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REVIEW

An overview of the rivastigmine 13.3 mg/24h transdermal patch as a treatment option for Alzheimer's disease

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ABSTRACT

Introduction: Rivastigmine, a cholinesterase inhibitor, was first approved for the treatment of Alzheimer's disease (AD) dementia more than 20 years ago. Initially available as an oral formulation, a transdermal system was subsequently developed with the aim of improving tolerability while providing similar efficacy. Transdermal rivastigmine is approved for the treatment of severe AD as well as mild-to-moderate AD.

Areas covered: Herein, the authors review randomized clinical trials, meta-analyses, and post-marketing observational studies involving the rivastigmine 13.3 mg/24 h patch for the treatment of patients with AD.

Expert opinion: Cholinesterase inhibitors are a mainstay of the symptomatic treatment of patients with AD. Rivastigmine is available as oral and transdermal formulations, with the latter providing improved tolerability and convenience while maintaining efficacy. The high-dose 13.3 mg/24 h patch might offer benefits for some patients compared to the lower dose patch (4.6 mg/24 h) in patients with mild-to-moderate or severe AD, showing improvements in daily functioning and global clinical status on top of the cognitive benefits. The ability to titrate up to a dose of 13.3 mg/24 h provides an option for patients with severe AD or with an inadequate response to lower doses of rivastigmine.

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KEYWORDS
Alzheimer's disease; cholinesterase inhibitor; dementia; rivastigmine; transdermal patch

1. Introduction

More than 50 million people worldwide have dementia [1]. It is the fifth leading cause of mortality [2] and is associated with global societal costs of US$1313 billion per year [3]. The most common cause of dementia is Alzheimer's disease (AD), with an estimated prevalence of 32 million people worldwide [4]. Across the full spectrum of AD, including prodromal and pre-clinical disease as well as dementia, 416 million people are affected, including 22% of those aged 50 years or older [4]. AD is the fourth leading cause of disability-adjusted life-years lost among people aged 75 years and older [5].

The pathophysiology of AD involves multiple neurodegenerative processes, including the deposition of amyloid-beta plaques in the brain, the development of neurofibrillary tangles composed primarily of hyperphosphorylated tau proteins (microtubular neuronal proteins), and persistent microglial activation with neuroinflammation [6–8]. These processes culminate in the loss of synaptic connections, neuronal cell death, and brain atrophy.

Clinically, AD is characterized by memory loss; impairments in cognitive function, visuospatial processing, and executive function; mood fluctuations; and behavioral changes [9]. This leads to patients experiencing difficulties with activities of daily living.

Treatment options for patients with AD include disease-modifying drugs such as lecanemab and donanemab that target amyloid-beta, as well as symptomatic treatments such as cholinesterase inhibitors (ChEIs) and glutamate regulators [10,11]. While only a minority of patients will benefit from disease-modifying therapies, cholinergic denervation is a common feature in all AD patients, making symptomatic treatments an important therapeutic approach regardless of disease-modifying drug use. ChEIs, including donepezil, rivastigmine, and galantamine are recommended for the treatment of patients with mild-to-moderate AD [9,12,13]. Certain dosages/formulations of donepezil and rivastigmine are also used to treat moderate-to-severe AD [13,14]. Memantine, an N-methyl-D-aspartate (NMDA) antagonist, is also approved for the treatment of moderate-to-severe AD [9,14], and the combination of memantine and a ChEI may be beneficial in some patients [9,12,13,15]. The use of higher doses of ChEIs has been associated with a lower risk of institutionalization in a nursing home and a lower risk of mortality [16,17].

Rivastigmine was first approved for the treatment of AD dementia more than 20 years ago, as oral capsules 1.5, 3, 4.5, and 6 mg (approved in the EU in 1998) and an oral solution 2.0 mg/mL (approved in 1999) [18]. A transdermal system was subsequently developed with the aim of improving tolerability

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Article highlights

- Early and sustained treatment with transdermal rivastigmine 13.3 mg/24 h provided clinical benefit to patients with Alzheimer's disease (AD) dementia.
- In patients with mild-to-moderate AD who had declined on the 9.5 mg/24 h patch, switching to 13.3 mg/24 h might offer improvements to some patients in daily function (ADCS-IADL) compared with continuing 9.5 mg/24 h.
- In a real-world setting, most patients who were titrated to the rivastigmine 13.3 mg/24 h patch continued on the same dose long term.
- The rivastigmine 13.3 mg/24 h patch was generally well tolerated during up to 48 weeks of treatment.
- Available evidence supports the use of rivastigmine 13.3 mg/24 h patch for the symptomatic treatment of AD dementia.

(particularly with respect to gastrointestinal side effects) while providing similar efficacy [19,20]. Transdermal patches at doses of 4.6 and 9.5 mg/24 hours (h) were approved in Spain in 2007, followed by the high-dose 13.3 mg/24 h patch in 2013. The 13.3 mg/24 h patch was approved for the treatment of severe AD in addition to mild and moderate AD.

The frequency of the different formulations may vary between countries. In Spain, where rivastigmine is the most common drug in monotherapy to treat AD (30.5% in 2020), the transdermal formulation is preferred, and the oral formulation is rarely prescribed [21]. In 2020, rivastigmine 9.5 mg/24 h was the most common dose prescribed (18%), although the proportion of patients receiving this dose had decreased since 2015 (when it accounted for 24%), while the proportion receiving 13.3 mg/24 h had increased from 2% in 2015 to 5% in 2020.

This narrative review summarizes the available body of evidence for the rivastigmine 13.3 mg/24 h transdermal patch. The article is based on literature obtained from PubMed searches up to the 31 May 2024. These literature searches identified randomized clinical trials, extension studies, observational studies and post-marketing studies of rivastigmine 13.3 mg/24 h transdermal patch for the treatment of AD dementia.

2. Rivastigmine

Rivastigmine (chemical name: (S)-3-[1-(dimethylamino)ethyl] phenyl ethylmethylcarbamate); molecular formula: $C_{14}H_{22}N_2O_2$; Figure 1) is a carbamate derivative that acts as a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [22,23]. The pharmacodynamic and pharmacokinetic properties of oral and transdermal rivastigmine have been reviewed previously [22,24–27]. An overview is provided here, focusing on data for the 13.3 mg/24 h patch where available.

