, rivastigmine should be slowly titrated and taken with food, particularly a fatty meal, which would delay absorption from the gut (prolonging t_{max}) and reduce fluctuations in plasma concentration associated with adverse events[61]. If the medication is stopped for more than 3 days, the titration phase should be restarted at the lowest dose to prevent severe vomiting that could lead to Boerhaave's syndrome[44]. In 2000, a case report was published describing spontaneous esophageal rupture in a female with AD treated with rivastigmine[62]. She accidentally reinitiated treatment with an oral 4.5mg dose, and was found to have a distal esophageal rupture. Following the event, the package insert was amended to include warning of esophageal rupture.□□□□□

Aside from GI symptoms, patients taking high-dose rivastigmine (6-12mg/day) also have a statistically significant increase in headaches, dizziness, abdominal pain, and syncope when compared to placebo[43, 44]. However, rivastigmine has not been linked to hepatotoxicity[59]. In addition, it is not associated with adverse effects on cardiac function, such as changes in heart rate, arrhythmia, and ECG measures (PR, QRS, and QTc intervals), unlike donepezil and galantamine[63-65]. These findings may be explained by rivastigmine's specificity for the central nervous system, which would cause fewer peripheral side effects pertaining to the heart[66]. It is worth noting there is a case report from 2010 suggesting a potential interaction between rivastigmine and beta-blockers leading to syncope and bradycardia[67]. Furthermore, use of rivastigmine is still cautioned in patients with sick sinus syndrome or other supraventricular conduction defects due to the drug's theoretical effect on heart rate, as it increases cholinergic activity[44].

4.2. Safety of rivastigmine transdermal patch

The development of a 24-hour transdermal rivastigmine patch provided for improved tolerability, particularly with GI symptoms, as it decreases the maximum concentration (C_{max}) and fluctuations in plasma concentrations by gradually releasing the drug over a 24 hour period[68, 69]. The patch is available in 4.6mg, 9.5mg, and

13.3mg/24hr doses[70]. By limiting C_{max} and bypassing first-pass metabolism, the transdermal patch has allowed patients to tolerate larger, more efficacious doses of rivastigmine as opposed to oral formulations[61, 71, 72]. The 13.3mg/24hr patch demonstrated greater efficacy without markedly increased side effects and was approved for the treatment of severe AD[73]. Aside from its effectiveness, the patch formulation also offers a practical benefit of being a simple, convenient, once-daily application on the skin, which is especially useful in patient populations with difficulty swallowing or high pill burdens.

The Investigation of transDermal Exelon in ALzheimer's disease (IDEAL) study was a 6 month, double-blind study that compared the $10cm^2$ rivastigmine patch (9.5mg/24hours), $20cm^2$ rivastigmine patch (17.4mg/24hrs), and 6mg BID rivastigmine capsules with placebo in 1,195 patients with mild-moderate AD[74]. The study found that, although the $10cm^2$ patch had similar efficacy to the capsules, there were two-thirds fewer incidences of nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%), with no significant difference from placebo (5.0% and 3.3% for nausea and vomiting, respectively). Weight loss, defined as a decrease equal to or greater than 7% of baseline weight, was seen in 8% of patients treated with the $10cm^2$ patch, 12% of those who received the $20cm^2$ patch, 11% of those who received the capsules, and 6% of those in the placebo group. While not commercially available, the $20cm^2$ patch produced cognitive scores superior to the $10cm^2$ patch with a tolerability profile similar to that of capsules.

