A prospective non-interventional study for evaluation of quality of life in patients with Alzheimer’s disease treated with rivastigmine transdermal patch

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Abstract
Objectives: The primary objective of this multicentre, prospective, observational study was to assess whether there is improvement in the patients’ quality of life under treatment with rivastigmine transdermal patch, as it is evaluated both by patients and their caregivers. Compliance to treatment and safety were secondary endpoints.

Methods: In total, 1509 patients with mild to moderate Alzheimer’s disease, already treated with rivastigmine transdermal patch 4.6 or 9.5 mg/24h, were enrolled within a 2.4-month period and prospectively followed up for 2 months on an outpatient basis. The ‘Quality of Life in Alzheimer’s disease (QOL-AD): Patient and Caregiver Report’ questionnaire was used to evaluate quality of life as an effectiveness measure.

Results and conclusion: A significant improvement in quality of life, as indicated by a change of 2.7 and 2.5 points in the mean patients’ and caregiver’s QOL-AD: Patient and Caregiver Report score respectively (both p < 0.001) from baseline to end of study was recorded. No serious adverse events were reported. Compliance was high, with 100% compliance reported for almost 9 out of 10 patients at study end.

Keywords
Neurology, mental health/psychiatry

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Introduction
Alzheimer’s disease (AD) is the most common form of dementia, accounting for almost two-thirds of dementia cases internationally. The cardinal manifestations of AD include, among others, impairment of episodic memory and language, inability to learn new tasks or to perform previously learned ones and inability to recognize objects and faces, all having an impact on quality of life (QOL) and leading to eventual loss of functionality and constant need for a caregiver.1

Treatment of AD includes pharmacologic interventions that are intended to slow progression, relieve symptoms and improve functionality. Currently, the main therapeutic strategy used for ameliorating the clinical manifestations of AD is enhancement of cholinergic neurotransmission by use of an acetylcholinesterase inhibitor (AChEI), namely rivastigmine, donepezil or galantamine.1,2 Rivastigmine transdermal patch has been more recently developed to provide smooth and continuous delivery of efficacious levels of the drug within the central nervous system, without peaks and troughs associated with side effects.3,4

This multicentre, prospective, observational (Phase IV) study aims to evaluate QOL from both the patients’ and their...
Materials and methods

This prospective, observational study enrolled consecutive AD patients treated with rivastigmine patch and followed up in (or referred by 75 private neurologists to) five tertiary dementia clinics in major Greek hospitals. The study enrolment period was 2.4 months (original design was for 3 months, but recruitment was ended when the planned number of subjects was reached). All subjects had previously been diagnosed with mild to moderate AD and had already been receiving medication with rivastigmine patch before entering the study, as part of routine clinical practice. Each investigator was in charge of patients’ enrolment and follow-up. Patients were followed up according to routine clinical practice for 2 months on an outpatient basis for this study. The term ‘caregiver’, when used throughout this text, refers to a person who assists the patient in overcoming the impairment dementia poses on his or her life. A caregiver could be a person dedicated to this task 24 h a day or simply the closest relative accompanying the patient at the physician’s office. Caregivers could be family members, friends or professionals.

During the first visit, the treating physician collected data concerning medical history, age, sex, weight, educational level, living status, caregiver status (professional or not professional caregiver), disease characteristics and comorbid diseases. Furthermore, patients and caregivers were asked to complete the ‘Quality of Life in Alzheimer’s disease: Patient and Caregiver Report’ (QOL-AD) questionnaire (see below for details). This measurement was repeated during the second visit, after approximately 2 months. At both visits, patients and caregivers were also asked about compliance (see below for details).

Patients were eligible to participate if they met all of the following criteria:

- Male or female patients, aged >50 years, followed up as outpatients;
- Diagnosis of mild to moderate AD according to the treating physician;
- Mini Mental State Examination (MMSE) score >10 and <26;
- Treatment with rivastigmine transdermal patch according to routine clinical practice and the decision of their treating physician;
- Patients and their caregivers able and willing to fill in the study questionnaire.

Patients who had participated in another clinical study within the previous month or to whom rivastigmine transdermal patch was contraindicated were excluded from participation.

Regarding the inclusion criteria, it should be noted that diagnosis of AD was based on the treating physician’s decision; imposing strict diagnostic criteria would dilute the real-life, observational traits of the study.

A signed written informed consent was necessary in all cases; absence of written consent by the patient or a legal representative precluded enrolment. The informed consent form was signed by the patients and caregivers. Ethics committee approval was obtained in all participating centres.

