Current Alzheimer Research, 2018, *15*, 964-974

REVIEW ARTICLE

Strategies for Continued Successful Treatment in Patients with Alzheimer's Disease: An Overview of Switching Between Pharmacological Agents

Rafael Blesa[1], Kazuhiro Toriyama[2,*], Kengo Ueda[2], Sean Knox[3] and George Grossberg[4]

[1]*Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain;* [2]*Novartis Pharma K.K., Tokyo, Japan;* [3]*Novartis Pharma AG, Basel, Switzerland;* [4]*Department of Psychiatry & Behavioral Neuroscience, Saint Louis University School of Medicine, St. Louis, MO, USA*

ARTICLE HISTORY

Received: February 21, 2018
Revised: May 11, 2018
Accepted: June 07, 2018

DOI:
10.2174/1567205015666180613112040

Abstract: ***Introduction:*** Alzheimer's disease (AD) is the most common cause of dementia, characterized by a progressive decline in cognition and function. Current treatment options for AD include the cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine, as well as the N-methyl-D-aspartate receptor antagonist memantine. Treatment guidelines recommend the use of ChEIs as the standard of care first-line therapy. Several randomized clinical studies have demonstrated the benefits of ChEIs on cognition, global function, behavior and activities of daily living. However, patients may fail to achieve sustained clinical benefits from ChEIs due to lack/loss of efficacy and/or safety, tolerability issues, and poor adherence to the treatment. The purpose of this review is to explore the strategies for continued successful treatment in patients with AD.

Methods: Literature search was performed for articles published in PubMed and MEDLINE, using prespecified search terms. Articles were critically evaluated for inclusion based on their titles, abstracts, and full text of the publication.

Results and Conclusion: The findings of this review indicate that dose up-titration and switching between ChEIs may help to improve response to ChEI treatment and also address issues such as lack/loss of efficacy or safety/tolerability in patients with AD. However, well-designed studies are needed to provide robust evidence.

Keywords: Alzheimer's disease, switching, AD treatment, cholinesterase inhibitors, dementia, adherence.

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that is often associated with aging [1]. AD is the most prevalent cause of dementia and is characterized by progressive decline in cognition and global function, thereby affecting activities of daily living (ADL) [2, 3].

Management of AD continues to remain a challenge for both patients and their caregivers given that the available pharmacological treatment options are only able to provide symptomatic relief. Tacrine, a potent cholinesterase inhibitor (ChEI), was the first drug approved for the treatment of AD. However, its use was discontinued due to a poor safety profile, particularly hepatotoxicity [4]. Currently, the mainstay of treatment approved worldwide for AD includes ChEIs (*e.g.* donepezil, galantamine, and rivastigmine) and an N-methyl-D-aspartate receptor antagonist (memantine). In addition, many new symptomatic treatment options are under development [5].

Besides symptomatic treatments, many disease-modifying therapies (DMTs) which aim to halt or reverse disease progression, are under extensive research. These DMTs aim to prevent Aβ aggregation, promote Aβ clearance, or target Tau phosphorylation, which are considered the pathogenic mechanisms leading to neuronal death. To date, all Phase III studies evaluating the efficacy of the available DMTs have failed. It may be some time before the first DMT shows proven clinical efficacy and becomes available as an approved treatment. Until the emergence of new therapies (including new symptomatic drugs), the mainstay for AD treatment is limited to the currently available drugs which may slow the progression of symptoms. Even after the emergence of DMTs, symptomatic therapies may still be a viable treatment option for patients with AD experiencing disease progression, therefore the argument could be made

*Address correspondence to this author at the Novartis Pharma K.K., Toranomon Hills Mori Tower, 23-1, Toranomon 1-chome, Minato-ku, Tokyo 105-6333, Japan; Tel: +818093454478;
E-mail: kazuhiro.toriyama@novartis.com

1875-5828/18 $58.00+.00

that it becomes imperative that these drugs must be used as optimally as possible to maximize the potential clinical outcomes in patients with AD [6].

In this review, we discuss the available therapeutic options for symptomatic treatment of AD, focusing on dose up-titration and switching among approved treatment options for optimal treatment outcomes. In addition, we have attempted to discuss the rationale of within-class switching based on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs and patient-related factors.

2. METHODS

A literature search was performed for articles in the English language on AD, published in PubMed and MEDLINE, using the search terms "Alzheimer's disease/Alzheimer's dementia", "cholinesterase inhibitors", "donepezil", "galantamine", "rivastigmine", "switch", "clinical", "efficacy", and "safety" (cut-off date: January 2017). All the studies retrieved from this search were critically evaluated for inclusion based on their titles, abstracts, and full text of the publications.

3. APPROVED TREATMENT OPTIONS FOR AD

3.1. ChEIs

Donepezil is indicated for the treatment of all stages of AD in the United States and Japan, and for mild-to-moderately severe AD in Europe [7-10].

Galantamine is indicated for the treatment of mild-to-moderate dementia of the Alzheimer's type in the US and Japan, and for mild-to-moderately severe dementia of the Alzheimer's type in Europe [11-13].

Rivastigmine is available as a transdermal patch and as an oral formulation [14-17]. Oral rivastigmine is approved in the US for the treatment of mild-to-moderate dementia of the Alzheimer's type, and in Europe for mild-to-moderately severe Alzheimer's dementia [14, 16]. The rivastigmine patch is approved in the US across all stages of AD, in Europe for the treatment of mild-to-moderately severe AD, and in Japan for mild-to-moderate AD [15, 17-19].

3.2. N-methyl-D-aspartate Receptor Antagonists (Memantine)

Memantine is approved for the treatment of moderate-to-severe dementia of the Alzheimer's type in the US, Europe and Japan [20-22].

The approved treatment options for AD have been described in detail in Table **1**.

4. INITIATION OF TREATMENT WITH ChEIs

Guidelines by the European Federation of Neurological Societies (EFNS) and National Institute for Health and Excellence (NICE) recommend ChEIs as the standard of care for AD. They recommend treatment initiation at a lower dose, with gradual up-titration to higher approved doses for optimal treatment outcomes. Patients can be switched to other ChEIs based on the adverse event (AE) profile, adherence, possibility of drug interactions, and dosing profiles [23, 24]. Similarly, guidelines developed at the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia recommend treatment with ChEIs for patients with mild-to-severe AD (grade 1A) [25]. Moreover, guidelines in Japan recommend the use of ChEIs as the initial treatment for AD; switching is preferred among the ChEIs in case of intolerability and/or lack of efficacy [26].

5. DOSE UP-TITRATION

To maximize the therapeutic benefit of treatment with ChEIs, there is growing scientific evidence that the treatment dose should be up-titrated and tailored to individual patients' needs based on their disease stage and other clinical characteristics [27]. ChEIs have been reported to show significant benefits on cognitive, global, functional, and behavioral outcomes in a dose-dependent manner in clinical studies [27-31].

