

Rivastigmine From Capsules to Patch: Therapeutic Advances in the Management of Alzheimer's Disease and Parkinson's Disease Dementia

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ABSTRACT

Objective: To discuss the pharmacology, mechanism of action, and chemical properties of the cholinesterase inhibitor (ChEI) rivastigmine; to provide a rationale for transdermal delivery and supportive clinical data, along with practical guidance on rivastigmine patch use in Alzheimer's disease and Parkinson's disease dementia.

Data Sources: Pivotal studies of rivastigmine capsules and patch were identified using PubMed and the rivastigmine US prescribing information. PubMed searches were performed in 2013 using *rivastigmine* as a keyword.

Study Selection: English-language articles related to rivastigmine considered of relevance to primary care physicians were included.

Data Synthesis: Pharmacologic differences exist between rivastigmine and other ChEIs. Clinical studies demonstrate symptomatic efficacy of oral rivastigmine across all stages of Alzheimer's disease and mild-to-moderate Parkinson's disease dementia. However, gastrointestinal adverse events limit access to optimal therapeutic doses. Strategies that lower maximum plasma concentrations (C_{max}) and prolong time to C_{max} , ie, transdermal delivery, may improve tolerability. Clinical registration studies have demonstrated improved tolerability of rivastigmine 9.5-mg/24-h patch versus 6-mg twice-daily capsules in mild-to-moderate Alzheimer's disease, and a positive benefit-risk profile of 13.3-mg/24-h versus 9.5-mg/24-h patch in patients needing enhanced efficacy. Clinical data comparing 13.3-mg/24-h versus 4.6-mg/24-h patch in severe Alzheimer's disease demonstrated efficacy on cognition and activities of daily living. These data led to approval of rivastigmine patch in severe Alzheimer's disease. Transdermal delivery also has practical advantages, including simple, once-daily administration and a visual indicator of compliance. Potential application site reactions can be minimized and need not be a barrier to treatment.

Conclusions: In addition to practical advantages, rivastigmine patch may improve clinical outcomes throughout the course of Alzheimer's disease by providing access to high-dose efficacy without compromising tolerability.

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Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment, behavioral changes, and deterioration in an individual's ability to perform activities of daily living (ADL).¹ Dementia may also arise in patients with Parkinson's disease.²

Cholinesterase inhibitors (ChEIs; rivastigmine, donepezil, and galantamine) are commonly prescribed for the symptomatic treatment of Alzheimer's disease in the United States. Among the ChEIs, rivastigmine is distinct in being the only ChEI approved in both oral and transdermal patch formulations,^{3,4} and the only ChEI approved for the symptomatic treatment of both Alzheimer's disease and mild-to-moderate Parkinson's disease dementia.^{3,4} The *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine is also approved for moderate-to-severe dementia of the Alzheimer's type in the United States.^{5,6} ChEIs are recommended as a first-line treatment in patients with mild-to-moderate Alzheimer's disease; rivastigmine and donepezil are indicated, alone or in combination with memantine, in moderate-to-severe disease stages.⁷

In the absence of disease-modifying agents, the primary objective of treatment with currently available Alzheimer's disease therapies is improvement or stabilization of symptoms.¹ In the clinical trial setting, Alzheimer's disease symptoms and treatment efficacy are commonly monitored using a variety of general and disease-specific assessment scales.⁸⁻¹⁶ In addition to demonstrating symptomatic efficacy, rivastigmine therapy may reduce caregiver burden and delay nursing home placement compared with remaining untreated.^{17,18} Importantly, adherence to Alzheimer's disease therapies, such as rivastigmine, is needed to improve or stabilize the patient's quality of life.¹⁹

The objective of the current review is to provide an overview of the pharmacology, mechanism of action, and chemical properties of rivastigmine. Findings of clinical studies with rivastigmine capsules, the rationale for transdermal delivery, supportive clinical data, and practical guidance on the use of rivastigmine transdermal patch in dementia management, particularly Alzheimer's disease, are discussed.

METHOD

Data sources included pivotal preclinical and clinical studies of rivastigmine capsules and rivastigmine transdermal patch identified using PubMed and the rivastigmine US prescribing information. PubMed searches were performed in 2013 using *rivastigmine* as a keyword. English-language articles related to rivastigmine considered of relevance to primary care physicians were included.

- Rivastigmine has proven symptomatic, dose-dependent efficacy in mild-to-moderate and severe Alzheimer's disease, and mild-to-moderate Parkinson's disease dementia.
- Development of a rivastigmine transdermal patch versus oral capsules has enabled access to high-dose efficacy without compromising tolerability.
- Available clinical evidence, alongside practical aspects of rivastigmine patch administration for both patients and caregivers, supports the use of rivastigmine transdermal patch throughout the course of Alzheimer's disease.