The transdermal patch formulation of rivastigmine can additionally result in dermatologic adverse events, which usually present as mild, localized erythema and/or pruritus that resolves within 48 hours[68]. This can be managed symptomatically with topical ointments and by alternating application sites. Less commonly, patients can develop allergic contact dermatitis, which appears more than 24 hours after patch removal. The IDEAL study (including a 28 week open-label period following the 24 week double-blind randomized phase) demonstrated good tolerability with the $10cm^2$ patch, as more than 90% of patients had no reaction or mild skin reactions and only 2% of cases required treatment discontinuation[74]. Similar results were found in the ACTivities of daily living and cognitION (ACTION) randomized trial and the open-label

and randomized periods of the OPtimising Transdermal Exelon In Mild-to-moderate AD (OPTIMA) trial, in which treatment was discontinued in about 2% of patients and fewer than one-quarter of each dosing group presented with mild, non-immunological skin lesions[73, 75].

When compared to other ChEIs, rivastigmine actually has a disproportionately higher frequency of death outcomes[76]. This is mostly due to the improper application of a new rivastigmine patch without removing the prior one, especially when it involves the initial loading dose patch[68]. Patch toxicity can present with nausea, vomiting, hypersalivation, miosis, fasciculations, and severe bradycardia that could potentially lead to sudden cardiac death. Caregivers should be educated on proper application of the transdermal patch, how to manage minor side effects, and when discontinuation is appropriate. The above findings have been summarized in Table 3.

5.0. Galantamine

Galantamine is a selective reversible inhibitor of acetylcholinesterase (AChE) that was first introduced to the United States as a treatment for Alzheimer's disease (AD) in 2000 under the trade name Razadyne® (Janssen Pharmaceuticals)[77]. It is available only in oral forms with a recommended starting dose of 8mg/day, increasing to a maintenance dose of 16mg/day after 4 weeks[78]. The drug reversibly and competitively inhibits acetylcholinesterase which, in turn, increases ACh activity at the level of the synapse and improves cholinergic tone[77-78]. Due to its innate ability to cross the blood-brain-barrier, users of the drug experience increased central cholinergic tone[79]. In addition to its inhibitory activity regarding AChE, Galantamine is also an allosteric modulator of nicotinic acetylcholine receptors (nAChR's), increasing the expression and activity of these receptors in central cholinergic neurotransmission[80]. This effect partially restores the impairments in the septo-hippocampal cholinergic system commonly seen in patients with AD[81]. When utilized in the treatment of AD, patients receiving the drug have been observed to have improved cognitive function following chronic administration and significant delay in the development of behavioral changes associated with the disease[82-83]. In oral form, Galantamine is available in immediate release (IR) and extended release (ER) forms, which require twice daily and

once daily doses, respectively. The ER form was developed to improve medication adherence and limit adverse effects associated with the IR; rate of discontinuation of the IR form was non-significantly increased compared to the ER form in a randomized controlled trial although safety profiles of the two forms were comparable [84]. Thus, the ER form of Galantamine may improve medication adherence with a similar safety profile and efficacy as the IR form. The recommended initial dose for IR Galantamine is 4mg PO q12hr and recommended maintenance dose is 8-12mg PO qhr. For the ER version, the recommended initial dose is 8mg PO qAM and recommended maintenance doses of Galantamine are 16 and 24mg qAM. Galantamine is metabolized primarily in the liver by the hepatic CYP 450 isoenzymes, namely CYP 2D6/3A4 and is associated with a low risk for drug-drug interactions due to its metabolism through several pathways[78].

According to a study in which the mean daily dose of Galantamine was 15.01 +/- 4.76mg, the discontinuation rate of the drug was approximately 20% at 12 weeks, 40% at 48 weeks, and 46.73% after 72 weeks. Reasons for discontinuation included safety problems (31.08%), transfer to another hospital (24.32%), loss of contact (19.93%), personal choice (11.15%), and other reasons (13.51%)[86]. This study, along with several others, used the MMSE (mini mental state examination) as a measure of cognitive function, administered at baseline and at 4, 12, 24, 36, 48, 60, and 72 week treatment timepoints[86]. Evaluation of MMSE at these various timepoints revealed significant improvement (versus predicted outcome) in >70% of patients following administration of galantamine (at the recommended dosages). In addition to the MMSE evaluation, CGI-I scoring (Clinical global impression improvement scale), a system developed to evaluate the clinical state of patients, revealed an 80% improvement in those prescribed gGalantamine.