The ACTION (ACTivities of daily living and cognitION in Patients with Severe Dementia of the Alzheimer's Type) study (N=716) was a 24-week, randomized, double-blind study that compared the efficacy, safety, and tolerability of rivastigmine patches (13.3 mg/24h and 4.6 mg/24h) in patients with severe AD. The high-dose patch demonstrated significantly less decline in overall cognition ($p<0.0001$) and function ($p=0.025$) as compared with the 4.6 mg/24h patch [32]. In a 24-week, open-label extension of the ACTION study (N=397), there were no clinically relevant differences in safety and tolerability between patients who were up-titrated from the 4.6 mg/24h rivastigmine patch to receive the 13.3 mg/24h patch, and patients who continued on the 13.3 mg/24h patch. However, a greater decline was observed in patients with delayed up-titration to the high-dose 13.3 mg/24h patch compared to patients who continued on the high-dose patch from the double-blind phase to the extension phase [33]. This indicates the importance of early and sustained intervention with the high-dose patch to achieve maximum clinical benefit. In another 24-week, double-blind study, Japanese patients (N=859) were randomized to receive either the 4.6 mg/24h or 9.5 mg/24h rivastigmine patch or placebo. Patients receiving the 9.5 mg/24h patch reported delayed deterioration on the Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-J cog; $p=0.005$) and the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC plus-J; $p=0.067$) [19]. Furthermore, in a global Phase III study conducted in patients with moderate-to-severe AD (N=1467), patients receiving donepezil 23 mg/day showed significantly greater cognitive benefits, as assessed by the Severe Impairment Battery (SIB) score, compared to patients who continued treatment with donepezil 10 mg/day ($p<0.001$) [28, 34]. Another study conducted in 61 Japanese patients reported no statistically significant difference in cognitive decline at any time after starting donepezil 10 mg/day [35]. These observations clearly highlight the dose-dependent efficacy of ChEIs. Therefore, it is suggested to maintain ChEI therapy on a higher dose, as long as it is tolerable, as it may provide a greater chance of slowing/delaying symptomatic disease progression [36].

Table 1. Approved treatment options for Alzheimer's disease.

Compound	Geographical area	Approved indication	Titration scheme	Additional remarks (if any)
Donepezil[a]	US	All stages of AD	5 mg/day for 4-6 weeks -->10 mg/day for at least 3 months--> 23 mg/day	A 23 mg sustained-release tablet formulation is approved in the US for treatment of moderate-to-severe AD; administered once patients have been on a dose of 10 mg o.d. for at least 3 months.
	EU	Mild-to-moderately severe AD	5 mg/day for 1 month -->10 mg/day	-
	Japan	Mild-to-severe AD	3 mg/day for 1-2 weeks -->5 mg for at least 4 weeks--> 10 mg/day*	*10 mg approved only for severe AD.
Galantamine[b]	US	Mild-to-moderate AD	4 mg b.i.d for 4 weeks-->8 mg b.i.d. over at least 4 weeks. Dose may be increased up to 12 mg b.i.d., if tolerated, after a minimum of 4 weeks at 8 mg b.i.d	-
	EU	Mild-to-moderately severe AD		
	Japan	Mild-to-moderate AD		
Rivastigmine[c]	US	Oral: Mild-to-moderate AD Patch: All stages of AD	Oral: 1.5 mg b.i.d. --> 3 mg b.i.d. --> 4.5 mg b.i.d.--> 6 mg b.i.d., if tolerated with a minimum of 2 weeks at each dose Patch: 4.6 mg/24h -->9.5 mg/24h --> 13.3 mg/24h, if tolerated for a minimum of 4 weeks at each dose*	A target maintenance dose of 9.5 mg/24h patch or 6 mg b.i.d. oral rivastigmine has been approved in most countries for the treatment of mild-to-moderate AD. *In the EU, patients may be switched to the 13.3 mg/24 h patch only after a minimum of 6 months of treatment with the 9.5 mg/24 h patch.
	EU	Oral and patch: Mild-to-moderately severe AD		
	Japan	Patch: Mild-to-moderate AD	4.5 mg --> increasing dose by 4.5 mg at 4-week intervals up to the target size of 18 mg. or 9 mg --> 18 mg after 4 weeks. (9 mg=4.6 mg/24 h, 18 mg=9.5 mg/24 h)	-
Memantine[d]	US	Moderate-to-severe AD	5 mg o.d.--> 10 mg o.d.--> 15 mg o.d. --> 20 mg o.d. memantine, if tolerated for a minimum of 1-week at each dose	In the US, memantine is available in extended release capsule form and is administered at an initial dose of 7 mg o.d. and increased in 7-mg increments to reach a maintenance dose of 28 mg o.d. with a minimum treatment period of 1 week at each dose level.
	EU			
	Japan			

[a]7-10; [b]11-13; [c]14-19, 32; [d]20-22. AD, Alzheimer's disease; b.i.d., twice daily; o.d., once daily.

6. SWITCHING BETWEEN ChEIs

Although continuous dose optimization is an option for treating all stages of AD, certain patients may fail to achieve sustained clinical benefits from ChEIs, sometimes resulting in discontinuation of the treatment. In these patients, switching between ChEIs is a reasonable therapeutic option because it is crucial to not give up on treatment after the first therapy has failed owing to a lack of clinical benefit [37, 38]. In a multicenter, 2-year prospective study, the incidence of switching between ChEIs was 9.2 per 100 person-years among 611 patients treated at baseline [39].

The rationale for switching to alternative ChEIs is based on the lack of clinical response owing to inappropriate drug distribution and the complex molecular mechanisms involved in the changes occurring in the brain. Moreover, differences in individual pharmacological properties of ChEIs make switching between ChEIs an attractive option. Thus, patients who are not able to tolerate or benefit from one ChEI may tolerate or benefit from another [38]. Most published studies have explored switching from donepezil to galantamine or rivastigmine. However, only a few studies have investigated the switch from galantamine to donepezil or rivastigmine and from rivastigmine to donepezil. In the subsequent sections of this article, we focus on the effects of switching from one ChEI to another owing to lack of efficacy, tolerability, or adherence. Studies investigating switching have been summarized in Table **2**.

Table 2. Studies showing switching options as a therapeutic strategy for Alzheimer's disease.

Reference	Study Design	Switch Type	Total Number of Patients; Duration	Results
Auriacombe et al, 2002[a]	Open-label, prospective	DPZ to oral RVG	382; 6 months	Oral rivastigmine well-tolerated 56.2% stabilized or improved on the CGIC 48.9 % stabilized or improved on the MMSE 57% stabilized or improved on the IADL scale
Edwards K *et al.* 2004[b]	Retrospective chart review	DPZ/RIV to GAL	16; 6 months	50% of patients reported stabilization/improvement in cognition, behavior and ADL after switch
Wilkinson DG *et al.* 2005[c]	Double-blind, open-label	DPZ to GAL	105; 52 weeks	Galantamine was generally well-tolerated; no change in cognitive performance with either a 4-day or 7-day washout period
Bartorelli *et al.* 2005[d]	Observational, prospective	DPZ to RVG oral; GAL to RVG oral	225, 3 months	66.7%-67.7% of patients stabilized or improved after the switch
Sadowsky *et al.* 2005[e]	Open-label	DPZ to RIV	61; 28 days	Rivastigmine was well tolerated after switching from donepezil without a wash out period
Figiel *et al.* 2008[f]	Open-label	DPZ to RVG	270; 26 weeks	69.7% patients showed improvement or no further decline in global functioning
Grossberg *et al.* 2009[g]	Randomized, controlled	Oral RIV to RIV patch	870; 28 weeks	Switching to the rivastigmine patch was well tolerated; ≤2.5% reported nausea and ≤1.9% reported vomiting
Sadowsky *et al.* 2009[h]	Open-label, prospective	DPZ+/-MEM to RVG patch	261, 5 weeks	Both immediate and delayed switches were well-tolerated with similar rates of discontinuation
Sadowsky *et al.* 2010[i]	Open-label, prospective	DPZ to RVG patch	234, 25 weeks	Both immediate and delayed switches were well tolerated. Cognitive, behavioral and global outcomes were maintained in both groups
Han HJ *et al.* 2011[j]	Open-label, prospective	Oral ChEIs to RVG patch	164; 24 weeks	82.8% and 64.3% of patients reported improvement or no decline on CGIC and the Korean version of MMSE scores, respectively
Tian *et al.* 2013[k]	Retrospective cohort study	DPZ to RVG patch	772, 12 months	Adherence was slightly improved in patients who switched from oral donepezil to rivastigmine patch
Sasaki and Horie 2014[l]	Outpatient	DPZ to GAL	44; 3 months	NPI scores improved significantly on BPSD Significant improvement in patients with moderate AD
Spalletta G *et al.* 2014[m]	Observational, longitudinal	Oral ChEIs to RVG patch	423; 6 months	Switching from oral ChEI to the rivastigmine patch showed favorable effects as compared to those switching from the rivastigmine patch to oral ChEI
Cagnin A *et al.* 2015[n]	Observational, prospective	Oral ChEIs to RVG patch	174; 6 months	56% of patients stabilized or increased the MMSE score as compared to baseline