FOCUS ON RIVASTIGMINE

Pharmacology, Mechanism of Action, and Chemical Properties of Rivastigmine

Rivastigmine ((S)-3-[1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate) is a slowly reversible ChEI; donepezil and galantamine are rapidly reversible.^{3,20} Administration of rivastigmine increases the concentration of acetylcholine (ACh) available for synaptic transmission through reversible inhibition of ACh hydrolysis by cholinesterases (ChEs).³ Rivastigmine does not interact with peripheral acetylcholinesterase (AChE) anionic sites.²¹ Rivastigmine is metabolized to an inactive metabolite (NAP-226-90) by central ChEs themselves, with little or no involvement of the hepatic cytochrome P450 system.²² The cytochrome P450 system is involved in the metabolism of approximately 60%–80% of drugs that affect the central nervous system.²³ The lack of involvement of the cytochrome P450 system means that rivastigmine has fewer clinically relevant drug-drug interactions in an elderly population likely to be receiving multiple concomitant medications for numerous comorbidities,²⁴ compared with donepezil and galantamine, which are metabolized primarily by these enzymes.²² Rivastigmine has relatively low plasma protein binding (40%),³ which is also expected to reduce its propensity for drug-drug interactions.²² The pharmacokinetic properties of rivastigmine, donepezil, and galantamine, along with their approved indications and doses, are summarized in Table 1.^{3,4,20–30}

The elimination time (plasma half-life) of rivastigmine is approximately 1.3–2 hours for capsules and 3.4 hours for the transdermal patch formulation.³⁰ The elimination half-life in the cerebrospinal fluid for capsules is approximately 0.3–3.0 hours.²² After a single 6-mg oral dose, inhibition of ChEI activity is detected in the cerebrospinal fluid for approximately 10 hours, with maximum inhibition of 60% occurring approximately 5 hours after dosing.^{3,31}

Pharmacologic differences exist between rivastigmine and other ChEIs in terms of their effects on AChE activity and protein levels in the cerebrospinal fluid.²⁹ In 1 study, rivastigmine was associated with a decrease in AChE protein levels, while an increase was observed following treatment with donepezil or galantamine.²⁹

Key Findings of Clinical Studies With Rivastigmine Oral Capsules in Alzheimer's Disease and Parkinson's Disease Dementia

Key findings from pivotal Alzheimer's disease studies and a study in Parkinson's disease dementia with rivastigmine oral capsules are summarized in Table 2.^{32–37} These studies indicate that, compared with placebo, rivastigmine provides benefits on a number of symptom domains, including cognition, global functioning, and performance of ADL in patients with mild, moderate, and severe Alzheimer's disease and mild-to-moderate Parkinson's disease dementia.^{32–37} In patients with mild-to-moderate Alzheimer's disease, the efficacy of rivastigmine has been shown to be dose-dependent; however, high doses are associated with an increase in the incidence of gastrointestinal adverse events, eg, nausea, vomiting, and diarrhea, particularly during dose titration.³⁸ In patients with mild-to-moderate Parkinson's disease dementia, the most common adverse events with long-term use of oral rivastigmine are nausea, tremor, fall, and vomiting.²

Rationale for Development of a Transdermal Patch

Gastrointestinal adverse events arise owing to the rapidly achieved maximum concentrations (C_{max}) in the central nervous system observed following oral dosing (Figure 1).³⁰ Strategies that lower C_{max} and prolong the time to maximum concentration (T_{max}) may improve tolerability³⁰ and permit access to maximum therapeutic doses. In a 26-week, randomized, double-blind, placebo-controlled study, there was a tendency for improved gastrointestinal tolerability when rivastigmine capsules 2–12 mg/d were administered in a thrice-daily regimen compared with twice daily.³⁷ Furthermore, the thrice-daily regimen permitted titration to higher doses compared with the twice-daily regimen; 71% of patients in the thrice-daily group and 60% in the twice-daily group reached a dose of 9–12 mg/d.³⁷

Another strategy that may improve gastrointestinal tolerability is transdermal delivery.³⁹ Rivastigmine is a small molecule (approximately 250 Da) with both lipophilic and hydrophilic properties, making it well suited to transdermal delivery.⁴⁰ Rivastigmine transdermal patch is a thin, “matrix” patch consisting of 4 layers: a backing layer, an acrylic matrix, a silicone matrix, and a release liner (Figure 2).⁴⁰ The backing layer (visible layer after application) is a nontoxic, waterproof layer that retains skin moisture beneath the patch and increases drug penetration.⁴⁰ The acrylic matrix contains the drug, antioxidants, and an acrylic polymer mixture that controls drug delivery.⁴⁰ The silicone matrix lies against the skin; it permits optimal skin adhesion while allowing nontraumatic patch removal.⁴⁰ The release liner is removed before application and designed to prevent leaching of ingredients before the patch is applied to the skin.⁴⁰

Rivastigmine once-daily transdermal patch (4.6 mg/24 h [5 cm²], 9.5 mg/24 h [10 cm²], and 13.3 mg/24 h [15 cm²]) provides continuous drug delivery from the skin into the blood stream and subsequently crosses the blood-brain barrier leading to sustained drug plasma and central nervous system concentrations over a 24-hour period (Figure 1).^{30,41}

Table 1. The Approved Indications, Doses, and Pharmacokinetic Properties of Rivastigmine, Donepezil, and Galantamine

