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Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease

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SUMMARY

Background Family caregivers comprise a critical component in the care of Alzheimer's disease (AD) patients. Among their many tasks, caregivers are responsible for administering and managing medications. Effective interventions incorporate the needs of both the AD patient and the caregiver, and understanding treatment preferences may maximize intervention effectiveness. Transdermal patches may offer advantages over conventional oral formulations.

Methods A 24-week randomized controlled trial compared the rivastigmine patch to the rivastigmine capsule and placebo in patients with probable AD. At baseline and Weeks 8 and 24, the AD Caregiver Preference Questionnaire (ADCPQ) was used to evaluate caregiver expectations, preferences and satisfaction with treatment. Double-dummy treatment blinding ensured that caregiver preference for the patch or capsule was not confounded by perceptions of efficacy or tolerability. Reasons for preference were also elicited. The analytic sample included caregivers who completed the ADCPQ at Weeks 8 and/or 24.

Results One thousand and fifty-nine caregivers completed the ADCPQ. More than 70% of caregivers preferred the rivastigmine patch to the capsule. The patch was significantly preferred to the capsule with respect to ease of following the schedule and ease of use. Caregivers indicated greater satisfaction overall, greater satisfaction with administration, and less interference with daily life with the patch *versus* the capsule (all $p \leq 0.01$).

Conclusion Caregivers of AD patients preferred the patch to the capsule for drug delivery. Preference for the rivastigmine patch could potentially lead to improved compliance and improved clinical benefits. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease (AD); caregiver; patch; randomized clinical trial (RCT); transdermal; treatment preference

INTRODUCTION

Family caregivers play a key role in health care for individuals with Alzheimer's disease (AD), providing 70% of care (Alzheimer's Association, 2006). As the world's population ages, informal caregiving is projected to increase (Burke *et al*., 2005; Family Caregiver Alliance, 2006).

Managing medications contributes to the workload associated with caring for AD patients (Slattum and Johnson, 2004). Simpler and more effective modes of administration may ease caregiver challenges, which in turn may impact patient health and functioning. Understanding treatment-related preferences of caregivers, and the reasons for those preferences, may help to maximize intervention effectiveness.

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Transdermal patches offer advantages over conventional oral formulations, including smoother drug delivery, steady drug levels in the plasma, and constant cholinesterase inhibition. These attributes may reduce side-effects and allow access to optimal doses, with the potential for improved efficacy. Patches also reduce the number of pills a patient needs to take each day and offer caregivers a visual reminder that the medication is being taken, therefore helping to monitor patient compliance. For example, patients can write on the patch with a marker pen if they wish to do so (e.g. days of the week), and when patients are bathing they or their caregiver may see the patch from yesterday and it will remind them to replace it with a new one. The IDEAL (Investigation of TransDermal Exelon in ALzheimer's disease) trial was a randomized controlled trial of a rivastigmine (Exelon®) patch *vs* rivastigmine capsules or placebo, in patients with AD. Main analyses (published separately in this issue) suggested that the 10 cm^2 rivastigmine patch provided efficacy similar to highest doses of capsules, with a placebo-like tolerability profile (Winblad *et al*., 2007). The trial also presented an opportunity to perform an additional sub-study to evaluate caregiver preferences.

Studies evaluating caregiver preferences have been performed in people caring for asthmatic children (Berger *et al*., 2004) and children with acute otitis media (Block *et al*., 2005). In these studies, caregiver satisfaction surveys revealed treatment preferences with regard to ease of use, dosing flexibility, tolerability, compliance and missed days of work and day-care (Berger *et al*., 2004; Block *et al*., 2005). However, no measures that specifically address caregiver preference for different AD medications have been developed. In the current study, caregiver preferences for the rivastigmine patch *vs* the capsule were evaluated using a newly developed caregiver preference tool for AD.

METHODS

Study design

The IDEAL trial was a 24-week randomized, double-blind, double-dummy evaluation of the rivastigmine patch *vs* the rivastigmine capsule and placebo in patients with probable AD according to National Institutes of Neurological and Communicative Diseases and Stroke—Alzheimer's Disease and Related Disorders Association (McKhann *et al*., 1984), and dementia of the Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994). Patients had Mini-Mental State Examination scores (Folstein *et al*., 1975) of 10–20, indicating moderate to severe dementia. All patients were living with someone in the community or in daily contact with a responsible caregiver. Patients and caregivers were recruited from 21 countries in North, Central and South America, Europe and Asia.