[a]50; [b]48; [c]61; [d]40; [e]58; [f]43; [g]56; [h]41; [i]57; [j]46; [k]55; [l]47; [m]45; [n]44. AD, Alzheimer's disease; ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia; CGIC, clinical global impression of change; ChEIs, cholinesterase inhibitors; DPZ, donepezil; GAL, galantamine; IADL, Instrumental ADL; MEM, memantine; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; RVG, rivastigmine.

6.1. Switching Owing to Lack of Efficacy

Lack of efficacy is defined as significant deterioration despite the use of symptomatic medication at an effective dose for at least 6 months. In this case, switching can be performed overnight with quicker titration until the minimal effective dose is reached [37].

A prospective, multicenter, 3-month observational trial in patients with mild-to-moderately severe AD (N=225) was conducted to determine the response to switching from another ChEI to rivastigmine when patients experienced deterioration (loss of at least two Mini-Mental State Examination [MMSE] points in the past 6 months) with initial treatment. A total of 188 patients switched from donepezil to rivastigmine, 33 switched from galantamine to rivastigmine, and four switched from donepezil to galantamine. Overall, 67.7% and 66.7% of patients in the donepezil-rivastigmine and galantamine-rivastigmine switch groups, respectively, responded to rivastigmine (Clinical Global Impression of Change [CGIC] score ≤4). Among the non-responders, >80% of patients had minimal worsening of the disease (CGIC score 5). MMSE scores also improved after switching

from both donepezil (p=0.008) and galantamine (p=0.05) to rivastigmine; however, this was observed when patients with an absolute change from baseline in MMSE score >5 were excluded [40].

A 5-week core-phase of the prospective, parallel-group, open-label SWAP study (SWitch from Aricept to Patch) evaluated the effects of "immediate" (n=131) or "delayed" (n=130) switching from 5-10 mg/day donepezil tablets to the 4.6 mg/24h rivastigmine transdermal patch following a 7-day withdrawal period [41]. This was followed by a 20-week extension phase with 9.5 mg/24h rivastigmine transdermal patch treatment [42]. Results from this study suggest that both switching strategies were well-tolerated. Global function remained stable during the course of the study and the mean change in CGIC scores was similar in both the immediate and delayed switch groups (4.1; 95% confidence interval [CI], 3.9-4.4 and 4.3; 95% CI, 4.1-4.4, respectively). At the end of the study, cognitive, behavioral, or global outcomes were maintained in the switch groups with a modest decline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) scores at Week 25 (-3.7; 95% CI, -4.9 to -2.4; p<0.0001). Most patients (55%) preferred the rivastigmine patch to the oral formulation. Results from this study indicate that the majority of patients receiving donepezil may be switched safely to the rivastigmine patch without a withdrawal period [42]. In another, 26-week open-label study (N=270), patients with mild-to-moderate AD not responding to donepezil were switched to receive rivastigmine 3-12 mg/day. Improvement/stabilization of AD was reported in 69.7% of patients (136/195, observed case analysis) who did not respond to the treatment or declined while taking donepezil and were immediately switched from donepezil to rivastigmine [43].

In a 6-month observational study conducted in 174 patients with AD who switched from oral ChEIs to the 9.5 mg/24h rivastigmine patch, the MMSE score increased or stabilized in 56% of patients as compared to baseline. The main reasons for switching were lack/loss of efficacy with previous oral ChEIs (57%), tolerability concerns (33%), or both (10%) [44]. Another study (EVOLUTION, N=423) assessing the effectiveness of switching in patients with mild and moderate AD showed favorable effects of switching from oral ChEIs to the rivastigmine patch as compared to those switching from the rivastigmine patch to oral ChEIs. In this study, the reasons for switching therapy included loss of efficacy with previous ChEIs (41.4%), lack of response (28.8%), reduced tolerability (14.2%), and poor compliance to treatment (9.9%) [45]. A 24-week, prospective, open-label, single-arm, multicenter study in patients with probable AD (N=164) was conducted to assess the effects of switching to the rivastigmine patch after a poor response from initial treatment with oral ChEIs (donepezil, galantamine or rivastigmine capsules). Poor response was defined as a decrease of at least two points on the Korean version of the MMSE (K-MMSE). At Week 24, 82.8% and 64.3% of patients reported an improvement or no decline on the CGIC and K-MMSE scores, respectively. Poor responders to oral ChEIs experienced improvement in symptom or disease stabilization when switched to the rivastigmine patch [46].

The efficacy of galantamine in patients with mild cognitive impairment/mild-to-moderate AD, who switched from donepezil to galantamine without a washout period or dose titration was elucidated in an outpatient study by Sasaki and Horie. Neuropsychiatric inventory scores improved significantly on behavioral and psychological symptoms of dementia, particularly in terms of delusions, agitation, and aberrant motor activity in patients with AD (p=0.027). Remarkable improvements were noted in patients with moderate AD (MMSE scores 10-19; p=0.007) while no improvement was noted in patients with mild cognitive impairment (MMSE scores ≥24; p=0.648) [47]. A retrospective chart review of 16 patients with AD who had been on donepezil or rivastigmine and were switched to galantamine (4 mg/day, n=5; 8 mg/day, n=7; 12 mg/day, n=4) reported stabilization/improvement in cognition, behavior and ADL in 50% of patients even 6 months after switching treatment [48]. Another 52-week observational study evaluated the efficacy of galantamine on cognition in patients with mild-to-moderate AD, who were either naïve to ChEIs (naïve group, n=42) or failed to respond to donepezil and were switched to galantamine (switch group, n=24). At the end of the study, no significant difference between naïve and switch groups was observed on the Korean version of ADAS-cog (p=0.162). However, the results of the study suggest that, as the efficacy of galantamine on cognition was not inferior in the switch group than in the naïve group, switching between ChEIs may be a viable option for patients not responding to treatment [49].

6.2. Switching Owing to Lack of Safety and Tolerability

In case of intolerance to initial therapy, it is recommended to wait for complete resolution of side effects before switching to another treatment [37]. Efficacy and safety of switching from donepezil to oral rivastigmine in patients not responding or not tolerating donepezil was evaluated in a prospective study with AD patients (N=382). A total of 74.4% and 54.5% of patients who were switched because of tolerability issues and lack of efficacy with donepezil (as assessed by CGIC), respectively, responded to rivastigmine. Discontinuation due to AEs with rivastigmine in patients who experienced tolerability problems or lack of efficacy with donepezil was 15.4% and 11.5%, respectively. Nausea (30.1%) and vomiting (14.1%) were the most common AEs reported during the study [50].

ChEIs are associated with a range of side effects, including gastrointestinal symptoms, particularly during the dose titration phase [51, 52]. It is believed that these side effects are related to high maximum concentration (C_{max}) and a short time to C_{max} (t_{max}) following oral administration, thereby leading to an increase in acetylcholine levels in the brain and periphery. Thus, strategies that lower C_{max} and prolong t_{max} may be expected to improve the tolerability of ChEIs [51, 53]. The transdermal patch formulation may be beneficial for AD patients who are being switched from the initial treatment because of tolerability reasons.