Variable	Rivastigmine (Exelon)	Donepezil (Aricept)	Galantamine (Razadyne)
Indications ^{3,4,25,26}	Mild-to-moderate Alzheimer's disease Mild-to-moderate Parkinson's disease dementia Severe Alzheimer's disease	Mild-to-moderate Alzheimer's disease Moderate-to-severe Alzheimer's disease	Mild-to-moderate Alzheimer's disease
Chemical class ²⁷	Carbamate	Piperidine	Tertiary alkaloid
Formulations ^{3,4,25,26}	Oral capsules Oral solution Transdermal patch	Oral capsules ODT	Oral tablets Oral solution Oral ER capsules
Initial doses ^{3,4,25,26}	1.5-mg BID capsules/solution ^{a,b} 4.6-mg/24-h (5 cm ²) patch ^{a,b}	5-mg QD capsules/ODT	4-mg BID oral tablets/solution 8-mg QD oral ER capsules
Maintenance doses ^{3,4,25,26}	3–6-mg BID capsules/solution ^a 1.5–6-mg BID capsules/solution ^b 9.5-mg/24-h (10 cm ²) patch ^{a,b} 13.3-mg/24-h (15 cm ²) patch ^{a,b,c}	5-mg QD capsules/ODT ^a 10-mg QD capsules/ODT ^{a,d} 23-mg/d QD capsules ^d	8–12-mg BID oral tablets/solution 16–24-mg QD oral ER capsules
ChE inhibition ^{20,28}	Slowly reversible	Rapidly reversible	Rapidly reversible
Treatment effect on CSF AChE activity ²⁹	↓	↑	↓
Treatment effect on CSF AChE protein levels ²⁹	↓	↑	↑
Interaction with peripheral AChE anionic site ²¹	No	Yes	Unknown
Metabolism ^{3,4,20,22–26}	Target enzymes (drug-drug interactions rare)	CYP2D6, CYP3A4	CYP2D6, CYP3A4
Elimination ²⁰	Kidney	Liver	Kidney and liver
Plasma protein binding ^{4,25,26}	40%	96%	18%
Plasma half-life ^{3,20,25,26,30}	1.3–2 h (capsules) 3.4 h (patch)	70 h	7 h

^aMild-to-moderate Alzheimer's disease.

^bMild-to-moderate Parkinson's disease dementia.

^cSevere Alzheimer's disease.

^dModerate-to-severe Alzheimer's disease.

Abbreviations: AChE = acetylcholinesterase, BID = twice daily, ChE = cholinesterase, CSF = cerebrospinal fluid, CYP = cytochrome P450 enzymes, ER = extended release, ODT = orally disintegrating tablets, QD = once daily.

Symbols: ↓ = decrease, ↑ = increase.

The 9.5-mg/24-h rivastigmine patch is associated with lower C_{max} and longer T_{max} than is observed with 6-mg twice-daily capsules, while drug exposure is comparable (Figure 1).⁴¹ It was hypothesized that this smoother pharmacokinetic profile would improve tolerability compared with oral capsules twice daily and may provide access to higher, more efficacious doses of rivastigmine.⁴¹

Practical Advantages of Transdermal Therapy for Alzheimer's Disease

In addition to potential benefits to the patient in terms of improved tolerability, there are numerous practical advantages of transdermal therapy for Alzheimer's disease, which include:

- Simple, once-daily administration
- Provides a visual reminder and reassurance that treatment is being taken, yet is small and discrete
- Can be labeled with a ballpoint pen, ie, with the day of the week, which may remind the caregiver to remove the previous day's patch and apply a new one
- Treatment option for patients with difficulty swallowing
- Alternative mode of delivery for patients with a large oral pill burden

- Can be taken independently of food intake, as transdermal delivery bypasses first-pass metabolism, which increases bioavailability.^{39,40,42–44}

The pivotal 24-week, randomized, placebo-controlled, double-blind, double-dummy Investigation of TransDermal Exelon in ALzheimer's Disease (IDEAL) study (ClinicalTrials.gov Identifier: NCT00099242) compared the efficacy, safety, and tolerability of 6-mg twice-daily rivastigmine capsules, 9.5-mg/24-h rivastigmine patch, and 17.4-mg/24-h rivastigmine patch (not an approved dose) versus placebo in 1,195 patients with mild-to-moderate Alzheimer's disease.⁴⁵ In a subanalysis of the IDEAL study, at week 24, 72% of caregivers of patients with Alzheimer's disease enrolled in the study preferred the patch formulation to capsules overall.⁴⁶ The most common reasons for patch preference were ease of following the schedule, ease of use, self-sufficiency, no/fewer side effects, and convenience.⁴⁶

Treatment adherence is a particular challenge in the management of Alzheimer's disease.⁴² Observational treatment reviews reported 1-year persistence rates ranging from 40%–54% with oral ChEIs.^{47,48} Alzheimer's disease treatment is usually administered by caregivers who are often elderly themselves and may have difficulty understanding complex treatment regimens and remembering when, where,