Prior to initiation of the study, the protocol, informed consent form, and other information given to patients and caregivers were reviewed by an Institutional Review Board in each country. The study was conducted according to the ethical principles of the Declaration of Helsinki, as revised in 2000.

Patients were randomized to: 10 cm^2 rivastigmine patch (delivering 9.5 mg/24-h), 20 cm^2 rivastigmine patch (17.4 mg/24-h), rivastigmine capsules (6 mg b.i.d.), or placebo. Every morning, a patch was applied by the caregiver to clean, dry, hairless, skin on patients' upper back. Normal daily activities including bathing were permitted. Twice-daily, all patients also took a capsule. Thus, patients were taking: active capsules and placebo patches, active patches and placebo capsules, or placebo as both capsules and patches. Doses of capsules and patches were titrated in 4-week steps. Patients in the target 10 cm^2 rivastigmine patch group received a 5 cm^2 rivastigmine patch for weeks 1–4, and then the target 10 cm^2 rivastigmine patch for the remainder of the study. Patients in the target 20 cm^2 rivastigmine patch group also started on a 5 cm^2 patch and were titrated every 4 weeks to a 10 cm^2, 15 cm^2 and 20 cm^2 patch. Patients in the rivastigmine capsule group started on 3 mg/day (1.5 mg b.i.d.) and were titrated every 4 weeks in steps of 3 mg/day to a maximum of 12 mg/day. Patients were maintained at their highest tolerated dose for another 8 weeks. Main efficacy outcomes, safety and tolerability are described fully elsewhere (Winblad *et al*., 2007).

Caregiver preference

The Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) was developed to assess aspects of AD treatment influential in caregiver preferences, including treatment expectations, expected preferences, treatment evaluation and satisfaction and overall treatment satisfaction. The ADCPQ was developed using the following methodology: (1) a focused literature review to aid in the development of a focus group guide, clinician interview guide, and first draft questionnaire; (2) three caregiver focus groups and six clinician interviews to elicit additional concepts and revise the questionnaire; and (3) ten

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further cognitive debriefing interviews with caregivers to assess the ease of comprehension and relevance of the revised questionnaire. The results of these interviews were then used to finalize the questionnaire for use and validation in this trial.

At Week 24, the ADCPQ required caregivers to respond to, 'Which of the following treatments [capsule or patch] would you prefer to give in the future to manage AD?'. Also at Week 24, caregivers were asked whether they preferred the patch or the capsule based on ease of use and ease following the schedule.

Week 8 questions on the ADCPQ included questions about overall preference for patch or capsule, and about treatment preference with respect to ease of use and ease of following the schedule. Also at Week 8, the ADCPQ required caregivers to evaluate ease of administration for capsule and patch treatments, satisfaction with treatments, and interference with daily life, using a Likert scale ranging from 1–4, where 1 represented the worst result (e.g. very difficult or dissatisfied) and 4 the best (e.g. very easy or satisfied).

Statistical analyses

To compare proportions of caregivers preferring the patch or the capsule, SAS statistical software Version 9.1.3 was used to conduct analyses involving tests of binomial proportions. Dichotomous endorsements for direct preference for the patch or capsule were tested by examining percentages and confidence intervals for direct preference variables. A 95% Confidence Interval (CI) was computed around proportions of caregivers showing preferences for the patch or capsule. The *p*-values were calculated using a normal theory approximation in accordance with Hahn and Meeker (1991).

For the Likert scale, mean preference scores were compared using paired *t*-tests. These analyses were replicated using a non-parametric test, the Wilcoxon signed-rank test, to confirm the results obtained from parametric paired *t*-tests. All statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

The Caregiver–Intent to Treat population (C-ITT) included all caregivers: who completed the ADCPQ at Weeks 8 and/or 24; were caregivers of randomized patients who received at least one dose of study drug; and completed the ADCPQ not more than 2 days after the last known date of study drug. The Caregiver–Intent to Treat population with Retrieved Dropouts (C-ITT + RDO) included all caregivers who completed the ADCPQ at Weeks 8 and/or 24, and were caregivers of randomized patients who received at least one dose of study drug. Missing data were reported and treated as missing; no imputation was used, because the amount of missing data at Week 24 was less than a pre-analysis defined threshold of 10%.

Qualitative analyses

Atlas Ti Version 5.0 was used to analyze qualitative data in the C-ITT + RDO population obtained from an open-ended question at Week 8, 'Please provide the reason for your preference below'. Two researchers reviewed each statement and reached consensus on a coding system. Each statement was assigned one or more codes as appropriate (more than one code applied when multiple aspects were raised in a statement). A frequency count was provided for all codes stratified by stated preference (patch *vs* capsule).