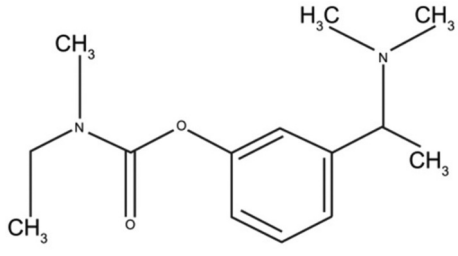

Figure 1. Chemical structure of rivastigmine.

Impaired cholinergic neurotransmission is implicated in the development of impaired cognitive function in AD [28]. Rivastigmine is a potent, selective, reversible inhibitor of both AChE and BuChE. By preventing the degradation of ACh, it increases levels in the cortex and enhances cholinergic neurotransmission [25]. During the course of AD, AChE levels remain stable or decrease, whereas BuChE levels tend to increase, and it has been suggested that inhibition of both enzymes has potential therapeutic benefits over inhibition of AChE alone [29].

Rivastigmine is a small molecule with both lipophilic and hydrophilic properties, making it suitable for transdermal delivery [30]. The once-daily rivastigmine patch comprises four layers, including the backing layer that is visible after application, an acrylic matrix layer that contains the drug, a silicone matrix adhesive layer, and the release liner (which is removed before application to the skin) [31].

The pharmacokinetic properties of transdermal rivastigmine are summarized in Table 1 [20,32–34]. Each transdermal patch of 5 cm^2 contains 9 mg of rivastigmine and releases 4.6 mg/24 h; each transdermal patch of 10 cm^2 contains 18 mg of rivastigmine and releases 9.5 mg/24 h; each transdermal patch of 15 cm^2 contains 27 mg of rivastigmine and releases 13.3 mg/24 h [32]. Transdermal administration of rivastigmine prolongs the time to maximum plasma concentration, lowers peak plasma concentration and reduces fluctuations in plasma concentrations compared with oral capsules, and the 9.5 mg/24 h patch provides similar exposure to the highest oral dose of 12 mg/day [20,30,34,35]. Administration by the transdermal route avoids the gastrointestinal system, which helps improve gastrointestinal tolerability compared with oral formulations [27]. Rivastigmine is metabolized by its target enzymes (AChE and BuChE), with no hepatic metabolism and minimal risk of interaction with drugs inhibited or induced by hepatic cytochrome P450 enzymes [27].

3. Clinical efficacy of rivastigmine 13.3 mg/24 h

The efficacy of the rivastigmine transdermal patch was originally demonstrated in the IDEAL study, which showed that the 9.5 mg/24 h (10 cm^2) patch provided similar improvements in global and cognitive function to oral rivastigmine 12 mg/day (the highest oral dose) in patients with mild to moderate AD [25,30]. This section will focus on efficacy data for the high dose 13.3 mg/24 h (15 cm^2) patch.

3.1. Cognitive and functional efficacy in severe AD

3.1.1. ACTION: 24-week double-blind study

The 24-week ACTION study evaluated the efficacy and tolerability of the 13.3 mg/24 h patch in patients with severe AD [36]. In this randomized, double-blind, double-dummy, multicenter trial, patients aged ≥50 years with AD and Mini-Mental State Examination (MMSE) scores ≥ 3 to ≤ 12 were randomized

Table 1. Pharmacokinetic properties of rivastigmine transdermal patch: mean values after a single 24-hour application of the 13.3 mg/24 hours patch, unless indicated otherwise [20,32–34].

C_{max}	Healthy subjects: 12.5–12.9 ng/mL AD patients: 14.1 ng/mL
t_{max}	Healthy subjects: 10–16 hours/AD patients: 8.0 hours
$AUC0_{0–24\ h}$	Healthy subjects: 204–216 ng·h/mL/AD patients: 233 ng·h/mL
Effect of bodyweight	AD patients: exposure increases with decreasing bodyweight[a]
Effect of application location	Exposure highest when patch applied to upper back, chest, or upper arm (20–30% lower when on abdomen or thigh)[a]
FI	AD patients: 0.7
Protein binding	≈40%[a]
V_d	1.8–2.7 L/kg[a]
Metabolism	Rapidly and extensively metabolized via cholinesterase-mediated hydrolysis to metabolite NAP226–90 (which itself has minimal activity)[a] Minimal metabolism by major CYP isoenzymes[a]
Elimination	Renal excretion of metabolite[a]
$t_{1/2}$	Healthy subjects: 2.78–2.90 hours
CL_R	Healthy subjects: 1.95–2.14 hours
Special populations	Age and race have minimal effect on pharmacokinetics[a] No dose adjustment needed for renal impairment[a] Exposure increased in mild – moderate hepatic impairment (titrate dose carefully)[a]
Drug interactions	Interactions with drugs that induce, inhibit, or are metabolized by CYP enzymes are not expected[a] No interactions with digoxin, warfarin, diazepam, fluoxetine, or other commonly prescribed medications[a]

[a]Not specific to 13.3 mg/24 h patch.

AD, Alzheimer's disease; AUC024 h, area under the plasma-concentration time curve from 0–24 hours; Cmax, peak plasma concentration; time to Cmax; CLR, renal clearance; FI, fluctuation index (measure of relative difference between peak and trough concentrations); t1/2, plasma elimination half-life; Vd, apparent volume of distribution.

to receive treatment with rivastigmine 13.3 mg/24 h patch ($n = 356$) or 4.6 mg/24 h patch ($n = 360$). Patients in the high-dose group started treatment with the 4.6 mg/24 h patch and were titrated up to 13.3 mg/24 h over the first 8 weeks. The 4.6 mg/24 h dose was selected as a low-dose active comparator in order to more clearly evaluate the efficacy of the high dose of 13.3 mg/24 h.

The primary outcomes were changes from baseline to week 24 in scores for the Severe Impairment Battery (SIB), reflecting cognition, and the AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV), reflecting daily functioning. Secondary endpoints included the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) at week 24, reflecting global function, and the change from baseline to week 24 in the 12-item Neuropsychiatric Inventory (NPI-12), reflecting behavior.