Table 2. Findings From Key Clinical Studies With Rivastigmine Oral Capsules

Design	Study ^a	Dose ^b	Symptom Domain				Overall Incidence of Patients Experiencing at Least 1 Adverse Event, %
			Activities of Daily Living	Behavior	Cognition	Global Function	
Mild-to-moderate Alzheimer's disease							
26-wk, double-blind, placebo-controlled RCT	Rösler et al, 1999 ³²	1–4-mg/d BID capsules, N = 243	X ^{c,d,e}	NA	X ^{c,d,e}	X ^{c,d,e}	71
		6–12-mg/d BID capsules, N = 243	✓ ^{d,e}	NA	✓ ^{d,e}	✓ ^{c,d,e}	91
	Corey-Bloom et al, 1998 ³³	versus placebo, N = 239	72
		1–4-mg/d BID capsules, ^f N = 233	X ^{c,d,e}	NA	✓ ^{c,d,e}	✓ ^{c,d,e}	> 85 across all treatment groups
	Feldman and Lane, 2007 ³⁷	6–12-mg/d BID capsules, ^f N = 231	✓ ^{c,d,e}	NA	✓ ^{c,d,e}	✓ ^{c,d,e}	
		versus placebo, N = 235	92
	Schneider et al, 1998 ³⁴	2–12-mg/d BID capsules, ^f N = 227	✓ ^{c,d}	NA	✓ ^{c,d}	✓ ^{c,d,e}	76
		2–12-mg/d TID capsules, ^f N = 229	✓ ^{c,d}	NA	✓ ^{c,d,e}	✓ ^{c,d,e}	Not included in pooled analysis
		versus placebo, N = 222	
		1–4-mg/d BID capsules, ^f N = 651	✓ ^d	NA	✓ ^e	✓ ^e	91
		6–12-mg/d BID capsules, ^f N = 828	✓ ^d	NA	✓ ^e	✓ ^e	92
		versus placebo, N = 647	76
Severe Alzheimer's disease							
26-wk, double-blind, placebo-controlled RCT	Lopez-Pousa et al, 2004 ³⁵	6–12-mg/d BID capsules, ^f N = 109	X ^d	X ^d	✓ ^d	✓ ^d	88
		versus placebo, N = 109	69
Parkinson's disease dementia							
24-wk, placebo-controlled RCT	Emre et al, 2004 ³⁶	3–12-mg/d BID capsules, ^f N = 362	✓ ^d	✓ ^d	✓ ^d	✓ ^d	84
		versus placebo, N = 179	71

^aSchneider et al³⁴ was a pooled analysis of data from three 26-week RCTs. Patients received 1–4 mg/d, 6–12 mg/d, or fixed doses of 3 mg/d, 6 mg/d, or 9 mg/d of oral rivastigmine.

^bNs based on the randomized population; percentage values for adverse event data based on the safety population.

^cIntent-to-treat population.

^dIntent-to-treat population with a last-observation-carried-forward imputation.

^eObserved case population.

^fKey efficacy assessments (indicated in bold text) were the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), Clinician Interview–Based Impression of Change (CIBIC), and Progressive Deterioration Scale in Rösler et al,³² Corey-Bloom et al,³³ and Schneider et al³⁴; the ADAS-cog and CIBIC-plus in Feldman and Lane³⁷; the Severe Impairment Battery and 10-item Neuropsychiatric Inventory in Lopez-Pousa et al³⁵; and the ADAS-cog and Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change in Emre et al.³⁶

Abbreviations: BID = twice daily, NA = not assessed, RCT = randomized controlled trial, TID = thrice daily.

Symbols: ✓ = $P < .05$ versus placebo, X = $P > .05$ versus placebo.

and how to administer treatment. For physicians, establishing a regular follow-up routine and a close working relationship with the caregiver will help ensure that treatments are being administered correctly and facilitate decision making as the disease progresses.⁴⁹ The advantages of patch versus oral therapy described previously may help improve adherence to treatment. In addition, a transdermal patch empowers the caregiver and may alleviate some of the anxiety associated with medication management.⁴²

Key Findings of Clinical Studies With Rivastigmine Patch in Alzheimer's Disease

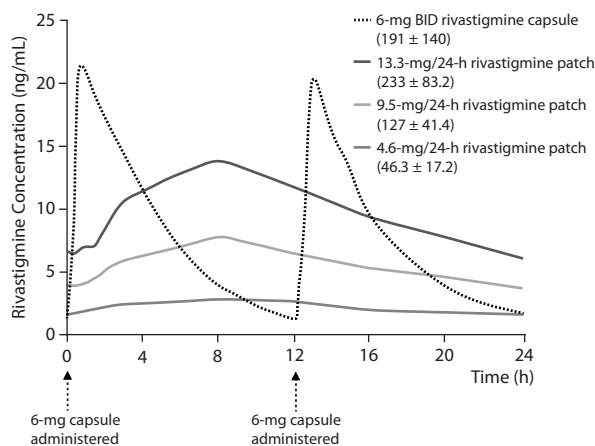
Key findings from pivotal studies of rivastigmine patch in patients with Alzheimer's disease are summarized below.^{45,50,51}

The IDEAL study. In IDEAL, the pivotal placebo-controlled trial of rivastigmine patch, 9.5-mg/24-h patch, 17.4-mg/24-h patch, and 6-mg twice-daily capsules demonstrated significantly greater efficacy versus placebo on

the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), while the 9.5-mg/24-h patch and 6-mg twice-daily capsules demonstrated significantly greater efficacy versus placebo on the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change scale (ADCS-CGIC) (coprimary outcomes; Table 3).⁴⁵

Rivastigmine patch demonstrated dose-dependent efficacy versus placebo on the ADAS-cog. However, the 17.4-mg/24-h patch did not achieve statistical significance versus placebo on the ADCS-CGIC in the main efficacy analysis population, only in supportive analyses.⁴⁵

Compared with placebo, the incidence of gastrointestinal adverse events was slightly higher, but not significantly so, with the 9.5-mg/24-h patch (Table 4).⁴⁵ In addition, a higher proportion (95.9%) of patients in the 9.5-mg/24-h patch group received the target dose at the end of the maintenance phase (week 24) versus capsules (64.4%), likely resulting from the improved gastrointestinal tolerability with the patch compared with capsules.^{52,53} Together, these