RESULTS

Caregiver population

Of 1,195 patients randomized to treatment, the caregivers of 1,141 (95.5%) patients completed the ADCPQ at Week 8 or Week 24 and formed the C-ITT + RDO population; 1,059 (92.8%) caregivers comprised the C-ITT population. Baseline characteristics of caregivers are presented in Table 1.

Caregiver preference

At Week 24, 72% of caregivers preferred the patch to the capsule for AD treatment administration (95% CI

Table 1. Baseline caregiver demographic characteristics

Characteristic	C-ITT ($n = 1,059$)	C-ITT + RDO ($n = 1,141$)
Gender		
Men	356 (33.6%)	389 (34.1%)
Women	703 (66.4%)	752 (65.9%)
Relationship to patient		
Spouse	451 (42.6%)	484 (42.4%)
Child	425 (40.1%)	453 (39.7%)
Sibling	38 (3.6%)	41 (3.6%)
Friend	30 (2.8%)	35 (3.1%)
Parent	8 (0.8%)	8 (0.7%)
Volunteer	3 (0.3%)	3 (0.3%)
Other	104 (9.8%)	117 (10.3%)
Lives with patient		
Yes	837 (79.0%)	899 (78.8%)
No	222 (21.0%)	242 (21.2%)

C-ITT = Caregiver–Intent to Treat population; C-ITT + RDO = Caregiver–Intent to Treat with Retrieved Dropouts population; Data shown for non-missing values only; no imputation used.

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Table 2. Preference outcomes at Weeks 8 and 24

Caregiver preference	Population	*n*	Proportion	95% Confidence Interval	*p*-value
Patch preferred to capsule at Week 24	C-ITT	985	0.72	0.69–0.75	<0.0001
	C-ITT + RDO	1067	0.71	0.68–0.73	<0.0001
Patch preferred to capsule on ease of use at Week 24	C-ITT	983	0.64	0.61–0.67	<0.0001
	C-ITT + RDO	1065	0.63	0.60–0.66	<0.0001
Patch preferred to capsule on ease of following schedule at Week 24	C-ITT	982	0.74	0.71–0.77	<0.0001
	C-ITT + RDO	1064	0.73	0.70–0.76	<0.0001
Patch preferred to capsule overall at Week 8	C-ITT	1027	0.68	0.66–0.71	<0.0001
	C-ITT + RDO	1087	0.68	0.65–0.71	<0.0001
Patch preferred to capsule on ease of use at Week 8	C-ITT	1028	0.55	0.52–0.58	0.0008
	C-ITT + RDO	1088	0.55	0.52–0.58	0.0013
Patch preferred to capsule on ease of following schedule at Week 8	C-ITT	1029	0.70	0.67–0.72	<0.0001
	C-ITT + RDO	1089	0.70	0.67–0.72	<0.0001

C-ITT = Caregiver–Intent to Treat population; C-ITT + RDO = Caregiver–Intent to Treat with Retrieved Dropouts population; Data shown for non-missing values only; no imputation used. *p*-values based on normal approximation (Hahn and Meeker, 1991).

0.69–0.75; $p < 0.0001$; C-ITT population) (Table 2). Similarly, more caregivers preferred the patch to the capsule on: ease of use at Week 24; ease following the schedule at Week 24; overall at Week 8; ease of use at Week 8; and ease following the schedule at Week 8 (all $p \leq 0.001$) (Table 2).

Caregivers preferred the patch to the capsule regardless of which treatment group the patient had been assigned (10 cm^2 patch, 20 cm^2 patch, capsule or placebo; all $p < 0.0001$) and regardless of patch size ($p < 0.0001$ for 10 cm^2 and 20 cm^2 patches).

At 8 weeks, caregivers indicated greater satisfaction overall ($p < 0.0001$), greater satisfaction with administration ($p < 0.0001$) and less interference with daily life ($p < 0.01$) with the patch *vs* the capsule.

Table 3 shows the C-ITT results; C-ITT + RDO findings were similar and supportive. Similar results (to two decimal places) were obtained from Wilcoxon signed-rank test and the paired *t*-test analyses in both the C-ITT and C-ITT + RDO populations.