Baseline characteristics were similar in the two groups. SIB and ADCS-ADL-SIV scores decreased from baseline in both groups, reflecting the progressive nature of the disease. However, significantly better outcomes were observed in the 13.3 mg/24 h group compared with the 4.6 mg/24 h group at both 16 and 24 weeks (Figure 2). At 24 weeks, the between-group least-squares mean difference was 4.9 points for SIB score ($p < 0.0001$; cognition) and 1.2 points for ADCS-ADL-SIV score ($p = 0.0247$; daily functioning) (Table 2). The distribution of ADCS-CGIC ratings at week 24 differed significantly between the groups ($p = 0.0023$), with a higher proportion of the 13.3 mg/24 h group showing an improvement in global functional status compared with the 4.6 mg/24 h group (Table 2). However, no significant between-group difference in the effect on NPI-12 score was seen [36].

A post hoc analysis stratified patients according to whether (60.8%) or not (39.2%) they had received concomitant memantine (up to 20 mg/day) during the study and found that rivastigmine 13.3 mg/24 h was associated with greater scores in cognition and ADL compared with 4.6 mg/24 h irrespective of whether or not patients received concomitant memantine [37].

Post hoc analyses of data from ACTION assessed whether the greater efficacy of the 13.3 mg/24 h patch versus the 4.6 mg/24 h patch in severe AD was driven by specific cognitive domains and ADL tasks [38,39]. Analysis of individual SIB items and domains derived from these items using factor analysis indicated that numerically less decline was seen in all domains and in most individual items with the 13.3 mg/24 h patch compared with the 4.6 mg/24 h patch. The largest LS mean treatment differences were seen for the domains '"visuospatial reasoning",' '"object naming",' '"recognition",' '"design copying",' '"social agency",' '"ideational praxis",' and '"comprehension".' This suggests that the 13.3 mg/24 h patch was effective at reducing impairment across a broad range of cognitive domains [38]. Numerically a greater effect was seen with the 13.3 mg/24 h patch versus the 4.6 mg/24 h patch for most ADCS-ADL-SIV items and for all four derived domains [39]. However, amongst the domains, a significantly superior effect was seen with the 13.3 mg/24 h patch only for 'Daily function' ($p = 0.038$), and not for 'Communication,' 'Independence,' or 'Environment.'

Another post hoc analysis of ACTION sought to identify baseline patient characteristics that could predict a response on the ADCS-CGIC (global function), and to determine whether an early ADCS-CGIC response could predict longer term outcomes [40]. An ADCS-CGIC score of 1–3 at week 24 was defined as 'improvement' and a score of 1–4 was defined as 'improvement or no change.' Significantly more patients in the 13.3 mg/24 h group than the 4.6 mg/24 h group had an 'improvement' in ADCS-CGIC (24.6% versus 16.2%, $p = 0.01$) or 'improvement or no change' (58.8% versus 45.4%, $p = 0.001$) at week 24. Logistic regression analysis identified treatment with 13.3 mg/24 h (versus 4.6 mg/24 h; odds ratio

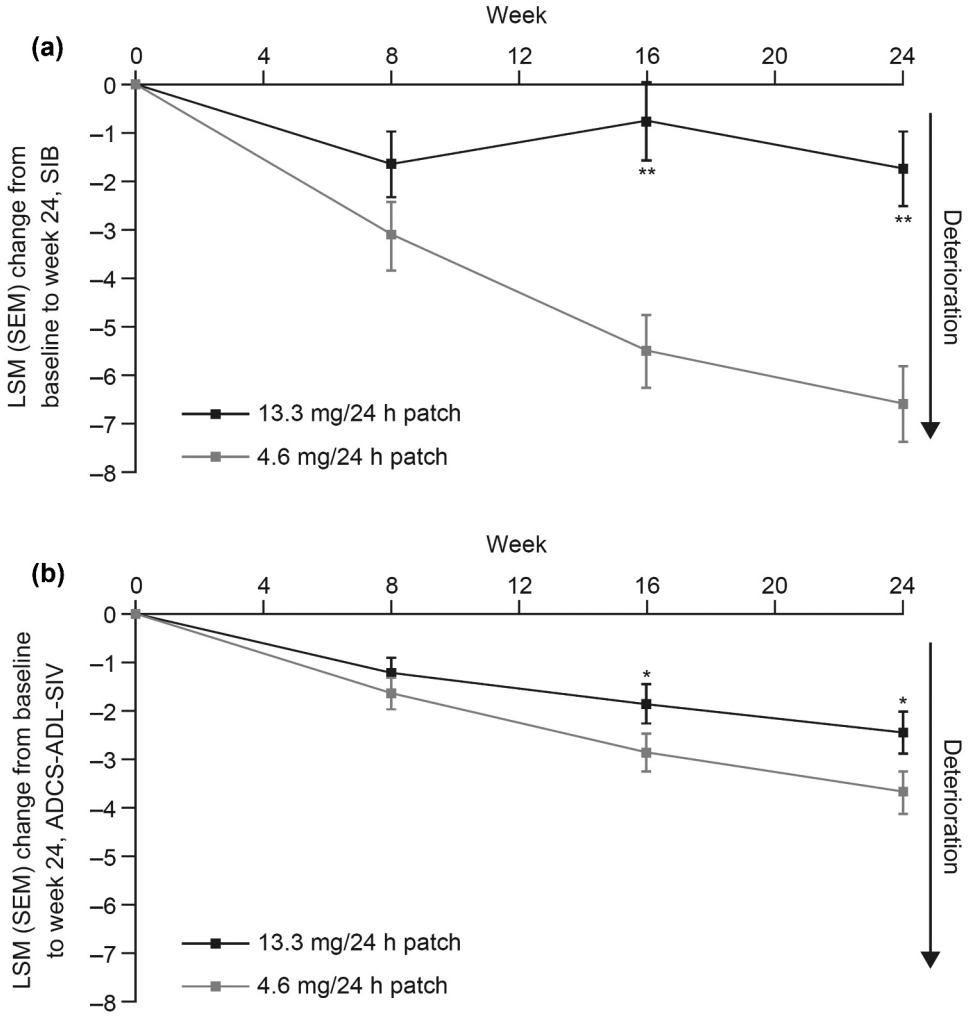

Figure 2. Efficacy of rivastigmine 13.3 mg/24 h patch versus 4.6 mg/24 h patch in patients with severe Alzheimer's disease dementia: least-squares mean change from baseline in (a) Severe Impairment Battery (SIB) score and (b) Alzheimer's disease cooperative study-ADL scale-severe Impairment Version (ADCS-ADL-SIV) score.