Figure 1. Pharmacokinetic Profile of Rivastigmine Oral Capsules and Transdermal Patch^{a,b}

^aReprinted with permission from Lefèvre et al.³⁰

^bValues in parentheses in the figure legend represent the area under the curve from 0 to 24 h (AUC₀₋₂₄) in ng·h/mL. Abbreviation: BID = twice daily.

findings confirmed the improved tolerability of rivastigmine transdermal patch versus a comparable oral dose. On the basis of the findings of this study, 9.5-mg/24-h rivastigmine patch was approved for the treatment of mild-to-moderate Alzheimer's disease in the United States³ and many other regions worldwide. The 17.4-mg/24-h patch dose is not currently approved, as the reported incidence of nausea and vomiting was not dissimilar to that observed with capsules (Table 4).^{45,52}

The *Optimizing Transdermal Exelon In Mild-to-moderate Alzheimer's Disease (OPTIMA)* study. In clinical practice, improved tolerability may result in fewer patients discontinuing treatment and provide easier access to maximum therapeutic doses, which could improve overall patient and caregiver outcomes. The 13.3-mg/24-h rivastigmine patch was used as a titration dose in IDEAL, but the study was not powered to investigate the efficacy, safety, and tolerability of this dose. The benefit-risk profile of treatment with 13.3-mg/24-h patch as a means of achieving higher-dose efficacy versus 9.5-mg/24-h patch was investigated in the OPTIMA study (ClinicalTrials.gov NCT00506415).⁵⁰ This was a 72- to 96-week multicenter trial, comprising a 24- to 48-week initial open-label phase with 9.5-mg/24-h patch, followed by a 48-week randomized, double-blind phase with 13.3-mg/24-h versus 9.5-mg/24-h patch.⁵⁰ Patients with mild-to-moderate Alzheimer's disease were enrolled in the initial open-label phase; those meeting predefined criteria for cognitive (based on a ≥ 2 -point decline in Mini-Mental State Examination [MMSE] score from previous visit or ≥ 3 -point decline on the MMSE from baseline) and functional (based on investigator's judgment) decline were randomized in the double-blind phase.⁵⁰

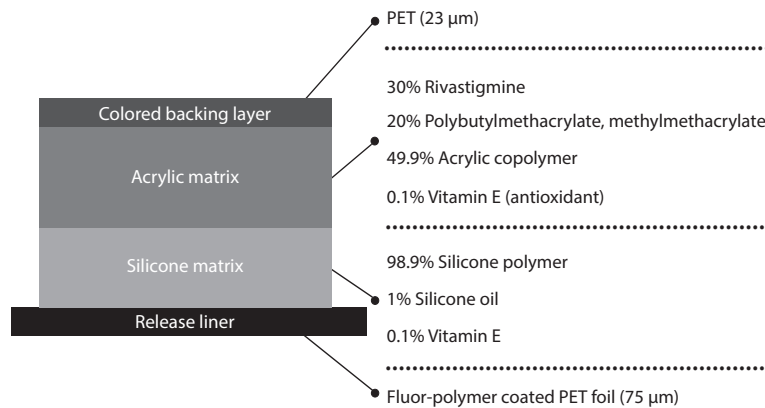
Of 1,584 patients enrolled in the initial open-label phase, 567 (35.8%) met the decline criteria and were randomized to the 13.3-mg/24-h (n = 280) or 9.5-mg/24-h (n = 287) rivastigmine patch.⁵⁰ Coprimary outcomes were the change

from baseline to week 48 on the instrumental domain of the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-IADL) and the ADAS-cog. During the double-blind phase, the 13.3-mg/24-h patch was associated with significantly greater efficacy on the ADCS-IADL at week 48, and the ADAS-cog at week 24, but not week 48 (week 48 being the primary endpoint; Table 3).⁵⁰ A modest increase in reported adverse events was observed with 13.3-mg/24-h versus 9.5-mg/24-h patch (75.0% versus 68.2%, respectively; Table 4). However, with the exception of “weight decreased” and insomnia, adverse events were transient, with the incidence decreasing over time (week 0–24: 13.3 mg/24 h, 64.6% and 9.5 mg/24 h, 54.8%; week 24–48: 42.3% and 40.2%, respectively).⁵⁰ Fewer patients on the 13.3-mg/24-h patch dose discontinued treatment due to adverse events compared with the lower 9.5-mg/24-h dose (9.6% versus 12.7%, respectively),⁵⁰ so it seems unlikely that weight loss presents a key issue. However, where clinically meaningful weight loss does occur, it may warrant consideration of possible counteracting interventions, such as protein-enriched nutritional supplements. Careful monitoring of weight in all patients with Alzheimer's disease should be considered.

The OPTIMA study was unique in that it evaluated rivastigmine patch in a declining patient population, which is more representative of real-world clinical practice.⁵⁰ However, the proportion of patients meeting the decline criteria, and hence the number enrolled in the double-blind phase, was lower than anticipated.⁵⁰ Of those randomized, the mean MMSE score at the start of the double-blind phase was 14.2 (moderate-to-severe dementia).⁵⁰ The ADAS-cog is best suited for patients with mild-to-moderate Alzheimer's disease, and floor effects may be apparent in more advanced disease stages.⁵⁴ These factors may have contributed to the lack of significant between-group differences observed at week 48 on the ADAS-cog. However, overall, the OPTIMA study demonstrated greater efficacy of 13.3-mg/24-h patch, particularly on functional outcomes, without compromising safety and tolerability. The 13.3-mg/24-h patch was subsequently approved by the US Food and Drug Administration (FDA) for the symptomatic treatment of mild-to-moderate Alzheimer's disease in the United States,³ providing an additional titration step for patients with a clinical need for enhanced efficacy.