In a 6-month observational study (N=174) evaluating the effectiveness of switching from oral ChEIs to the rivastigmine patch, 56% of patients reported improvement or no further deterioration of the MMSE score compared to base-

line. The main reasons for switching were lack/loss of efficacy (57%), tolerability problems (33%) or both (10%). The most frequently reported AEs were skin reactions (16%) and gastrointestinal symptoms (7%); only 9% and 3% of patients discontinued because of these AEs, respectively [44], indicating that the rivastigmine patch can be considered as a therapeutic strategy to improve treatment persistence [44, 50]. This is consistent with the observation in the double-blind randomized controlled trial determining efficacy and safety of the rivastigmine patch and capsule in which one-third of gastrointestinal AEs were observed with the patch compared with the capsule [54].

In the 5-week core phase of the SWAP study, patients were randomly assigned 1:1 to either an immediate switch or delayed switch group (7-day withdrawal period) from 5-10 mg/day donepezil to the 4.6 mg/24h rivastigmine patch. Both an immediate or delayed switch from donepezil to rivastigmine was safe and well-tolerated in patients with mild-to-moderate AD. Only 3.8% of patients from the immediate switch group and 0.8% from the delayed switch group who received the rivastigmine patch reported nausea. Furthermore, no discontinuations were reported due to nausea and vomiting. Results from this study indicated that most patients were able to switch directly to the rivastigmine patch without a washout period [41]. In addition, data from the extension-phase of the study revealed similar results. At least one AE (from application site reaction, agitation and fall) was reported in 70.5% (184/261) of the overall patient population, with a greater number of patients from the immediate switch group (n=96 [73.3%]) in comparison with the delayed switch group (n=88 [67.7%]). Only ten (3.8%) and 11 (4.2%) patients experienced both nausea and vomiting in the immediate and delayed switch groups, respectively [42].

Studies investigating the switch from donepezil to the rivastigmine patch indicate that this transition has a good safety profile, is well tolerated and can be performed without a washout period [50, 55].

The IDEAL (Investigation of TransDermal Exelon in ALzheimer's disease) study was a 24-week randomized controlled trial evaluating efficacy and safety of rivastigmine patches (9.5 mg/24h and 17.4 mg/24h) *versus* oral rivastigmine (3-6 mg b.i.d.) or placebo. All patients who completed the double-blind phase were eligible to enter the 28-week extension phase of the study. These patients (N=870) were switched directly to the 9.5 mg/24h patch, irrespective of their treatment during the double-blind phase, and up-titrated to the 17.4 mg/24h patch. During the first four weeks of the extension phase, the rivastigmine patch was well tolerated by patients previously randomized to rivastigmine; nausea and vomiting were reported in ≤2.5% and ≤1.9% of the patients, respectively [56]. The rivastigmine patch demonstrated good skin tolerability in both the IDEAL and SWAP studies [42, 56].

A post-hoc analysis of data from three clinical trials [41, 44, 58] conducted by Sadowsky CH *et al.* compared the tolerability of switching from donepezil to the rivastigmine patch (4.6 mg/24h) or rivastigmine capsules (3-12 mg/day). Results from this analysis indicate better tolerability of the rivastigmine patch *versus* rivastigmine capsules; there were fewer gastrointestinal AEs (nausea: 3.8% *versus* 32.9%; vomiting: 4.2% *versus* 24.1%, respectively) and discontinuations due to AEs (14.6% *versus* 19.3%, respectively) with the patch [57]. Evidence from an open-label study suggests that switching patients from donepezil to rivastigmine without a washout period is well tolerated [58]. In a more recent observational, retrospective, multicenter study conducted in patients with AD (N=1022), improved ease of administration (56.65%), tolerability (36.79%), efficacy (31.60%), and adherence (18.59%) were the main reasons for switching to the rivastigmine patch from any oral ChEI [59]. Based on the literature review conducted by Sadowsky C, *et al.*, it has been recommended that patients receiving a high dose of oral rivastigmine can be switched directly to the 9.5 mg/24h rivastigmine patch, whereas those on the lower doses of oral rivastigmine should be switched to the 4.6 mg/24h patch and continue treatment for 4 weeks before up-titration to a high-dose patch [60]. A double-blind study (N=105) conducted by Wilkinson *et al.* investigated the switch from donepezil to galantamine and explored the optimum length of a washout period, given the longer half-life of donepezil than galantamine. Results from this study suggest that galantamine was generally well-tolerated; however, patients reported fewer gastrointestinal AEs if the washout period was 4 days rather than 7 days [61].

To date, no published studies have assessed the clinical effects of switching patients from galantamine or rivastigmine to donepezil because of the lack/loss of efficacy or safety/tolerability issues [62]. From these reported clinical observations, it seems that within-class switch among ChEIs is valuable when the first prescribed ChEI is not tolerable or efficacious. Additionally, switching from oral ChEIs to the rivastigmine patch seems to be well-tolerated.

7. FACTORS AFFECTING CLINICAL RESPONSE TO ChEIs

In this section, we discuss differences in the pharmacokinetic and pharmacodynamic characteristics of ChEIs and how they may explain the benefit of within-class switching. These differences can be attributed to the diversity of the chemical structures, each of which belongs to an independent chemical class [63] (Fig. **1**). Results from meta-analyses described in systematic review papers indicate that there is no difference amongst ChEIs in terms of cognition, ADL or global functions in patients with AD [64]. This may be true when considering collective treatment response in a patient population, but it may not be necessarily true in an individual patient as patients with AD have diverse characteristics and may respond differently to treatment.

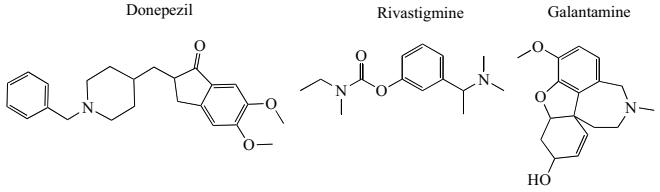

Fig. (1). Chemical structures of cholinesterase inhibitors.

7.1. Pharmacodynamics

Donepezil and galantamine function as rapidly reversible selective inhibitors of acetylcholinesterase (AChE), whereas

rivastigmine is a slowly-reversible dual inhibitor of AChE and butyrylcholinesterase (BuChE) [65]. Galantamine, a relatively weak AChE inhibitor (half maximal inhibitory concentration [IC_{50}] value of ~2.8-3.9 μM), appears to have similar clinical efficacy as that of donepezil (IC_{50}: 15-24 nM) and rivastigmine (IC_{50}: 4 nM) and this effect may be attributed to its allosteric potentiation ligand (APL) activity. It increases the probability of nicotinic acetylcholine receptor (nAChR) channel opening induced by nicotinic agonists and potentiates the agonist response of the nAChR subtypes [66]. The levels of nAChR subtypes are significantly reduced in patients with AD, compared with age-matched controls [67].

Rivastigmine exhibits a unique pharmacological property that enhances potency and selectivity in a different manner via dual AChE-BuChE inhibition. The potential clinical relevance of BuChE inhibition by rivastigmine in patients with AD has been demonstrated by the dynamic shift of cholinesterase activity. Following 12 months of treatment with 3-12 mg/day rivastigmine in patients with mild AD, inhibition of AChE and BuChE activities in the cerebrospinal fluid was reported to be 45% and 58%, respectively [68]. In another 13-week open-label study in patients with mild-to-moderate AD, rivastigmine was associated with a decrease in AChE and BuChE activity by 42.6% and 45.6%, respectively [69].