Data shown are least-squares mean change from baseline ±standard error. * $p < 0.05$, ** $p < 0.0001$ versus 4.6 mg/24 h. ADCS-ADL-SIV, Alzheimer's Disease Cooperative Study-ADL scale-Severe Impairment Version; SIB, Severe Impairment Battery.

1.65, $p = 0.01$) and age (OR 1.04, $p = 0.003$) as significant predictors of 'improvement' at week 24 in patients with severe AD. Treatment with 13.3 mg/24 h (OR 1.69, $p = 0.001$) and age (OR 1.03, $p = 0.002$) were also predictors of 'improvement or no change' at week 24, as was being treatment naive (OR 2.09, $p = 0.03$). Receiver operating characteristic curve analysis found that an ADCS-CGIC score of 4 ('no change') at week 8 or week 16 was the optimal threshold for predicting 'improvement' on the ADCS-CGIC at week 24, while a score of 5 ('minimal worsening') at week 8 or 16 was the optimal threshold for predicting 'improvement or no change' at week 24 [40].

3.1.2. ACTION: 24-week open-label extension

Patients who completed the 24-week double-blind ACTION study could continue into a 24-week open-label extension (OLE) study [41]. Patients either continued to receive treatment with the 13.3 mg/24 h patch ($n = 197$) or were titrated up from the 4.6 mg/24 h patch to 13.3 mg/24 h ($n = 199$). All patients were initially switched to 9.5 mg/24 h for the first 4 weeks of the OLE, after which they all received 13.3 mg/24 h for the remaining 20 weeks.

During the OLE, cognitive and functional decline was seen in both groups; however, there was numerically less decline in patients who continued on the 13.3 mg/24 h patch throughout the OLE compared with those who switched from the 4.6 mg/24 h patch to the 13.3 mg/24 h patch at the start of the OLE. At week 48, the change from (double-blind) baseline in SIB score was −4.7 points in the group who continued on the 13.3 mg/24 h patch versus −7.0 points in the group who switched from 4.6 mg/24 h to 13.3 mg/24 h. At week 48, the change from (double-blind) baseline in ADCS-ADL-SIV score was −3.9 points in the group who continued on the 13.3 mg/24 h patch versus −4.6 points in the group who switched from 4.6 mg/24 h to 13.3 mg/24 h. The percentages of patients whose ADCS-CGIC ratings showed improvement, no change, or worsening status at the end of the OLE were similar in the continuation and switch groups. Overall, at week 48, 16.5% of patients had improved, 26.2% had no change, and 57.2%

Table 2. Efficacy outcomes after 24 weeks' treatment with rivastigmine 13.3 mg/24 h patch or 4.6 mg/24 h patch in patients with severe Alzheimer's disease dementia (ACTION trial) adapted from [36] with permission of John Wiley & sons, Inc. Copyright © 2013.

Parameter	Rivastigmine 13.3 mg/24 h patch (N = 338)	Rivastigmine 4.6 mg/24 h patch (N = 335)	p
SIB score			
Baseline, mean (SD)	69.3 (21.5)	68.3 (22.8)	
LS mean change from baseline at week 24 (SE)	−1.7 (0.8)	−6.6 (0.8)	
LS mean difference (95% CI)	4.9 (2.8–7.0)		<0.0001
ADCS-ADL-SIV score			
Baseline, mean (SD)	29.7 (11.3)	29.1(11.9)	
LS mean change from baseline at week 24 (SE)	−2.4 (0.4)	−3.6 (0.4)	
LS mean difference (95% CI)	1.2 (0.2–2.3)		0.0247
ADCS-CGIC rating, n (%)			0.0023
Marked improvement	3 (1.0)	4 (1.3)	
Moderate improvement	11 (3.5)	11 (3.5)	
Minimal improvement	63 (20.1)	36 (11.4)	
No change	107 (34.2)	92 (29.2)	
Minimal worsening	76 (24.3)	99 (31.4)	
Moderate worsening	44 (14.1)	60 (19.0)	
Marked worsening	9 (2.9)	13 (4.1)	
NPI-12 score			
Baseline, mean (SD)	17.3 (15.4)	16.8 (16.7)	
LS mean change from baseline at week 24 (SE)	−0.1 (0.8)	1.5 (0.8)	
LS mean difference (95% CI)	−1.6 (−3.8 to 0.6)		0.1437

ADCS-ADL-SIV, Alzheimer's Disease Cooperative Study-ADL scale-Severe Impairment Version; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; CI, confidence interval; LS, least-squares; NPI-12, Neuropsychiatric Inventory; SD, standard deviation; SE, standard error; SIB, Severe Impairment Battery.

had worsened. These post-hoc results may suggest that early and sustained treatment with the rivastigmine 13.3 mg/24 h patch provides maximum clinical benefit in this patient population [41].

3.2. Cognitive and functional efficacy in mild-to-moderate AD

The double-blind OPTIMA trial compared the efficacy of the rivastigmine 13.3 mg/24 h patch with that of the 9.5 mg/24 h patch in patients with mild-to-moderate AD who had experienced cognitive and functional decline on the 9.5 mg/24 h patch during an initial open-label phase [42]. Patients aged 50–85 years with AD dementia and a MMSE score of ≥ 10 and ≤ 24 participated in an open-label phase of 24–48 weeks during which they received treatment with the 9.5 mg/24 h patch. Patients who met criteria for functional decline (investigator-assessed) and cognitive decline (≥2-point decline in MMSE from previous visit or ≥ 3-point decline from baseline) at weeks 24, 36 or 48 then entered a double-blind phase and were randomized to receive either the 13.3 mg/24 h patch or 9.5 mg/24 h patch for an additional 48 weeks [42].