The *ACTivities of Daily Living and CognitION (ACTION)* study. Until recently, treatment options for severe Alzheimer's disease have been limited. Both donepezil and memantine are approved for the treatment of moderate-to-severe Alzheimer's disease in the United States.^{5,25} The approval of rivastigmine patch for the treatment of severe Alzheimer's disease in June 2013³ was based on the ACTION study, a 24-week, double-blind comparison of 13.3-mg/24-h and 4.6-mg/24-h patch (ClinicalTrials.gov Identifier: NCT00948766).^{51,55} This was the first study of rivastigmine patch in patients with severe Alzheimer's disease. In order to fully evaluate the efficacy, safety, and tolerability of 13.3-mg/24-h patch in this patient

Figure 2. The 4 Layers of the Rivastigmine Patch^a



^aReprinted with permission from Winblad and Machado.⁴⁰
Abbreviation: PET = polyethylene terephthalate.

Table 3. Summary of Clinical Efficacy Demonstrated in the IDEAL, OPTIMA, and ACTION Studies (ITT-LOCF analysis)^a

Design	Study	Disease Stage	Dose ^b	Symptom Domain ^{c,d}			
				Activities of Daily Living	Behavior	Cognition	Global Function
Placebo-controlled	IDEAL	Mild-to-moderate Alzheimer's disease	12-mg/d BID capsules, N = 297	✓	X	✓	✓
			9.5-mg/24-h patch, N = 293	✓	X	✓	✓
			17.4-mg/24-h patch, N = 303 versus placebo, N = 302	✓	X	✓	X
Active-controlled	OPTIMA	Mild-to-moderate Alzheimer's disease	13.3-mg/24-h patch, N = 280 versus 9.5-mg/24-h patch, N = 287	✓	X	X^e	NA
	ACTION	Severe Alzheimer's disease	13.3-mg/24-h patch, N = 356 versus 4.6-mg/24-h patch, N = 360	✓	X	✓	✓

^aData from Winblad et al,⁴⁵ Cummings et al,⁵⁰ and Farlow et al.⁵¹

^bNs based on the randomized population.

^cPrimary endpoint week 24 in IDEAL and ACTION and week 48 in OPTIMA.

^dCoprimary endpoints (indicated in bold text) were the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) and Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC) in IDEAL; ADAS-cog and ADCS–Instrumental Activities of Daily Living scale in OPTIMA; and the Severe Impairment Battery and ADCS–Activities of Daily Living scale–Severe Impairment Version in ACTION.

^eSignificantly greater efficacy with 13.3-mg/24-h versus 9.5-mg/24-h patch observed at week 24, but not at week 48.

Abbreviations: ACTION = ACTivities of Daily Living and CognitION, IDEAL = InvestigatIon of TransDermal Exelon in Alzheimer's Disease, ITT-LOCF = intent-to-treat population with a last-observation-carried-forward imputation, NA = not applicable (not investigated), OPTIMA = OPTimizing Transdermal Exelon In Mild-to-moderate Alzheimer's Disease.

Symbols: ✓ = *P* < .05 versus placebo, X = *P* > .05 versus placebo.

population, the 4.6-mg/24-h patch was selected as a low-dose active comparator.⁵¹ In this study, 13.3-mg/24-h patch demonstrated superior efficacy to 4.6-mg/24-h patch at week 24 on the Severe Impairment Battery¹² and ADCS-ADL–Severe Impairment Version (ADCS-ADL-SIV; coprimary endpoints; Table 3).^{9,51} These scales have been developed for use in patients with more advanced dementia who may have difficulty completing assessments intended for use in mild-to-moderate Alzheimer's disease.^{9,12} In addition to demonstrating significantly greater efficacy on cognition and performance of ADL compared with 4.6-mg/24-h patch, the high-dose patch was generally well tolerated, with no unexpected safety concerns of treatment (Table 4).⁵¹ The FDA approval of rivastigmine patch in severe Alzheimer's disease provides an additional therapeutic option for patients in the later stages of the disease.

Key Findings of Clinical Studies With Rivastigmine Patch in Parkinson's Disease Dementia

Given that oral rivastigmine was already approved for Parkinson's disease dementia,⁴ and based on the findings of the IDEAL study,⁴⁵ rivastigmine 9.5-mg/24-h patch was also approved in the United States for the symptomatic treatment of mild-to-moderate Parkinson's disease dementia.³

The long-term safety of 9.5-mg/24-h patch compared with 6-mg twice-daily capsules was demonstrated in a 76-week, open-label, prospective study in 583 patients with mild-to-moderately severe Parkinson's disease dementia (ClinicalTrials.gov Identifier: NCT00623103).² The incidence of predefined adverse events (muscle rigidity, bradykinesia, and fall) was similar between groups; however, tremor was reported by a higher proportion of the capsule group compared with the patch group (24.5% and

Table 4. Incidence of Adverse Events and Gastrointestinal Adverse Events, and Discontinuations Due to Adverse Events and Skin Irritation in the IDEAL, OPTIMA, and ACTION Studies (safety population)^a