Donepezil is a highly specific AChE inhibitor, designed to exhibit very high selectivity for AChE [70]. Donepezil also shows high affinity for the sigma-1 receptor as well, which is believed to play a role in the pathophysiology of neuropsychiatric diseases, including AD [71]. Although it is not obvious if rivastigmine or galantamine show similar affinity for the sigma-1 receptor, the pleiotropic effect of donepezil may exhibit a unique pharmacological profile other than AChE inhibition.

7.2. Pharmacokinetics

Differences in route of administration (oral/ transdermal) or metabolism may influence the efficacy and safety of a drug. Orally administered drugs are absorbed through the gastrointestinal wall, and their plasma drug-concentration levels increase rapidly to the peak (C_{max}). Drug plasma levels then drop and may reach their lowest level (C_{min}) until the next dose is administered [72]. Larger and more frequent plasma level fluctuations may lead to an increased incidence of cholinergic side effects, including gastrointestinal AEs such as nausea and vomiting [73]. Thus, by reducing C_{max} and slowing t_{max}, the occurrence of these AEs may be reduced and may help in achieving sustained efficacy [72, 73]. To achieve such a pharmacokinetic profile, a novel rivastigmine transdermal delivery system was developed. The patch shows a steady rivastigmine concentration-time profile as compared with the oral formulations. Systemic exposure (area under the concentration-time curve from zero to infinity [AUC_{∞}]) for the 9.5 mg/24h patch was approximately five times higher than that with the oral dose of 3 mg rivastigmine, whereas C_{max} with the patch was 20% lower than that observed with the oral solution [53]. Rivastigmine is metabolized to an inactive metabolite, NAP-226-90, by AChE and BuChE, with no involvement of the cytochrome P-450 (CYP) system. Conversely, donepezil and galantamine are metabolized primarily by these enzymes [74]. This implies that rivastigmine has fewer clinically relevant drug-drug interactions, making it ideal for use in the elderly population being treated with multiple medications for numerous co-morbidities [75].

7.3. Patient-Related Factors

CYP2D6 is the key CYP-450 isoenzyme involved in the metabolism of donepezil and galantamine. The genetic polymorphism in CYP2D6 has been well investigated, and a large number of allelic variants are known, which may have been reported to be responsible for decreased, increased, or no enzyme activity. In a 6-month study, *CYP2D6*10,* a mutant genotype, was found to be associated with a better response to donepezil treatment in patients with AD. Moreover, the steady-state plasma concentration of donepezil in patients with mutant genotypes was higher than that in patients with the wild-type genotype [76]. Another study showed that patients with the single-nucleotide polymorphism (SNP) rs1080985 in the *CYP2D6* gene had a rapid metabolism and hence a poor response to donepezil. This rapid metabolism is attributed to high enzymatic activity as a consequence of a higher gene expression associated with the G allele. Hence, the presence of this SNP may influence clinical response to donepezil in patients with AD [77]. There are no reports describing the effect of this particular SNP in the *CYP2D6* gene on metabolism and/or efficacy of rivastigmine, as rivastigmine is not metabolized by the CYP-450 isoenzymes [74].

Differential effect of drugs in patients with AD may also be attributed to the SNPs of AChE. In a computational study conducted by Saravanaraman *et al.*, results from molecular dynamics and docking study revealed that various non-specific SNP forms of AChEs exhibit different dynamic properties, which in turn affects their ligand-binding properties. Of the reported 153 SNPs, four non-specific SNPs (A415G, P104A, V302E, and Y119H) that were predicted to be functionally unfavorable were found to be structurally stable. However, their conformational alterations were found to interfere with the binding of AChE inhibitors, suggesting it to be a reason for the differential effect of ChEIs in patients with AD [78]. Similar results were observed in another study conducted in patients with AD who underwent treatment with AChE inhibitors (N=158). Of the 25 SNPs located in 3 cholinergic system genes (*CHAT*, *CHT* and *ACHE*), treatment response in patients with AD was found to have significant association with two SNPs of *CHAT* (rs2177370, rs3793790) [79]. Moreover, there are reports describing the difference in response in patients with specific SNP of molecules related to the pleiotropic mode of actions of ChEIs. The pleiotropic APL effect of galantamine is explained by the allosteric activation of nAChR, by which galantamine potentiates ACh signals transmitted through the nAChR. The *CHRNA7* gene is reported to encode α7 nAChR, one of the major nAChR subunits in the central nervous system (CNS), on chromosome *15q14*. In a retrospective study conducted in 233 patients with mild-to-moderate AD, the ratio of responders to non-responders with galantamine treatment was significantly higher in women with the SNP2 of *CHRNA7* rs8024987 compared with female non-carriers ($p<0.01$) [80]. A similar difference was not observed in patients treated

with other ChEIs, suggesting the involvement of the APL effect of galantamine through α7nAChR.

Similar observations have been reported in patients carrying a BuChE SNP and their clinical response to rivastigmine. Although many SNPs have been reported for the gene, the most prevalent non-synonymous substitutions SNP of BuChE is the K-variant (A539T). Carriers of this variant have been reported to have 33% lower enzyme activity in plasma. The allele frequency of the K-variant is reported to be around 10%, with some differences due to ethnicity [81]. In a post-hoc analysis of a study in 994 patients [82], BuChE wild-type carriers younger than 75 years showed significantly greater treatment response to rivastigmine over 2 years than patients receiving donepezil. However, BuChE K-variant carriers experienced similar long-term treatment effects with both agents [83], suggesting that the greater effect of rivastigmine may be attributed to the inhibition of BuChE, which is fully expressed in the wild-type carriers. Furthermore, the efficacy of rivastigmine was also shown to be better in patients carrying wild-type BuChE compared with those with the K-variant in an open-label study in 146 patients with AD. The difference was more evident in a subpopulation carrying allele *ApoE4* [84].

These findings must be carefully interpreted considering the limitation of these analyses; some are retrospective analyses of studies with different study objectives and results being observed for a specific population (*e.g.* female subjects or patients younger than 75 years). Further elucidation in prospective studies with sufficient statistical power is required. Together with the polymorphism in the coding genes related to the cholinergic pathway, those present in the noncording region merits in-depth research as the non-coding microRNAs (CholinomiRs') are believed to coordinate the cognitive and inflammatory aspects of cholinergic signaling by targeting major cholinergic transcripts including AChE [85].

In addition to the SNPs of molecules related to cholinergic pathway, some other patient conditions may also be implicated for the differential treatment response to ChEIs. BuChE expressed in the neuron and glial cells is reported to be co-localized with senile plaques in AD brain and its enzyme activity positively correlates with the number of senile plaques in human autopsy brain samples [86, 87]. Molecular interactions of BuChE with amyloid beta protein (Aβ) and the role of BuChE in neuro-inflammation have also been reported [88-90]. The inhibitory potency of various ChEIs towards BuChE may also suggest the possibility of differential treatment response to ChEIs in patients with AD [91].

Apart from the intrinsic patient factors which may influence the treatment response to ChEIs, the potential impact of concomitant medications on cholinergic system cannot be ruled out. The negative effect of anti-cholinergic agents on cognition is widely reported [92, 93]. Combination of anticholinergic drugs and ChEIs leads to pharmacological antagonism which results in lack/loss of efficacy of ChEIs in patients with AD [94]. Hence, caution should be exercised during concurrent use of anti-cholinergic drugs and ChEIs.