The primary outcomes were the change from baseline to week 48 (double-blind phase) for the Instrumental Activities of Daily Living domain (items 7–23) of the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-IADL) scale and the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog). Secondary outcomes included time to functional decline (ADCS-IADL), and changes from baseline to week 48 (double-blind phase) for the Trail Making Test parts A and B (TMT-A and TMT-B), 10-item Neuropsychiatric Inventory (NPI-10), and NPI-caregiver distress scale (NPI-D) [42].

During the double-blind phase, cognitive and functional decline was observed in both groups, although the decline was numerically smaller in the 13.3 mg/24 h group compared with the 9.5 mg/24 h group at all timepoints for both ADCS-IADL and ADAS-cog scores. The decline in ADCS-IADL score (function) was significantly less in the 13.3 mg/24 h group versus the 9.5 mg/24 h group at weeks 16, 24, 32 and 48 weeks of the double-blind phase (Figure 3). At week 48, the between-group difference in LS mean scores was 1.7 points ($p = 0.002$); Table 3. The between-group difference in ADAS-cog score (cognition) did not achieve statistical significance at week 48 (Figure 3; Table 3). There were no significant differences between the groups with respect to time to ADCS-IADL (functional) decline, performance on the TMT-A and TMT-B tests (executive function), or NPI-10 and NPI-D scores (behavioral scales). Overall, these results showed that patients with mild-to-moderate AD who had shown a decline during treatment with the rivastigmine 9.5 mg/24 h patch might experience benefit from receiving a higher dose 13.3 mg/24 h patch, particularly with respect to functional outcomes [42].

Post hoc analyses data from OPTIMA assessed whether the greater efficacy of the 13.3 mg/24 h patch versus the 9.5 mg/24 h patch in mild-to-moderate AD was driven by selected cognitive functions and ADL tasks. One analysis considered the individual items of the ADCS-IADL, as well as groups of items requiring 'higher level functioning' or reflecting the ability to live independently ('autonomy') [43]. Numerically less decline in 'higher level functioning' factors, 'autonomy' factors, and 12 of 17 individual ADCS-IADL items were seen with the 13.3 mg/24 h patch at all timepoints during the study. Differences were statistically significant ($p < 0.05$) at weeks 32 and 48 for 'higher level functioning,' weeks 24–48 for 'autonomy,' and at one or more timepoint between weeks 8 and 48 for 10 of the individual items [43]. A post hoc factor analysis of ADAS-cog data found that the greater cognitive efficacy of the 13.3 mg/24 h patch appeared to be driven primarily by effects on memory rather than on language [44]. Significantly less decline was seen for the memory domain with 13.3 mg/24 h versus 9.5 mg/24 h at weeks 12, 24, and

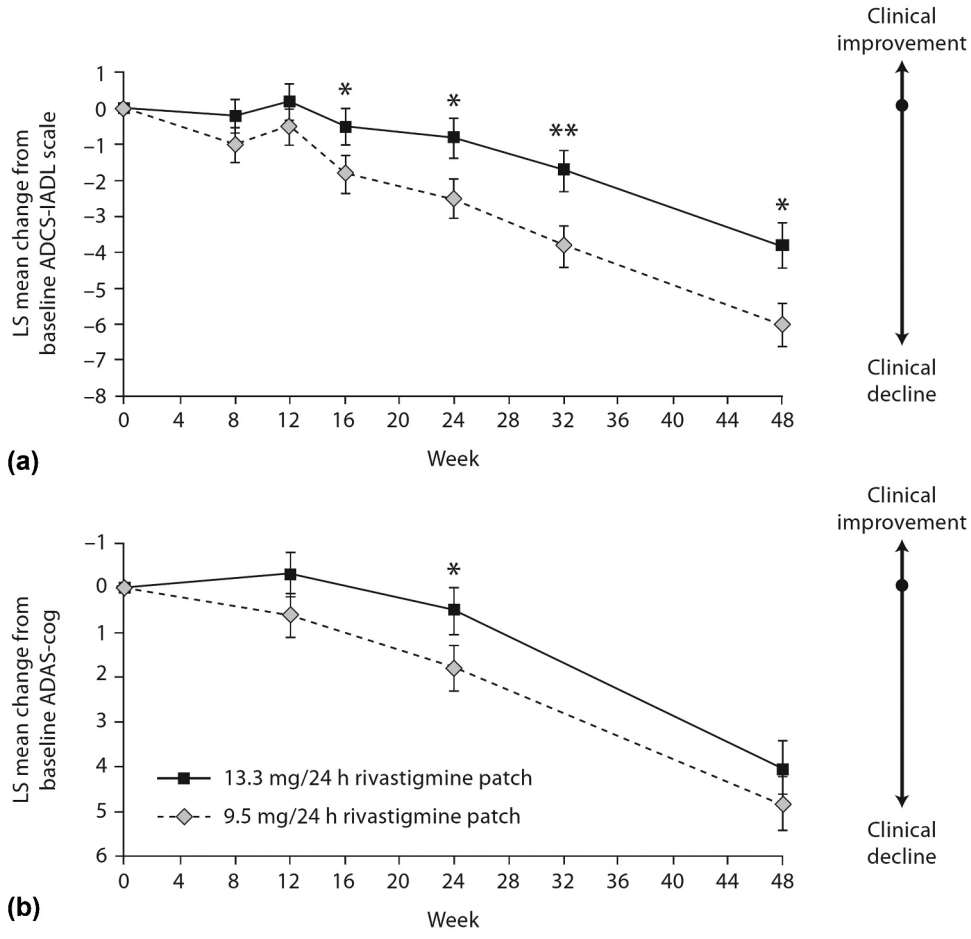

Figure 3. Efficacy of rivastigmine 13.3 mg/24 h patch versus 9.5 mg/24 h patch in patients with mild-to-moderate Alzheimer's disease dementia: least-squares mean change from baseline in (a) Instrumental activities of daily living domain (items 7–23) of the Alzheimer's disease Cooperative study–activities of daily living scale (ADCS-IADL) and (b) Alzheimer's disease assessment scale – cognitive subscale (ADAS-cog).