5.1. Safety of Galantamine

The most frequently encountered adverse effects of Galantamine are those associated with the cholinesterase inhibitor class as a whole, namely GI symptoms[84]. These side effects more often include nausea, vomiting, and diarrhea and less frequently include anorexia and weight loss[68]. Other associated side effects include cardiovascular symptoms such as bradycardia and neuropsychiatric symptoms

including dizziness, confusion, extrapyramidal symptoms, and sleep disturbances. While serious side effects can be observed, most adverse effects following Galantamine administration have been described as mild to moderate in severity[68,84]. In a multicenter, randomized, controlled trial in Europe and Canada that investigated the efficacy and safety of Galantamine early on, at least 5% more patients in the Galantamine group compared to the placebo group reported nausea, vomiting, diarrhea, dizziness, headache, anorexia, and weight loss, with nausea being the most commonly reported[85]. Most patients rated their nausea as mild to moderate in severity and the median duration of the nausea was 6 days for the 24mg dose group and five days for the 32mg dose group. Additionally, the events in the study more commonly associated with discontinuation were nausea and vomiting, with nausea as the reason for discontinuation among 10% (42/438) of patients taking Galantamine and vomiting as the reason for discontinuation of Galantamine treatment among 5% (24/438) of patients. Most adverse effects associated with Galantamine occurred in the higher dose group (32mg) and during dose escalation periods, with over half of the patients who discontinued Galantamine treatment due to adverse events (43/79) discontinuing during the dose escalation phase of the study[85]. It is possible that beginning on a lower dose and slowly increasing the dose could reduce adverse effects. In another study investigating the long-term safety of Galantamine in the treatment of 642 patients with AD, at least one adverse effect was reported in 28.5% of patients and at least one serious adverse effect occurred in 8.41% of patients[86]. The most frequently reported adverse effects in the study included nausea (5.30%), decreased appetite (3.43%), vomiting (2.49%), insomnia (1.40%), agitation (1.09%), dizziness (1.09%), and headache (1.09%). The most common significant adverse events were delusions (0.62%) and serious cardiovascular effects (0.78%). Due to these rare events, concerns regarding safety and tolerability of Galantamine may be a limitation of its use in older adults with polypharmacy.

Overall, routine Galantamine administration has been found to be safe and effective for long-term treatment in patients with mild-to-moderate AD[87-88]. Meta-analysis has also indicated that it may be a safe drug in elderly patients with severe cognitive defects and deemed the medication the most effective among available AChE

inhibitors in the treatment of AD[89]. In addition to these studies, the largest prospective, randomized, placebo controlled, 2-year multicenter study investigating a cholinesterase inhibitor used in the treatment of mild to moderate AD was the first to establish a lower mortality rate associated with Galantamine as compared to the placebo[90]. Galantamine has the potential to be first line in the long-term treatment of AD due to its demonstrated safety and efficacy, favorable pharmacokinetics, and high tolerability. The findings discussed above have been summarized in Table 4.

6.0. Conclusion

Major Neurocognitive Disorders (formerly Dementias) are characterized by a decline in cognition limiting the patient's day-to-day social and/or occupational function. AD is the most common cause of Major Neurocognitive Disorders. Due to its growing world-wide prevalence, AD is a significant cause of disability, mortality and caregiver burden . The cholinergic hypothesis suggests that atrophy and loss of cholinergic neurons especially in the nucleus basalis of Meynert is the hallmark of the pathophysiology of AD and results in cognitive and functional symptoms. Consequently pharmacotherapy, namely the use of ChEIs to increase cholinergic neuro-transmission, is currently the mainstay in the symptomatic treatment of AD.