In summary, the main reasons for the potential difference in responsiveness to each ChEI can be attributed to the different chemical structure of the compounds and the diverse pathology of AD, which is not yet fully understood. Although the individual responses to each ChEI vary due to their PK/PD properties and patient factors including genetics, response of an individual patient to a particular compound with the help of biomarkers is still not predictable. Responders and non-responders can be identified only after a treatment trial period with careful observation. In this context, it is recommended to initiate therapy with any of the ChEIs, taking into account expected therapeutic benefits and potential safety issues [95]. Moreover, patients should be reviewed regularly using cognitive, global, functional and behavioral assessment(s), which may help physicians to detect lack of efficacy of a treatment.

8. SWITCHING AND PATIENT ADHERENCE

Achieving maximal benefits from treatment is dependent upon patient adherence to the type of treatment used. A decline in cognition, mood, and behavior can pose a challenge for patient adherence to a given medication [96]. Switching may positively affect treatment adherence through enhanced motivation of patients and caregivers by the expectation of the treatment option. A retrospective cohort study examined patient adherence using "proportion of days covered" (PDC) in 772 patients with AD who were new donepezil users and were subsequently switched to the rivastigmine patch [55]. Results from the analysis indicated that adherence improved in patients switching from oral donepezil to transdermal rivastigmine. Patients who switched within the first year of initiating donepezil to rivastigmine patch exhibited increased adherence (PDC, 60.6% *versus* 69.3%; p=0.0004). Patients who switched from donepezil to the rivastigmine patch within the first 3 months (PDC, 80.4% *versus* 90.7%; p=0.04) exhibited even better adherence than those who switched between 7 and 9 months (PDC, 61.3% *versus* 71.0%; p=0.05). Switching after 2 years did not result in increased patient adherence. Hence, the time to switch between the rivastigmine patch and donepezil tablets was a predictor of difference in PDC. This could be attributed to better tolerability with the transdermal patch, and/or perceived convenience and ease of use of transdermal patches. It is suggested that an early decision to switch to another ChEI is beneficial for a patient's outcome from the viewpoint of treatment persistence [55]. Improvement of tolerability by switching may also contribute to improved efficacy attributed by improved adherence and/or up titration to higher doses. Side effects of oral ChEIs, such as nausea and vomiting, are practical concerns while up-titrating to efficacious doses and may negatively affect drug adherence as well as motivation of patients and caregivers to stay on drug treatment. In a population-based cohort study using British Columbia claims data, approximately 50% of patients receiving ChEIs were reported to discontinue therapy within 12 months of treatment initiation. A total of 3231/24,526 patients (new ChEI users) switched to a second ChEI within 90 days of discontinuation of the first ChEI [97]. Similar results were reported in an Austrian cohort study (N=15,809) [98]. Considering the long disease course of AD, and the high rate

of treatment discontinuation in clinical practice, regular assessment of disease progression and appropriate switching among ChEI may present a useful measure for better clinical outcomes by avoiding discontinuation of the treatment.

CONCLUSION

As donepezil, galantamine, rivastigmine, and memantine are the only available therapeutic options for the treatment of patients with AD, it is vital that clinicians optimize the use of available treatments until new preventive DMTs or symptomatic medications become available. Guidelines recommend ChEIs as the first choice of treatment, particularly for mild-to-moderate AD. Based on the disease stage and clinical characteristics, the therapeutic dose should be up-titrated to the maximum approved dose, as long as it is tolerable, as it may help to improve response to ChEI treatment. Switching between ChEIs may also help to address issues such as lack/loss of efficacy or safety/tolerability in patients with AD. However, most of the switching studies referred to in this review are of an open-label design with potential bias, therefore well-designed studies are needed to provide robust evidence. In addition, future therapies will need to address multiple aspects of AD, for example, different pathogenic mechanisms and convergence of symptoms that may occur during the natural course of dementia.

DISCLOSURES

Rafael Blesa has received consulting fees from Novartis, Janssen-Cilag, Lundbeck and Nutricia, and lecture fees from Novartis and Nutricia. **George T. Grossberg** has served as a consultant for Acadia, Allergan, Avanir, Axovant, GE, Genentech, Lundbeck, Novartis, Otsuka, Roche, and Takeda Pharmaceuticals; he has received research support from Cognoptix, Janssen, and the National Institutes of Health, provided safety monitoring for EryDel, Merck, and Newron, and is on the speaker's bureau for Acadia. **Kazuhiro Toriyama and Kengo Ueda** are full time employees of Novartis. **Sean Knox** was full time employee of Novartis at the time of development and finalization of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This review article is sponsored by Novartis Pharma K.K., Tokyo, Japan. The publication processing fees were funded by Novartis Pharma K.K., Tokyo, Japan. All authors of this review article met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and gave their approvals for this article to be published. The authors would like to thank Preetinder Kaur for providing medical writing support.

REFERENCES

[1] Shah S, Reichman WE. Treatment of Alzheimer's disease across the spectrum of severity. Clin Interv Aging 1(2): 131-42 (2006).

[2] Birks JS, Chong LY, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 9: CD001191 (2005).

[3] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, *et al.* Alzheimer's disease. Lancet 388: 505-17 (2016).

[4] Tacrine. Drugs in Clinical Trials. Alzheimer Research Forum. Available from: http://www.alzforum.org/drg/drc/detail.asp?id=90

[5] Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep 67(2): 195-203 (2015).

[6] Salomone S, Caraci F, Leggio GM, Fedotova J, Drago F. New pharmacological strategies for treatment of Alzheimer's disease: focus on disease-modifying drugs. Br J Clin Pharmacol 73(4): 504-17 (2012).

[7] Donepezil. The United States Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf.

[8] Donepezil. Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/577.

[9] PMDA, List of approved drugs, FY2007. Available from: https://www.pmda.go.jp/files/000152974.pdf.

[10] Aricept® approved in Japan as treatment for dementia with lewy bodies. Eisai press release. Available from: http://www.eisai.com/news/news201452.html.

[11] Galantamine. The United States Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021615lbl.pdf.

[12] Galantamine. Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/10335/SPC/Reminyl+Tablets/.

[13] PMDA, List of approved drugs, FY2010. Available from: https://www.pmda.go.jp/files/000153090.pdf.

[14] Rivastigmine Capsule. The United States Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020823s016,021025s008lbl.pdf.

[15] Rivastigmine Patch PI. The United States Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022083lbl.pdf.

[16] Rivastigmine Capsule. Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/20232.

[17] Rivastigmine Patch, Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/medicine/20232.

[18] PMDA, List of approved drugs, FY2011. Available from: https://www.pmda.go.jp/files/000153539.pdf.

[19] Nakamura Y, Imai Y, Shigeta M, Graf A, Shirahase T, Kim H, *et al.* A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. Dement Geriatr Cogn Dis Extra 1(1): 163-79 (2011).

[20] Memantine, the United States Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf.

[21] Memantine, Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000463/WC500058763.pdf.

[22] PMDA, Memantine review report, 2010. Available from: http://www.pmda.go.jp/files/000207435.pdf#page=2.

[23] NICE Technology Appraisal Guidance 217, issued in March 2011. Available from: https://www.nice.org.uk/guidance/ta217.

[24] Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, *et al.* EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 17(10): 1236-48 (2011).

[25] Moore A, Patterson C, Lee L, Vedel I, Bergman H; Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. Can Fam Physician 60(5): 433-38 (2014).

[26] Kudo T. How do we use symptomatic drugs to treat dementia? in practical pharmacology for alzheimer's disease. Cham: Springer International Publishing pp. 119-35 (2016).

[27] Molinuevo JL, Frölich L, Grossberg GT, Galvin JE, Cummings JL, Krahnke T, *et al.* Responder analysis of a randomized comparison of the 13.3 mg/24 h and 9.5 mg/24 h rivastigmine patch. Alzheimer's Res Ther 7(1): 9 (2015).