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Data shown are least-squares mean change ±standard error from baseline during the 48-week double-blind phase of the OPTIMA trial. * $p < 0.05$, ** $p < 0.0001$ versus 9.5 mg/24 h.

Table 3. Efficacy outcomes during 48 weeks' double-blind treatment with rivastigmine 13.3 mg/24 h patch or 9.5 mg/24 h patch in patients with mild-to-moderate Alzheimer's disease dementia who had shown decline on 9.5 mg/24 h patch during an initial open-label phase (OPTIMA trial) adapted from [42] with permission of Karger publishers, Basel, Switzerland. Copyright © 2012.

Parameter	Rivastigmine 13.3 mg/24 h patch (N = 265)	Rivastigmine 9.5 mg/24 h patch (N = 271)	p
ADCS-IADL score			
Baseline, mean	27.5	25.8	
LS mean change from baseline at week 24	−1.5	−2.8	
Difference in LS mean change (95% CI)	1.7 (0.5–2.9)		0.005
LS mean change from baseline at week 48	−4.4	−6.2	
Difference in LS mean change (95% CI)	2.2 (0.8–3.6)		0.002
ADAS-cog score			
Baseline, mean	34.4	34.9	
LS mean change from baseline at week 24	1.0	2.2	
Difference in LS mean change (95% CI)	−1.3 (−2.5 to −0.2)		0.027
LS mean change from baseline at week 48	4.1	4.9	
Difference in LS mean change (95% CI)	−0.8 (−2.1 to 0.5)		0.227

ADAS-cog, Alzheimer's Disease Assessment Scale – cognitive subscale; ADCS-IADL, Instrumental Activities of Daily Living domain (items 7–23) of the Alzheimer's Disease Cooperative Study – Activities of Daily Living scale; CI, confidence interval; LS, least squares.

48 ($p < 0.05$), with three items showing numerically less decline in this dose group at all timepoints (following commands, orientation, and word recognition). No significant difference between the groups was seen for the language domain.

A post hoc responder analysis of OPTIMA compared proportions of patients who were 'improvers' (ADAS-cog score improved by ≥ 4 points from baseline and no decline on ADCS-IADL) or 'non-decliners' (no decline on either scale) [45]. A significantly greater percentage of patients in the

13.3 mg/24 h group compared with the 9.5 mg/24 h group were 'improvers' at week 24 (16.6% versus 7.0%, $p < 0.001$) and at week 48 (7.9% versus 3.7%, $p = 0.023$). A significantly greater percentage of patients in the 13.3 mg/24 h group compared with the 9.5 mg/24 h group were 'non-decliners' at week 24 (26.8% versus 16.2%, $p = 0.002$), but not at week 48. Analyses of baseline predictors of response at weeks 24 or 48 produced inconsistent results.

3.3. Meta-analyses

A Bayesian network meta-analysis of 37 randomized controlled trials of any pharmacological treatments for mild-to-moderate AD found that the rivastigmine 13.3 mg/24 h patch had the highest probability of functional improvement for daily living (based on the ADCS-ADL scale), with a surface under the cumulative ranking curve (SUCRA) value of 93.7% [46]. A Bayesian network meta-analysis of 41 randomized controlled trials of cholinesterase inhibitors and memantine found that the rivastigmine 13.3 mg/24 h patch was the best option with respect to improvements in activities of daily living (SUCRA 93.2%) and clinical global impression (83.6%) [47].

3.4. Real-world evidence

A drug utilization study evaluated rivastigmine dose titration patterns over 11 months in patients with dementia treated in a real-world setting across four European countries [48]. Among the 614 participants, 258 (42.0%) were receiving the 4.6 mg/24 h patch at the start of the study period. Of these 258 patients, 88 (34.1%) continued the 4.6 mg/24 h dose throughout the study, while 107 (41.5%) were titrated up to the 9.5 mg/24 h patch after a mean of 58.4 (SD 60.1) days, with 28/107 further titrated to 13.3 mg/24 h.

Among 182/614 patients (29.6%) who were receiving the 9.5 mg/24 h patch at study start, 114/182 (62.6%) remained on this dose throughout the study, while 27 (14.8%) were titrated up to 13.3 mg/24 h after a mean of 115 (SD 98.0) days. Among 168/614 patients (27.4%) who were receiving the 13.3 mg/24 h patch at study start, 127 (75.6%) continued the same dose throughout the study period for a mean duration of 342.2 (SD 17.9) days.

Overall, the results indicated that most patients who were receiving the 9.5 mg/24 h or 13.3 mg/24 h patches at the start of the study continued the same dose during the next 11 months. Notably, one-third of patients who were receiving the 4.6 mg/24 h patch at study start were not titrated up to the recommended maintenance dose; the reasons for this were not clear.

4. Safety and tolerability of rivastigmine 13.3 mg/24 h

The rivastigmine 13.3 mg/24 h patch was generally well tolerated during up to 48 weeks of treatment in clinical trials in patients with mild-to-moderate or severe AD.

4.1. Severe AD

In ACTION, the overall incidence of adverse events (AEs) was similar in the 13.3 mg/24 h and 4.6 mg/24 h groups (74.6% versus 73.3%), as was the incidence of serious AEs (SAEs) (14.9% versus 13.6%) [36]. More patients in the 13.3 mg/24 h group than the 4.6 mg/24 h group discontinued due to SAEs (8.2% versus 4.5%) or non-serious AEs (13.5% versus 10.9%). Gastrointestinal-related AEs were more common in the 13.3 mg/24 h group versus the 4.6 mg/24 h group (nausea: 6.2% versus 2.8%; vomiting: 7.0% versus 2.5%; diarrhea: 6.5% versus 5.3%). Approximately a quarter of all patients experienced an application site reaction reported as an AE (24.5% with 13.3 mg/24 h versus 24.2% with 4.6 mg/24 h) [49].