The currently available ChEIs are in the same family of compounds, but are unique from one another. They differ subtly in their mechanisms of action, in their tolerability and safety and FDA- approved indications.. All are considered first-line, symptomatic treatments of the various phases of AD and may even have potentially disease-modifying effects. There are no significant contraindications for any of them, but if there is a concern for drug-drug interaction, then Rivastigmine can be preferred as it is not metabolized by the Cyp 450.

7.0. Expert opinion

As the evidence continues to grow regarding the multifactorial pathophysiology of AD, much research is being done targeting in particular the amyloid / neuritic plaque and the neurofibrillary tangles. Other treatment approaches focus on possible contributors to neuronal death in AD such as oxidative stress and free radical toxicity as

well as neuro-inflammation caused by alterations in the microbiome. Defect in the brain's glymphatic system in AD is another possible contributor. Though these approaches have disease-modifying potential, the cholinesterase inhibitors may continue to be useful in addition to these agents.

Combination therapies may be the wave of the future, but for now, the cholinesterase inhibitors, especially if introduced early in the course of the disease (AD) have proven benefits (in cognition, activities of daily living, behavior, and decreased caregiver strain), a generally benign side-effect profile and affordability, leading to their continued use as first-line treatments.

There is also evidence of a significant cholinergic deficit in the Lewy Body Spectrum disorders, from Major Neurocognitive Disorder (MNCD) Lewy- Body Type to MNCD Parkinson's Type, hence the use of cholinesterase inhibitors off-label is attractive is these disorders too.

Even in Vascular dementia there is some degree of decreased cholinergic neurotransmission, hence the potential value of cholinesterase inhibitors.

Growing evidence shows that the cholinesterase inhibitors may have modest disease-modifying effects. When they are combined with other disease-modifying drugs in the pipeline, they may even provide more robust benefits.

The cholinesterase inhibitors, if given early in the course of AD and continued throughout the course of the disease may decrease the risk of the evolution of problem behaviors later in the disease.

Whether the cholinesterase inhibitors provide benefits in Mild Neurocognitive Disorder (MCI) is controversial. They don't seem to delay or prevent conversion to AD, but may still proffer symptomatic benefits.

Giving cholinesterase inhibitors to individuals at-risk for AD, years before they develop symptoms is an interesting question which has yet to be investigated.

Also not known is whether giving higher than currently FDA-approved doses of the cholinesterase inhibitors may confer more benefits, especially if we can improve tolerability by treating/preventing gastrointestinal side-effects.

Demanding further exploration are the unique properties of some cholinesterase inhibitors , e.g. dual inhibition (acetyl and butyryl cholinesterase) and

nicotinic receptor agonism. Would a cholinesterase inhibitor with nicotinic receptor modulating effects be better for apathetic AD patients? Is a butyryl cholinesterase inhibitor preferred for later stages of AD when levels of butyryl cholinesterase rise? These are some areas for further research.

Combining two cholinesterase inhibitors with complementary but different profiles has also not been investigated, probably due to concern about amplified side-effects. Developing novel modes of delivery may help to allay concerns about side-effects, particularly the gastrointestinal

With the failure of current therapies for AD in the pipeline, the cholinesterase inhibitors are becoming more attractive as first line treatments for AD and other Major Neurocognitive Disorders. These are interesting compounds which are attractive for their symptomatic benefits, safety and tolerability as well as research and disease-modifying potential.

Along with pharmacotherapies such as the cholinesterase inhibitors, a holistic approach to AD treatment involves stressing non-pharmacological approaches which promote a healthy brain in a healthy body. Lifestyle modification including regular physical and mental exercise, social activity, restful sleep, promotion of mindfulness and spirituality, a healthy diet (such as the Mediterranean diet), smoking cessation, optimal control of cardiovascular risk-factors such as obesity, hypertension, hyperglycemia and hyperlipidemia are also useful in slowing AD progression and perhaps even as disease-modifying/preventative strategies.