Qualitative analysis of reasons for preference

Each participant could provide more than one reason for preferring either the patch or the capsule, and the average numbers of reasons provided per participant were 1.2 reasons among those preferring the patch and 1.1 reasons among those who preferred the capsule. In the C-ITT + RDO population, 742 (68%) preferred the patch and 345 (32%) preferred the capsule. At least one reason for treatment preference was provided by 639 (86%) who preferred the patch and 306 (89%) who preferred the capsule. The most common reasons for preferring the patch were ease of following the schedule and ease of use (Figure 1). The minority of

Table 3. Satisfaction outcomes at Week 8

	n	Patch		Capsule		Mean difference	*p*-value
		Mean	SD	Mean	SD		
Easy to use	1034	3.38	0.55	3.39	0.57	−0.01	0.6112
Easy to follow schedule	1034	3.39	0.54	3.31	0.56	0.08	<0.0001
Easy to administer	1033	3.38	0.46	3.30	0.49	0.08	<0.0001
Interferes with daily life	1032	4.28	0.87	4.22	0.90	0.06	0.0083
Satisfaction with administration	1033	3.35	0.45	3.25	0.46	0.10	<0.0001
Satisfaction overall	1033	3.37	0.59	3.28	0.58	0.09	<0.0001

C-ITT = Caregiver–Intent to Treat population; C-ITT + RDO Caregiver–Intent to Treat with Retrieved Dropouts population; Data shown for non-missing values only; no imputation used.
Mean scores calculated on a Likert scale ranging from 1 to 4, where 1 represented the worst result (e.g. very difficult or very dissatisfied) and 4 the best (e.g. very easy or very satisfied); this assessed satisfaction at Week 8 only; Week 24 satisfaction data were not collected.
p-values calculated using Wilcoxon matched pairs and paired *t*-tests (identical results were obtained from both tests).

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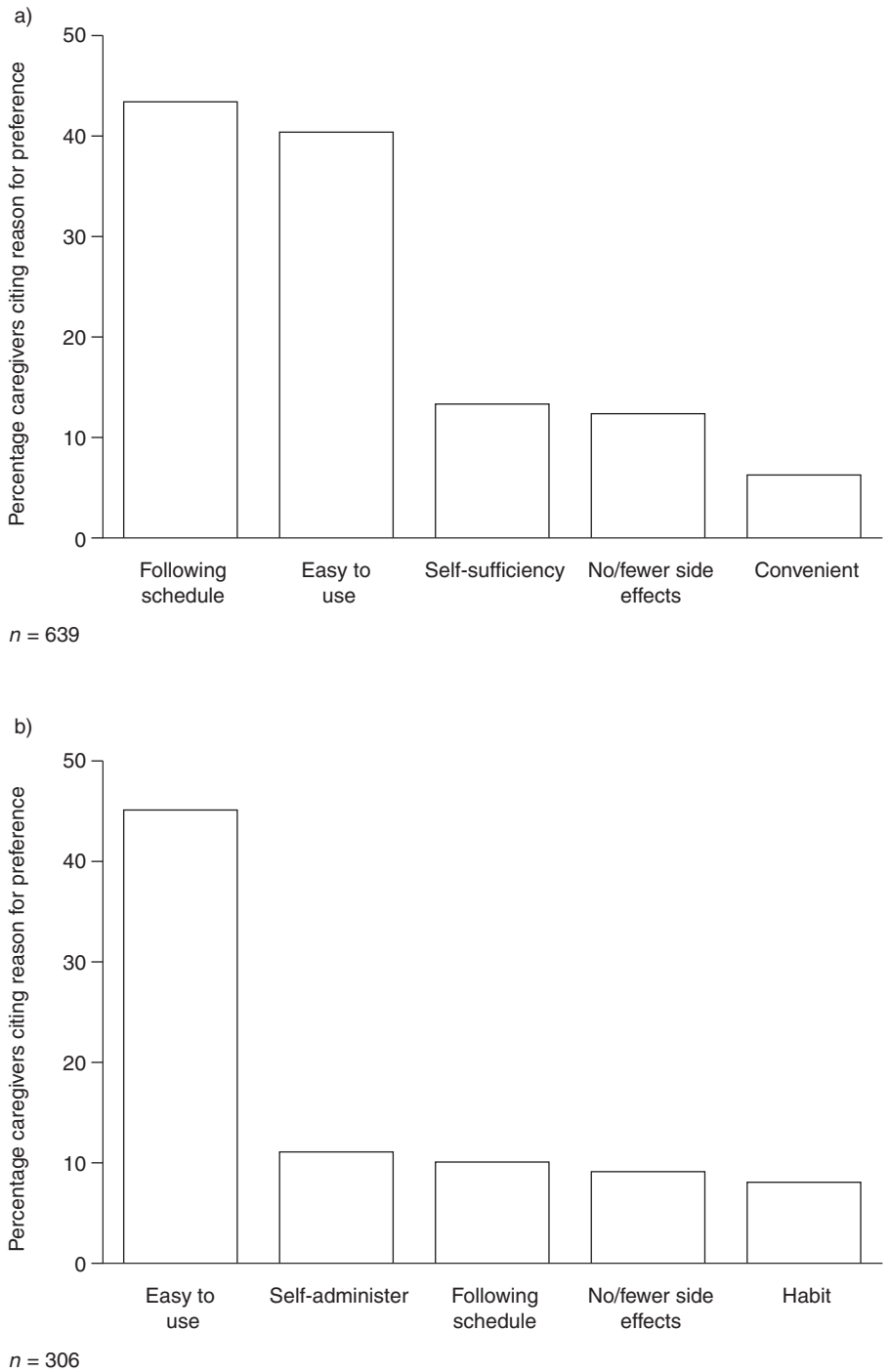