No new safety signals were identified during the 24-week open-label extension of ACTION [41]. The incidence of AEs was similar in patients who continued on the 13.3 mg/24 h patch (57.9%) and those who were titrated up from 4.6 mg/24 h to 13.3 mg/24 h (59.8%). The frequency of gastrointestinal AEs was lower in patients who continued on the 13.3 mg/24 h patch (nauseas 1.5%, vomiting 3.0%, diarrhea 2.5%) than in those who switched from the 4.6 mg/24 h patch to the 13.3 mg/24 h patch (nausea 4.0%, vomiting 8.0%, diarrhea 5.0%), suggesting that gastrointestinal AEs are associated with initial dose increases. Patients who used the 13.3 mg/24 h patch experienced fewer side effects during the 24-week open-label extension (57.9%) compared to the initial 24-week double-blind study (74.6%), indicating that the patch becomes better tolerated over time.

4.2. Mild-to-moderate AD

During the 48-week double-blind phase of the OPTIMA trial, the overall incidence of AEs was higher in the 13.3 mg/24 h group than in the 9.5 mg/24 h group (75.0% versus 68.2%), but there was no difference in the rate of SAEs (15.7% versus 15.5%), and the rate of AEs leading to treatment discontinuation was lower in the 13.3 mg/24 h group than in the 9.5 mg/24 h group (9.6% versus 12.7%) [42]. During the double-blind phase, the overall incidence of AEs decreased over time in both the 13.3 mg/24 h and 9.5 mg/24 h groups, from 64.6% versus 54.8% in weeks 0–24 of to 42.3% versus 40.2% in weeks 24–48, indicating that tolerability improved over time with the 13.3 mg/24 h patch as well as with the 9.5 mg/24 h patch (Figure 4) [42]. During the double-blind phase, the most common type of AE by primary system organ class were gastrointestinal disorders (29.3% versus 19.1% with 13.3 mg/24 h and 9.5 mg/24 h, respectively). Application site reactions occurred in 22.9% of patients during the 9.5 mg/24 h open-label phase, and in 12.0% of the 9.5 mg/24 h group and 11.4% of the 13.3 mg/24 h group during the double-blind phase [49].

4.3. Real-world evidence

In the European drug utilization study, the tolerability profile of the rivastigmine patch was consistent with the known profile for the drug [48]. Across all doses (4.6–13.3 mg/24 h), AEs were reported for 36.4% of patients, and led to discontinuation for

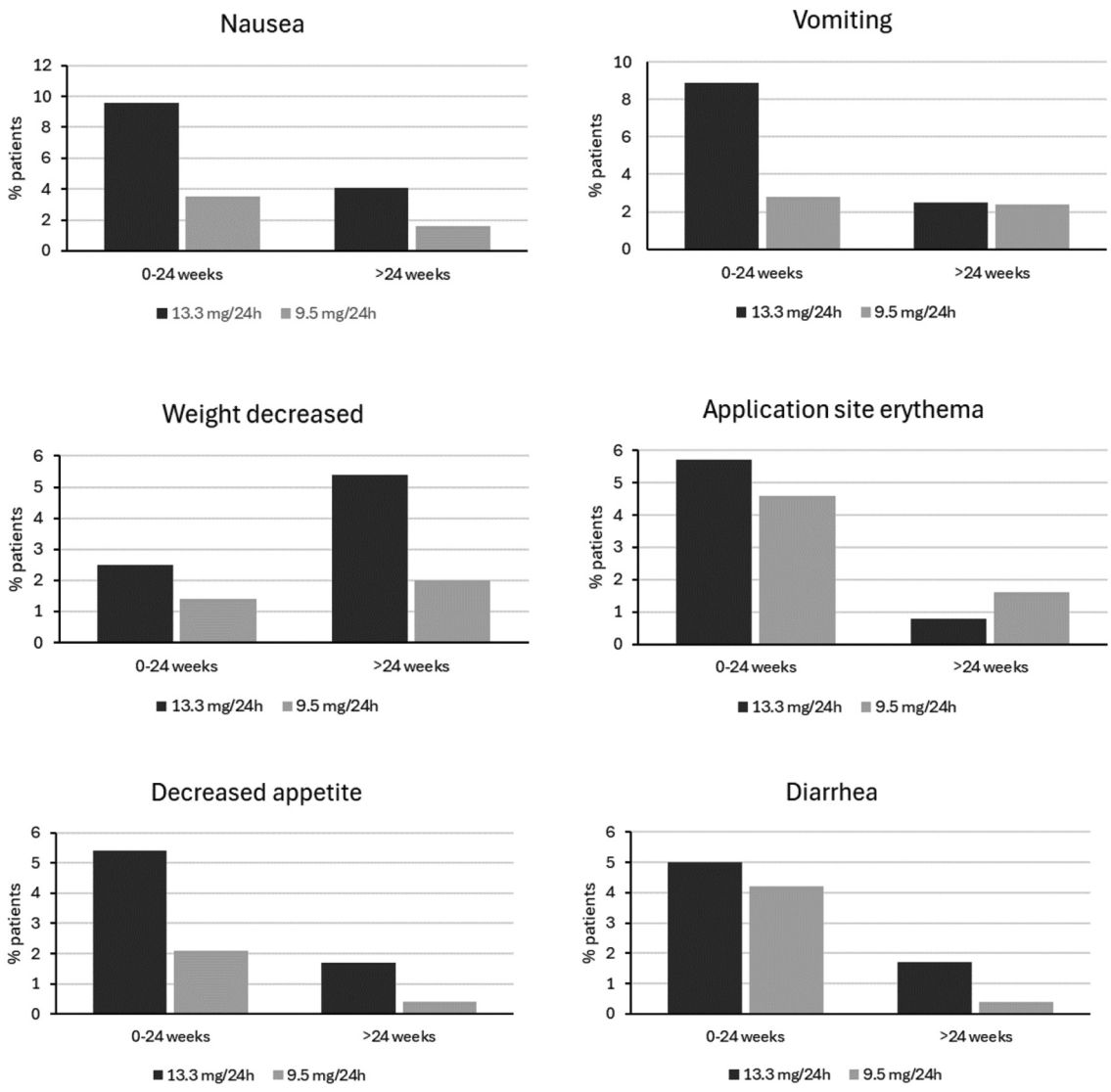

Figure 4. Adverse events with transdermal rivastigmine 13.3 mg/24 h versus 9.5 mg/24 h according to time period (0–24 weeks and >24 weeks) during the 48-week double-blind phase of the OPTIMA trial in patients with mild to moderate Alzheimer's disease who had declined on the 9.5 mg/24 h patch [42].