Study	Disease Stage	Dose ^b	Overall Incidence of Adverse Events, %	Gastrointestinal Adverse Events, %				Discontinued Due to Adverse Events, %	Discontinued Due to Skin Irritation, %
				Nausea	Vomiting	Diarrhea	Weight Decreased		
IDEAL	Mild-to-moderate Alzheimer's disease	12-mg/d BID capsules, N = 294	63**	23**	17**	5	5*	9	1
		9.5-mg/24-h patch, N = 291	51	7	6	6	3	11	2
		17.4-mg/24-h patch, N = 303	66**	21**	19**	10**	8**	10	2
		Placebo, N = 302	46	5	3	3	1	6	0
OPTIMA	Mild-to-moderate Alzheimer's disease	9.5-mg/24-h patch, N = 283	68	5	5	5	3	13	1 ^c
		13.3-mg/24-h patch, N = 280	75	12	10	6	7	10	1 ^c
ACTION	Severe Alzheimer's disease	4.6-mg/24-h patch, N = 359	73	3	3	5	3	11 ^d	3
		13.3-mg/24-h patch, N = 355	75	6	7	7	7	14 ^d	2

^aData from Novartis Pharmaceutical Corporation,³ Winblad et al,⁴⁵ Cummings et al,⁵⁰ and Farlow et al.⁵¹

^bNs based on the safety population.

^cDiscontinuation due to application site pruritus.

^dDiscontinuations due to nonserious adverse events.

*For IDEAL study only: $P \leq .01$ versus placebo.

**For IDEAL study only: $P \leq .001$ versus placebo.

Abbreviations: ACTION = ACTivities of Daily Living and CognitION, IDEAL = Investigation of TransDermal Exelon in Alzheimer's Disease, OPTIMA = Optimizing Transdermal Exelon In Mild-to-moderate Alzheimer's Disease.

9.7%, respectively), and there was a slightly higher rate of discontinuation due to Parkinson's disease motor symptoms with capsules versus patch (4.4% and 2.4%, respectively).²

Optimizing Rivastigmine Transdermal Patch Therapy Across All Alzheimer's Disease Severity Stages

Clinical data demonstrate a dose response to treatment with rivastigmine.³⁸ Furthermore, clinical data support the hypothesis that rivastigmine delivered using a transdermal patch may improve clinical outcomes in patients with mild-to-moderate and severe Alzheimer's disease, by providing access to high-dose efficacy without compromising tolerability.^{45,50,51} When appropriate, patients should be up-titrated to maximum-tolerated doses to achieve optimal therapeutic outcomes, regardless of the disease stage. Currently, it is recommended that rivastigmine patch treatment be initiated with 4.6-mg/24-h patch applied to the skin once daily.³ After a minimum of 4 weeks, if well tolerated, the patch dose can be increased to 9.5 mg/24 h.³ Patients tolerating 9.5-mg/24-h patch for a minimum of 4 weeks may then be up-titrated to the maximum effective dose of 13.3 mg/24 h.³ For patients with severe Alzheimer's disease, 13.3-mg/24-h patch is the recommended effective dose.³

For patients switching to rivastigmine patch from rivastigmine capsules or oral solution, it is recommended that those receiving below 3-mg twice-daily oral rivastigmine be switched to 4.6-mg/24-h patch with further titration as stated previously, while those receiving 3–6 mg twice daily can be switched directly to the 9.5-mg/24-h patch dose.³ Patch treatment should be initiated the day following the last oral dose.³

In addition to optimizing monotherapy, a number of studies and post hoc analyses have investigated the efficacy,

safety, and tolerability of concomitant treatment with ChEIs and memantine in patients with moderate-to-severe Alzheimer's disease.⁵⁶ However, these data do not support consistent findings, and despite widespread "real world" use, a robust clinical effect of combination therapy is yet to be demonstrated.⁵⁶ To our knowledge, no randomized, controlled trials have evaluated the effects of combination treatment with rivastigmine patch and memantine in patients with severe Alzheimer's disease. During both the OPTIMA and ACTION studies discussed previously, patients were permitted to be receiving concomitant memantine, but as far as possible, could not initiate, titrate, or discontinue memantine use during the study, to allow assessment of the efficacy and tolerability of various doses of rivastigmine patch.^{50,51} A retrospective subanalysis of the ACTION study, in which 61% of all patients were receiving concomitant memantine, reported greater efficacy of 13.3-mg/24-h versus 4.6-mg/24-h patch on the Severe Impairment Battery and ADCS-ADL-SIV, regardless of whether or not the patient received concomitant memantine, and no notable effect of memantine on the safety and tolerability of 13.3-mg/24-h patch.⁵⁷

The OPTIMA study provides evidence that increasing the rivastigmine patch dose may provide clinical benefits in a declining patient population.⁵⁰ Although it remains to be demonstrated in a clinical trial setting, early initiation of rivastigmine patch therapy (when functional and cognitive abilities are better preserved) may lead to optimal therapeutic outcomes. As well as early initiation of treatment, patients may benefit from staying on treatment long term. In OPTIMA, patients who did not meet the decline criteria after 48 weeks of open-label treatment with 9.5-mg/24-h patch were given the option to continue open-label treatment