Figure 1. Percentage of caregivers by reason provided for preference of the a) rivastigmine patch or b) rivastigmine capsule. Each respondent could provide more than one reason.

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caregivers who preferred the capsule most frequently cited the reason as ease of use.

DISCUSSION

The majority of caregivers involved in the study preferred the rivastigmine patch to the capsule for the treatment of patients with AD. Significantly more caregivers preferred the patch to the capsule overall, and specific preference was established based on ease of use and ease of following the schedule. Moreover, caregivers were more satisfied with the patch, and found that it interfered less with daily life. The double-dummy, double-blind study design meant that preferences for the patch were probably not influenced by perceptions of efficacy or tolerability. Some early preferences for the patch might have reflected a 'novelty factor' relating to a new treatment, but by Week 24 this should have worn off and not affected the results.

The ADCPQ was developed because no tools to assess caregiver preference in the AD setting were available. This means that there was no reference against which the findings can be compared. However, variability was low, indicating a reasonable level of consistency. Moreover, the questionnaire was developed through in-depth caregiver and physician interviews and was believed to have good clinical utility—it was clearly understood by, and relevant to, the caregivers involved in the trial. The ADCPQ findings were limited to caregiver preferences (preferences were not collected directly from patients). It was believed that caregivers are largely responsible for medication management in this setting: 79% of caregivers lived with the patient in this study. Nevertheless, this may be a weakness and future studies might attempt to collect patient preference data also.

Elderly patients are less likely to comply with treatment schedules (Raehl *et al*., 2006). Cognitive and physical impairments mean that up to a third of elderly patients living in the community may have difficulties opening medicine bottles, one in ten cannot read the instructions, and nearly half make mistakes when trying to interpret their medication schedules (Beckman *et al*., 2005a, 2005b). Two-thirds of elderly patients have been shown to have a least one limitation of capacity relating to taking their medications, either in terms of opening the bottle, reading the label, or medical competence (Beckman *et al*., 2005b). Compliance with oral AD therapies has been reported to be low (Roe *et al*., 2002). Compliance with AD therapy is often a central responsibility of the caregiver, and the management and administration of these medications contributes substantially to caregiver burden (Slattum and Johnson, 2004). Data from this study indicate that the rivastigmine patch may provide significant advantages to caregivers on aspects such as ease of medication administration and management of treatment schedules. It seems reasonable to speculate that preference for the rivastigmine patch might lead to better compliance.

As Alzheimer's disease progresses, patients' abilities to perform everyday tasks decline, so it is recommended that caregivers should apply the rivastigmine patch, along with other medication management tasks. However, in mild stages, and/or in cases when the caregiver is temporarily unavailable, patients would be able to apply their own patches. Although in the current study the patch was applied to the patient's upper back, pharmacokinetic studies have shown that it may also be applied to the upper arm or chest (Lefèvre *et al*., 2007), which may be more easily reached by the patient.

The main IDEAL results demonstrated that the rivastigmine patch provided benefits across a range of symptoms and was well tolerated (Winblad *et al*., 2007). These results, combined with strong caregiver preference and greater satisfaction with the patch, indicate that a rivastigmine patch may have the potential to improve overall patient outcomes of treatment. The rivastigmine patch may provide a valuable, new approach to dementia therapy.

KEY POINTS

- Family caregivers are frequently responsible for administering and managing medications for AD patients.
- In the current study, more than 70% of caregivers preferred the rivastigmine patch to the capsule.
- Caregivers of AD patients indicated greater satisfaction overall, greater satisfaction with administration, and less interference with daily life with the patch *vs* the capsule.
- Simpler and more effective modes of administration, such as patches, may ease caregiver challenges, which in turn may help to maximize effectiveness of therapy in patients with AD.

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