[28] Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q, *et al.* Effectiveness and tolerability of high-dose (23 mg/d) *versus* standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. Clin Ther 32(7): 1234-51 (2010).

[29] Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, *et al.* Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. Dement Geriatr Cogn Disord 25: 399-407 (2008).

[30] Cummings J, Froelich L, Black SE, Bakchine S, Bellelli G, Molinuevo JL, *et al.* Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm^2) in Alzheimer's disease. Dement Geriatr Cogn Disord 33(5): 341-53 (2012).

[31] Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomized controlled trials. Int J Geriatr Psychiatry 19(7): 624-33 (2004).

[32] Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h *versus* 4.6 mg/24 h in severe Alzheimer's dementia. CNS Neurosci Ther 19(10): 745-52 (2013).

[33] Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Velting DM. A 24-Week, open-label extension study to investigate the long-term safety, tolerability, and efficacy of 13.3 mg/24 h rivastigmine patch in patients with severe Alzheimer disease. Alzheimer Dis Assoc Disord 29(2): 110-16 (2015).

[34] Sabbagh M, Han S, Kim S, Na HR, Lee JH, Kandiah N, *et al.* Clinical recommendations for the use of donepezil 23 mg in moderate-to-severe Alzheimer's disease in the Asia-Pacific region. Dement Geriatr Cogn Dis Extra 6(3): 382-95 (2016).

[35] Nozawa M, Ichmiya Y, Nozawa E, Utumi Y, Sugiyama H, Murayama N, *et al.* Clinical effects of high oral dose of donepezil for patients with Alzheimer's disease in Japan. Psychogeriatrics 9: 50-55 (2009).

[36] Johannsen P. Long-term cholinesterase inhibitor treatment of Alzheimer's disease. CNS Drugs 18(12): 757-68 (2004).

[37] Massoud F, Léger GC. Pharmacological treatment of Alzheimer disease. Can J Psychiatry 56(10): 579-88 (2011).

[38] Massoud F, Desmarais JE, Gauthier S. Switching cholinesterase inhibitors in older adults with dementia. Int Psychogeriatr 23(3): 372-378 (2011).

[39] Gardette V, Andrieu S, Lapeyre-Mestre M, Coley N, Cantet C, Ousset PJ, *et al.* Predictive factors of discontinuation and switch of cholinesterase inhibitors in community-dwelling patients with Alzheimer's disease: a 2-year prospective, multicenter, cohort study. CNS Drugs 24(5): 431-42 (2010).

[40] Bartorelli L, Giraldi C, Saccardo M, Cammarata S, Bottini G, Fasanaro AM, *et al.* Effects of switching from an AChE inhibitor to a dual AChE-BuChE inhibitor in patients with Alzheimer's disease. Curr Med Res Opin 21(11): 1809-18 (2005).

[41] Sadowsky CH, Dengiz A, Olin JT, Koumaras B, Meng X, Brannan S; US38 study group. Switching from donepezil tablets to rivastigmine transdermal patch in Alzheimer's disease. Am J Alzheimers Dis Other Demen 24(3): 267-75 (2009).

[42] Sadowsky CH, Dengiz A, Meng X, Olin JT. Switching from oral donepezil to rivastigmine transdermal patch in Alzheimer's disease: 20-week extension phase results. Prim Care Companion J Clin Psychiatry 12(5): 1-5 (2010).

[43] Figiel GS, Sadowsky CH, Strigas J, Koumaras B, Meng X, Gunay I. Safety and efficacy of rivastigmine in patients with Alzheimer's disease not responding adequately to donepezil: an open-label study. Prim Care Companion J Clin Psychiatry 10: 291-98 (2008).

[44] Cagnin A, Cester A, Costa B, Ermani M, Gabelli C, Gambina G; SWITCH study working group. Effectiveness of switching to the rivastigmine transdermal patch from oral cholinesterase inhibitors: a naturalistic prospective study in Alzheimer's disease. Neurol Sci 36(3): 457-63 (2015).

[45] Spalletta G, Caltagirone C, Padovani A, Sorbi S, Attar M, Colombo D, *et al.* Cognitive and affective changes in mild to moderate Alzheimer's disease patients undergoing switch of cholinesterase inhibitors: a 6-month observational study. PLoS One 9(2): e89216 (2014).

[46] Han HJ, Lee JJ, Park SA, Park HY, Kim JE, Shim YS, *et al.* Efficacy and safety of switching from oral cholinesterase inhibitors to the rivastigmine transdermal patch in patients with probable Alzheimer's disease. J Clin Neurol 7(3): 137-42 (2011).

[47] Sasaki S, Horie Y. The effects of an uninterrupted switch from donepezil to galantamine without dose titration on behavioral and psychological symptoms of dementia in Alzheimer's disease. Dement Geriatr Cogn Dis Extra 4(2): 131-39 (2014).

[48] Edwards K, Therriault O'Connor J, Gorman C. Switching from donepezil or rivastigmine to galantamine in clinical practice. J Am Geriatr Soc 52: 1965 (2004).

[49] Hwang T-Y, Ahn I-S, Kim S, Kim K. Efficacy of galantamine on cognition in mild-to-moderate Alzheimer's dementia after failure to respond to donepezil. Psychiatry Investig 13(3): 341-48 (2016).

[50] Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. Curr Med Res Opin 18(3): 129-38 (2002).

[51] Čolović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol 11(3): 315-35 (2013).

[52] Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. Int J Clin Pract 127(Suppl 1): 45-63 (2002).

[53] Lefèvre G, Pommier F, Sedek G, Allison M, Huang HL, Kiese B, *et al.* Pharmacokinetics and bioavailability of the novel rivastigmine transdermal patch *versus* rivastigmine oral solution in healthy elderly subjects. J Clin Pharmacol 48(2): 246-52 (2008).

[54] Winblad B, Cummings J, Andreasen N, Grossberg G, Onofrj M, Sadowsky C, *et al.* A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-rivastigmine patch *versus* capsule. Int J Geriatr Psychiatry 22(5): 456-67 (2007).

[55] Tian H, Abouzaid S, Chen W, Kahler KH, Kim E. Patient adherence to transdermal rivastigmine after switching from oral donepezil: a retrospective claims database study. Alzheimer Dis Assoc Disord 27(2): 182-86 (2013).

[56] Grossberg G, Sadowsky C, Fröstl H, Frölich L, Nagel J, Tekin S, *et al.* Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension. Alzheimer Dis Assoc Disord 23(2): 158-64 (2009).

[57] Sadowsky CH, Farlow MR, Meng X, Olin JT. Safety and tolerability of rivastigmine transdermal patch compare, with rivastigmine capsules in patients switched from donepezil: data from three clinical trials. Int J Clin Pract 64(2): 188-93 (2010).

[58] Sadowsky CH, Farlow MR, Atkinson L, Steadman J, Koumaras B, Chen M, *et al.* Switching from donepezil to rivastigmine is well-tolerated: results of an open─label safety and tolerability study. Prim Care companion J Clin Psychiatry 7(2): 43-48 (2005).

[59] López-Pousa S, Arranz FJ. Characteristics of patients with Alzheimer's disease who switch to rivastigmine transdermal patches in routine clinical practice. Patient Prefer Adherence 7: 47-54 (2013).

[60] Sadowsky C, Davila Perez JA, Bouchard RW, Goodman I, Tekin S. Switching from oral cholinesterase inhibitors to the rivastigmine transdermal patch. CNS Neurosci Ther 16: 51-60 (2010).

[61] Wilkinson DG, Howe I. Switching from donepezil to galantamine: a double-blind study of two wash-out periods. Int J Geriatr Psychiatry 20(5): 489-91 (2005).

[62] Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg G, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin 19 (8): 707-14 (2003).