Table 5. Recommendations for Application and Removal of Rivastigmine Patch^a

Patch application
Change the application site every day
Avoid reapplying to the same area of skin for 14 days
Use recommended application sites (upper or lower back, chest, and upper arm)
Only apply 1 patch at a time
Apply to clean, dry, hairless, unbroken skin that is free of redness, irritation, burns, or cuts
Trim, rather than shave, hair at the application site
Once applied, avoid exposing the patch to external heat sources for extended periods
Do not apply to skin that has residual powder, lotion, or cream on it
Patch removal
Remove gently to avoid damaging the skin
Moisturize the skin following patch removal
Residual adhesive can be removed using an oil-based substance
Avoid alcohol- and detergent-based cleansers

^aBased on Novartis Pharmaceutical Corporation,³ Emre et al,⁴⁴ and Ale et al.⁶²

for an additional 48 weeks.⁵⁰ Of those patients (N=457), a high proportion (86.4% [395/457]) completed the study and received up to 96 weeks of open-label treatment with 9.5-mg/24-h patch.⁵⁸ These findings suggest that, in patients with mild-to-moderate Alzheimer's disease, 9.5-mg/24-h patch is a sustainable option for long-term stabilization of functional and cognitive decline.⁵⁸ During an open-label extension to the IDEAL study, no new safety and tolerability issues were reported, and patients who received the rivastigmine patch for a maximum of 52 weeks tended to show less cognitive decline from baseline than those who switched to the rivastigmine patch from placebo at the end of the double-blind phase.⁵⁹ Similarly, in a 24-week open-label extension of the ACTION study, there were no clinically relevant differences in safety and tolerability between those who continued to receive the 13.3-mg/24-h patch for a maximum of 48 weeks and those who switched from the 13.3-mg/24-h patch (from the 4.6-mg/24-h patch) after 24 weeks of double-blind treatment.⁶⁰ Furthermore, patients switched from 4.6-mg/24-h to 13.3-mg/24-h patch tended to show greater cognitive and functional decline than those who received 13.3-mg/24-h patch throughout.⁶⁰ Open-label extension studies must always be interpreted with caution, as there exists a possibility that those patients who tolerated therapy or responded well are more likely to continue and enter the extension phase. However, taken together, these findings suggest that patients with delayed up-titration do not "catch up" in terms of potential cognitive and functional benefits compared with those who have received long-term rivastigmine patch treatment.

As well as symptomatic benefits, rivastigmine patch treatment has been shown to be cost-effective by reducing the number of institutional days compared with receiving no active treatment.^{17,61}

Practical Guidance on Rivastigmine Patch Use

Some patients receiving transdermal therapy may experience application site reactions, including allergic and

nonallergic contact dermatitis.⁶² It should be noted that it is not possible to directly compare the incidence of skin reactions in the OPTIMA, ACTION, and IDEAL studies owing to differences in study design, patient samples, and the way in which skin reactions were reported across these trials. However, the low incidence of discontinuation due to skin reactions in the IDEAL, OPTIMA, and ACTION studies (Table 4) suggests that, in the majority of cases, skin reactions do not pose a clinical problem, and with appropriate management, are likely to be mild and tolerable, and need not be a barrier to treatment with rivastigmine patch.⁶³ A number of steps can be taken to minimize development of skin reactions associated with patch use (Table 5).^{3,44,62}

CONCLUSIONS

As a molecule, rivastigmine has proven symptomatic efficacy in a number of indications, including mild-to-moderate and severe Alzheimer's disease,^{32-35,37,45,50,51} and mild-to-moderate Parkinson's disease dementia.^{2,36} Rivastigmine's low propensity for drug-drug interactions may be advantageous when managing elderly patients, who typically have multiple comorbidities and concomitant medications.

The efficacy of rivastigmine is dose dependent, although gastrointestinal adverse events, particularly with oral formulations, may limit access to optimal therapeutic doses in some patients.³⁸ Rivastigmine transdermal patch provides continuous drug delivery, reducing the fluctuations in plasma and central nervous system drug concentrations observed following oral administration. The improved pharmacokinetic profile of rivastigmine patch is associated with fewer gastrointestinal events, compared with an equivalent oral dose,⁴⁵ and may permit easier access to optimal therapeutic doses.

Clinical studies provide evidence for a positive benefit-risk profile of rivastigmine patch in mild-to-moderate and severe Alzheimer's disease.^{45,50,51} On the basis of the findings of the IDEAL⁴⁵ and OPTIMA⁵⁰ studies, 9.5-mg/24-h and 13.3-mg/24-h patch, respectively, were approved for the treatment of mild-to-moderate Alzheimer's disease in the United States.³ More recently, the ACTION study data⁵¹ led to approval of the 13.3-mg/24-h patch by the FDA for the symptomatic treatment of severe Alzheimer's disease.³ The improved tolerability profile of transdermal versus oral formulations, to a level not dissimilar to placebo,⁴⁵ and the acceptable tolerability profile of 13.3-mg/24-h versus 9.5-mg/24-h patch⁵⁰ may translate into more patients reaching and maintaining effective therapeutic doses in clinical practice. The available clinical evidence, alongside the potential benefits of rivastigmine patch administration for both patients and caregivers, support the use of the rivastigmine transdermal patch throughout the course of Alzheimer's disease.

Drug names: donepezil (Aricept and others), galantamine (Razadyne and others), memantine (Namenda), rivastigmine (Exelon and others).

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