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Table 1 -Adverse and Neurocognitive Effects of Donepezil

Authors on Study	**Type of Study**	**Number of Patients in Study**	**Summary of Findings**
Adlimoghaddam et al, 2018[31]	Systematic review	2,272 (combined across studies examined)	Donepezil was found to benefit patients cognition and global functioning. The most consistent improvement was in severe impairment battery (SIB) scores. However, more patients treated with high dose donepezil discontinued their treatment due to various adverse events (AEs).
Farlow et al, 2010[30]	RCT	1,371	Patients with moderate to severe AD, donepezil 23 mg/d was associated with greater benefits in cognition compared with donepezil 10 mg/d. The between treatment difference in global functioning was not significant in the overall population.

Hong et al, 2019[43]	RCT	110	Dose titration before escalating to donepezil 23 mg/day showed better safety in terms of cholinergic AEs.
Isik et al, 2012[26]	Prospective interventional study	52	The ECG parameters including heart rate, PR, QT, QTc interval and QRS duration and postural blood pressure changes were recorded at baseline and at each donepezil dose level (5 and 10 mg/d). No significant differences were noted following treatment as compared to baseline.
Jin et al, 2019[33]	Systematic review, meta-analysis	44,873 (combined across studies examined)	Compared to placebo, donepezil had more efficacious outcomes on the Neuropsychiatric Inventory (NPI) and had a higher risk of AEs.

Kim et al, 2011[34]	Systematic review, meta-analysis	Pooled data on ChEIs from 40 studies/RCTs	Cholinesterase inhibitors may increase the risk of syncope, with no effects on falls, fracture, and accidental injury in cognitively impaired older adults.

RCT=Randomized Controlled Trial

Table 2-Disease-Modifying Studies:

Authors on Study	**Type of Study**	**Number of Patients in Study**	**Summary of Findings**
Atri et al, 2018[39]	3 RCTs	2,525	In patients with mild to moderate AD, the use of idalopirdine compared with placebo did not improve cognition over 24 weeks of treatment. These findings do not support the use of idalopirdine for the treatment of AD.

Clinical trial: NCT02002819 [41]	Phase II RCT	36	Study completion date: December 2019
Clinical trial: NCT01703117 [42]	Phase II RCT	48	Study completion date: November 2020
Dubois et al, 2014[36]	RCT	216	A 45% reduction of the rate of hippocampal atrophy was observed in prodromal AD following 1 year of treatment with donepezil compared with placebo
MINDSET: Axovant Sciences Inc. [40]	Phase III RCT	1,315	At 24 weeks, patients treated with 35 mg of intepirdine did not experience improvement in cognition or in measures of activities of daily living as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and by the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), respectively, compared to patients treated with placebo.

Peterson et al, 2005[37]	RCT	769	There were no significant differences in the probability of progression to Alzheimer's disease between either vitamin E or the donepezil group and the placebo group.

Table 3- Adverse Effects of Oral and Transdermal Rivastigmine

Authors on Study	**Type of Study**	**Number of Patients in Study**	**Summary of Findings**
Blanco-Silvente et al, 2017 (23)	Systematic review, meta-analysis	16,106 (combined across 43 studies/RCTs examined)	Rivastigmine, oral, had a worse outcome on all-cause discontinuation than donepezil and galantamine.