[63] Sugimoto H, Yamanishi Y, Iimura Y, Kawakami Y. Donepezil hydrochloride (E2020) and other acetylcholinesterase inhibitors. Curr Med Chem 7(3): 303-39 (2000).

[64] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 25(1): CD005593 (2006).

[65] Onor ML, Trevisiol M, Aguglia E. Rivastigmine in the treatment of Alzheimer's disease: an update. Clin Interv Aging 2(1): 17-32 (2007).

[66] Samochocki M, Höffle A, Fehrenbacher A, Jostock R, Ludwig J, Christner C, *et al.* Galantamine is an allosterically potentiating

ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. J Pharmacol Exp Ther 305(3): 1024-36 (2003).

[67] Burghaus L, Schütz U, Krempel U, de Vos RA, Jansen Steur EN, Wevers A, *et al.* Quantitative assessment of nicotinic acetylcholine receptor proteins in the cerebral cortex of Alzheimer patients. Mol Brain Res 76(2): 385-88 (2000).

[68] Poirier J. Evidence that the clinical effects of cholinesterase inhibitors are related to potency and targeting of action. Int J Clin Pract Suppl 127: 6-19 (2002).

[69] Nordberg A, Darreh-Shori T, Peskind E, Soininen H, Mousavi M, Eagle G, *et al.* Different cholinesterase inhibitor effects on CSF cholinesterases in Alzheimer patients. Curr Alzheimer Res 6(1): 4-14 (2009).

[70] Sugimoto H, Ogura H, Arai Y, Limura Y, Yamanishi Y,. Research and development of donepezil hydrochloride, a new type of acetylcholinesterase inhibitor. Jpn J Pharmacol 89(1): 7-20 (2002).

[71] Ishikawa M, Sakata M, Ishii K, Kimura Y, Oda K, Toyohara J, *et al.* High occupancy of sigma1 receptors in the human brain after single oral administration of donepezil: a positron emission tomography study using [11C]SA4503. Int J Neuropsychopharmacol 12(8): 1127-31 (2009).

[72] Kurz A, Farlow M, Lefèvre G. Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. Int J Clin Pract 63(5): 799-805 (2009).

[73] Imbimbo BP. Pharmacodynamic-tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. CNS Drugs 15(5): 375-90 (2001).

[74] Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet 41(10): 719-39 (2002).

[75] Grossberg GT, Stahelin HB, Messina JC, Anand R, Veach J. Lack of adverse pharmacodynamic drug interactions with rivastigmine and 22 classes of medications. Int J Geriatr Psychiatry 15(3): 242-47 (2000).

[76] Zhong Y, Zheng X, Miao Y, Wan L, Yan H, Wang B. Effect of CYP2D6*10 and APOE polymorphisms on the efficacy of donepezil in patients with Alzheimer's disease. Am J Med Sci 345(3): 222-26 (2013).

[77] Pilotto A, Franceschi M, D'Onofrio G, Bizzarro A, Mangialasche F, Cascavilla L, *et al.* Effect of a CYP2D6 polymorphism on the efficacy of donepezil in patients with Alzheimer disease. Neurology 73(10): 761-67 (2009).

[78] Saravanaraman P, Chinnadurai RK, Boopathy R. A new role for the nonpathogenic nonsynonymous single-nucleotide polymorphisms of acetylcholinesterase in the treatment of Alzheimer's disease: a computational study. J Comput Biol 21(8): 632-64 (2014).

[79] Yoon H, Myung W, Lim S-W, Kang HS, Kim S, Won HH, *et al.* Association of the choline acetyltransferase gene with responsiveness to acetylcholinesterase inhibitors in Alzheimer's disease. Pharmacopsychiatry 48(3): 111-17 (2015).

[80] Weng PH, Chen JH, Chen TF, Sun Y, Wen LL, Yip PK, *et al.* CHRNA7 polymorphisms and response to cholinesterase inhibitors in Alzheimer's disease. PLoS One 8(12): e84059 (2013).

[81] Darvesh S, Hopkins DA, Geula C. Neurobiology of butyrylcholinesterase. Nat Rev Neurosci 4(2): 131-38 (2003).

[82] Bullock R, Bergman H, Touchon J, Gambina G, He Y, Nagel J, *et al.* Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. Curr Med Res Opin 22(3): 483-94 (2006).

[83] Blesa R, Bullock R, He Y, Bergman H, Gambina G, Meyer J, *et al.* Effect of butyrylcholinesterase genotype on the response to rivastigmine or donepezil in younger patients with Alzheimer's disease. Pharmacogenet Genomics 16(11): 771-74 (2006).

[84] Han HJ, Kwon JC, Kim JE, Kim SG, Park JM, Park KW, *et al.* Effect of rivastigmine or memantine add-on therapy is affected by butyrylcholinesterase genotype in patients with probable Alzheimer's disease. Eur Neurol 73(1-2): 23-28 (2015).

[85] Simchovitz A, Heneka MT, Soreq H. Personalized genetics of the cholinergic blockade of neuroinflammation. J Neurochem 142(2): 178-87 (2017).

[86] Gómez-Ramos P, Morán MA. Ultrastructural localization of butyrylcholinesterase in senile plaques in the brains of aged and Alzheimer disease patients. Mol Chem Neuropathol 30(3):161-73 (1997).

[87] Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br Med J 2(6150): 1457-59 (1978).

[88] Morán MA, Mufson EJ, Gómez-Ramos P. Colocalization of cholinesterases with beta amyloid protein in aged and Alzheimer's brains. Acta Neuropathol 85(4): 362-69 (1993).

[89] Guillozet AL, Smiley JF, Mash DC, Mesulam MM. Butyrylcholinesterase in the life cycle of amyloid plaques. Ann Neurol 42(6): 909-18 (1997).

[90] J Podoly E, Shalev DE, Shenhar-Tsarfaty S, Bennett ER, Ben Assayag E, Wilgus H, *et al.* The butyrylcholinesterase K variant confers structurally derived risks for Alzheimer pathology. J Biol Chem 284(25): 17170-79 (2009).

[91] Ogura H, Kosasa T, Kuriya Y, Yamanishi Y. Comparison of inhibitory activities of donepezil and other cholinesterase inhibitors on acetylcholinesterase and butyrylcholinesterase *in vitro*. Meth Find Exp Clin Pharmacol 22(8): 609-13 (2000).

[92] Risacher SL, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, *et al.* Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. JAMA Neurol 73(6): 721-32 (2016).

[93] Fox C, Smith T, Maidment I, Chan WY, Bua N, Myint PK, *et al.* Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. Age Ageing 43(5): 604-15 (2014).

[94] Caraci F, Sultana J, Drago F, Spina E. Clinically relevant drug interactions with anti-Alzheimer's drugs. CNS Neurol Disord Drug Targets 16(4): 501-13 (2017).

[95] Rountree SD, Atri A, Lopez OL, Doody RS. Effectiveness of antidementia drugs in delaying Alzheimer's disease progression. Alzheimers Dement 9(3): 338-45 (2012).

[96] Cooper C, Carpenter I, Katona C, Schroll M, Wagner C, Fialova D, *et al.* The AdHOC Study of older adults' adherence to medication in 11 countries. Am J Geriatr Psychiatry 13(12): 1067-76 (2005).

[97] Fischer A, Carney G, Bassett K, Dormuth CR. Tolerability of cholinesterase inhibitors: a population-based study of persistence, adherence and switching. Drugs Aging 34(3): 221-31 (2017).

[98] Haider B, Schmidt R, Schweiger C, Forstner T, Labek A, Lampl C. Medication adherence in patients with dementia: An Austrian cohort study. Alzheimer Dis Assoc Disord 28(2): 128-33 (2014).