Adverse events occurring in ≥ 5% of patients in either group in at least one time period (0–24 weeks or >24 weeks) are shown.

8.3% of patients. Common AEs leading to discontinuation included application site reactions, dizziness, nausea and vomiting.

5. Conclusion

Rivastigmine has been available for the treatment of AD for more than 20 years. Among the various formulations and doses of rivastigmine that are available, the 13.3 mg/24 h transdermal patch was introduced most recently.

The ACTION trial in patients with severe AD showed that the 13.3 mg/24 h patch had superior efficacy compared with the 4.6 mg/24 h patch with respect to cognition, activities of daily living, and global functioning. The efficacy of the 13.3 mg/24 h patch was sustained during up to 48 weeks of treatment and was not affected by concomitant treatment with memantine. The results indicated that early and sustained treatment with the rivastigmine 13.3 mg/24 h patch might provide maximum clinical benefit in patients with severe AD. The OPTIMA trial showed that for patients with mild-to-moderate AD who had declined on the 9.5 mg/24 h patch, switching to 13.3 mg/24 h led to significantly less decline in daily function (ADCS-IADL) during the subsequent 48 weeks compared with continuation on 9.5 mg/24 h. Significantly less decline in cognition was seen with 13.3 mg/24 h versus 9.5 mg/24 h at 24 weeks. Meta-analyses suggest the rivastigmine 13.3 mg/24 h patch compares favorably with other drugs with respect to functional outcomes in patients with AD.

The rivastigmine 13.3 mg/24 h patch was generally well tolerated in clinical trials. AEs were consistent with the known tolerability profile of the drug, and included gastrointestinal events and administration site reactions, which tended to decrease in incidence over time. A real-world

study indicated that most patients who received the rivastigmine 13.3 mg/24 h patch continued on that dose in the long term.

Overall, available evidence supports rivastigmine 13.3 mg/24 h transdermal patch as a useful treatment option for patients with mild, moderate, or severe AD.

6. Expert opinion

Cholinesterase inhibitors are one of the mainstays of the symptomatic treatment of patients with AD. Rivastigmine is available both as an oral formulation and as transdermal patches, with the latter formulation helping to improve tolerability while maintaining efficacy.

As discussed in this paper, the high-dose patch (13.3 mg/24 h) has been associated with potential additional benefits compared with lower dose patches in patients with mild-to-moderate or severe AD. In particular, it has been linked to maintaining daily functioning and global clinical status, in addition to providing cognitive benefits. Reduced functioning affects the ability of patients to live independently, and the level of support needed from caregivers [16]. The effects of the high-dose rivastigmine patch on activities of daily living may help patients retain independence for longer. Notably, in OPTIMA, the 13.3 mg/24 h patch provided efficacy with respect to 'higher level functioning' and 'autonomy' (reflecting the ability to live independently) in patients who were no longer responding sufficiently to the 9.5 mg/24 h patch [42]. Network meta-analyses suggest that, compared with other agents, the rivastigmine 13.3 mg/24 h patch has been reported to provide functional benefits in activities of daily living and overall functional status [46,47].

Transdermal rivastigmine is generally well tolerated when dosing recommendations are followed, and no unexpected safety concerns have been identified with the 13.3 mg/24 h patch. Although higher doses are associated with an increased incidence of side effects, these remain within the expected profile of the drug; gastrointestinal AEs (such as nausea/vomiting and diarrhea) and application site reactions are among the most common AEs, although they are generally mild or moderate in severity. The higher the patch dose, the greater the amount of rivastigmine that is released into the body. This leads to a dose-dependent inhibition of acetylcholinesterase activity [34]. Because acetylcholine is a proemetic neurotransmitter [50], a lower metabolism of acetylcholine and an increase in its concentration lead to a higher proportion of AEs such as nausea and vomiting. Tolerability appears to improve over time [42]. Skin reactions can be mitigated by regularly changing the application site and, where necessary, using emollients and topical corticosteroids [51].

Transdermal patches may be more convenient than oral capsules for patients and their caregivers, and can potentially improve treatment compliance [52,53]. In one study, over 70% of caregivers preferred rivastigmine patches to capsules, finding the patches were easier to use and caused less interference with daily life [53]. Another study found that compliance with treatment improved with use of the patch [52].

Treatment with transdermal rivastigmine is initiated at a dose of 4.6 mg/24 h, after which it should be titrated to the usual maintenance dose of 9.5 mg/24 h, with further titration to 13.3 mg/24 h recommended for patients who deteriorate during treatment with the 9.5 mg/24 h patch [32]. Interestingly, a study in a routine practice setting found that a substantial proportion of patients remained on 4.6 mg/24 h patches during an 11-month follow-up period [48]. While it was not clear whether this was because adequate clinical improvement was seen at this dose or if it was due to tolerability issues, clinicians need to monitor patients regularly to ensure that patients receive optimal treatment.

There are several areas in which further research is needed. Identifying optimal combination therapy regimens using currently available agents remains a priority, along with evaluating treatment approaches in younger patients. Additionally, further work is also needed to evaluate the role of therapies in prodromal AD and in individuals at high risk of developing AD, including the use of biomarkers and genetic risk profiles to provide personalized preventive or therapeutic regimens for individuals [54]. Disease-modifying anti-amyloid drugs against AD are now available in the US and elsewhere and will soon be available in the European Union. Various other approaches are also being evaluated, including targeting the tau pathway, targeting inflammation, and enhancing interneuronal communication [55,56]. Given the complex nature of AD, combination strategies are likely to play a critical role, for example, pairing a cognition-enhancing agent (e.g. a ChEI) with a disease-modifying therapy, such as an anti-amyloid-β or anti-tau agent [54].

Given the role of cholinergic deficits early in the pathophysiology of AD, ChEIs are likely to remain a key component of the treatment of AD. Transdermal rivastigmine is a valuable option, providing similar efficacy to oral rivastigmine but with improved tolerability. The ability to titrate up to a dose of 13.3 mg/24 h provides a useful option for patients with severe AD or with an inadequate response to lower doses of rivastigmine.

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