Hansen et al, 2008 (50)	Systematic review, meta-analysis	Pooled data on ChEIs from 26 studies/RCTs	When compared to donepezil, patients treated with oral rivastigmine demonstrated higher withdrawal rates and a greater incidence of AEs, including nausea, vomiting, dizziness, and weight loss.
Feldman et al, 2007 (55)	RCT	1,018	Patients treated with oral rivastigmine showed no significant difference in the progression rate to AD over 4 years when compared to placebo.
Isik et al, 2014 (64)	Retrospective comparative study (no control group)	85	The ECG parameters including heart rate, PR, QT, QTc interval and QRS duration were recorded at baseline in patients treated with either rivastigmine formulation (12mg/d oral dose and 10cm^2/d transdermal patch). Neither rivastigmine formulation was associated with arrhythmogenic effects when compared to baseline. There was no significant difference in mean change from baseline measurements between the two groups except for heart rate.
Lefevre et al, 2008 (73)	RCT	30	Fewer GI-related AEs were seen with 9.5mg/24h rivastigmine patch than 3mg oral dose.

Farlow et al, 2013 (74)	RCT	716	The 13.3mg/24h rivastigmine patch demonstrated superior improvements over 4.6mg/24h patch in Severe Impairment Battery (SIB) and AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV) scores, without a significant increase in AEs.
Winblad et al, 2007 (75)	RCT	1,195	When compared to 6mg BID oral rivastigmine, the 10cm^2 patch (9.5mg/24h) produced 2/3rds fewer reports of nausea and vomiting while showing similar efficacy. The 20cm^2 patch (17.4mg/24h) demonstrated superior efficacy with similar tolerability to oral formulation. Fewer than ¼ of each patch treatment group developed skin reactions.
Alva et al, 2015 (76)	RCT	567	Patients treated with 15cm^2 rivastigmine patch (13.3mg/24h) had an increased incidence of AEs than 10cm^2 patch (9.5mg/24h). Every treatment group reported higher incidences of each AE type during weeks 0-24 than weeks 24-28 of the

			double blind period.
Ali et al, 2015 (77)	Retrospective database analysis	12,124	Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) and the Canada Vigilance Adverse Reaction Database (CVARD) showed a significantly higher frequency of death as an AE of rivastigmine than donepezil and galantamine.

Table 4- Galantamine Safety & Efficacy Studies

Authors on Study	**Type of Study**	**Number of Patients in Study**	**Summary of Findings**

Wilcock, 2000 [88]	Randomized, double-blind, parallel group, placebo-controlled trial	653 participants	Galantamine demonstrated tolerability and efficacy when used to treat patients with mild to moderate AD
Lilienfeld, 2002[84]	Multicenter Trial	Four large, randomized, double-blind placebo-controlled trials	Galantamine has the potential to become a first-line therapy for the treatment of dementia
Pirttila et al, 2004 [89]	Multicenter Trial	491 participants	Galantamine at a dose of 24mg/day is safe and effective in the long-term treatment of mild to moderate AD
Aronson et al, 2009[93]	Post-Hoc Analysis of double-blind, placebo-controlled trial	838 participants	The optimal dosage of Galantamine in patients with mild AD is 16mg/day; Patients with moderate AD gain additional benefit with 24 mg/day

Richarz et al, 2014[90]	Prospective Open-Label Trial	75 participants	Galantamine was safe and well-tolerated in the treatment of mild AD over a 3 year period; Cognition, behavior, and activities of daily living improved during 12 months of treatment and cognition remained improved at 3 year follow-up
Hager et al, 2014[92]	Multicenter randomized placebo-controlled study	2,045 participants	Long term treatment with Galantamine significantly reduced mortality and decline in cognition and activities of daily living in patients with mild to moderate AD
Mucke, 2015[78]	Review article	Multiple studies with varying numbers of participants	Potential for Galantamine has not nearly been exhausted
Nakagawa et al, 2017[86]	Observational study in clinical setting	661 participants	Study findings support long-term efficacy and safety of Galantamine in the maintenance of cognitive function and clinical state in AD patients

Mohammad et al, 2017[85]	Review Article	Multiple studies with varying numbers of participants	Similar safety profiles to other ChE's analyzed
Li et al, 2019[91]	Meta-analysis	36 studies with varying numbers of participants	Galantamine is effective in treating all aspects of AD and is first choice treatment; Additional data is necessary to monitor long-term effects