The primary objective of this study was to assess whether there is improvement in the patients’ QOL under treatment with rivastigmine transdermal patch. ‘QOL-AD’ was used for evaluation of patient’s QOL on rivastigmine patch. This questionnaire has been developed for individuals with dementia, based on patient, caregiver and expert input. The particular questionnaire was chosen because it is brief, straightforward and especially designed to obtain a rating of the patient’s QOL from both the patient and the caregiver’s point of view. It was developed so as to maximize construct validity and to ensure that the measure focuses on QOL domains thought to be important in cognitively impaired older adults. Caregivers complete it as a questionnaire about their patients’ QOL and patients are subjected to a structured interview about their own QOL. The measure consists of 13 items, rated on a 4-point scale, with 1 being poor and 4 being excellent. Total scores range from 13 to 52. A higher score indicates better QOL. The questionnaire examines 13 aspects of the patient’s life, such as physical activity, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability for housekeeping, ability for entertainment, money and life as a whole. The measure has been used in clinical trials from several countries. It is available in the Greek language (MAPI Research Institute, Linguistic Validation Department, 27 rue de la Villette, 69003 Lyon, France). QOL-AD was completed by both patients and caregivers at enrolment (Visit 1) and 2 months later (Visit 2).

Evaluation of safety and tolerability issues was the secondary objective. For that purpose, data on the patient’s compliance to treatment or discontinuation of rivastigmine patch were registered. Specifically, all adverse events (AEs) were monitored and recorded (including their severity, possible correlation to rivastigmine patch, time of onset, duration and any actions required). Compliance was evaluated by asking patients and caregivers to provide an estimation of the actual received percentage of doses of their prescribed medication by choosing between 100%, 99%–75%, 74%–50% or less than 50%.

All patients enrolled were included in the analysis. The sample size of 1509 patients was estimated to be sufficient to detect a mean difference of 2 points or more in the QOL-AD score between Visit 1 and Visit 2 with power >95%. Continuous variables are presented as mean and standard deviation (SD) and/or median and interquartile range (IQR). Qualitative variables are presented as absolute and relative
frequencies. The Wilcoxon signed rank test was used to evaluate differences in baseline and follow-up measurements for QOL-AD. Chi-square tests were used for comparisons of percentages. Missing values were not replaced. In order to control for type I error due to multiple testing, a Bonferroni correction was used and a p < 0.001 was considered significant. Spearman correlation coefficient was used to explore the association of duration of treatment with changes in QOL-AD score of patients between the two visits. All p-values reported are two-tailed. Analyses were conducted using the SPSS statistical software package (version 17.0).

Results

In total, 1509 patients with mild to moderate AD already treated with rivastigmine patch were enrolled. Included patients fulfilled all the inclusion criteria and none of the exclusion criteria. The follow-up visit was completed by 1507 participants. Adverse reactions were the reason for two discontinuations. The participants’ demographic profile and concomitant diseases are presented in Table 1. Mean age was 74.4 years (SD = 6.9 years, range from 53 to 92 years) and 57% were men. Mean weight was 72.6 kg (SD = 10.4 kg). All the patients were living in the community, and 84.7% of them were living with their families. The most common concomitant diseases were hypertension (42.8%) and depression (37.8%), followed by hyperlipidaemia (23.9%) and diabetes (22.7%). Other less frequent comorbid diseases were stroke, anxiety disorder, coronary heart disease and panic disorder. The vast majority of patients with concomitant diseases (84.4%–98.4%) were on medication because of their comorbidity.

Mean duration of treatment for AD was 5.1 weeks (SD = 5.0 weeks) with median value equal to 4 (IQR: 3–6) for the rivastigmine patch of 4.6 mg/24 h and 12.1 weeks (SD = 14.9 weeks) with median value equal to 8 (IQR: 4–12.5) for the rivastigmine patch of 9.5 mg/24 h. No patient was treated for more than 24 weeks.

Primary objective – changes in QOL-AD

There were statistically significant differences in all items of the QOL-AD as reported by both caregivers and patients between Visit 1 and Visit 2, as presented in Table 2. The proportion of caregivers and patients who reported good or excellent QOL in all items of QOL-AD increased significantly between Visit 1 and Visit 2 (p < 0.001). The proportion of patients that changed from Poor/Fair to Good/Excellent scores in items of the QOL-AD scale between Visit 1 and Visit 2 ranged from 5.2% (Living situation) to 15.6% (Memory) and the corresponding proportion was 13.1% for Energy and 12.8% for Mood. The mean percentage of increase of patients with Good/Excellent scores in items of the QOL-AD scale was 37.1% for patients’ responses and 36.1% for caregivers’ responses. The total score of QOL-AD as reported by patients had a mean value of 28.7 (SD = 6.2) with median equal to 28 (IQR: 25–33) at Visit 1 and a mean value of 31.4 (SD = 6.6) with median equal to 31 (IQR: 26–37) at Visit 2. The total score of QOL-AD as reported by caregivers had a mean value of 29.1 (SD = 5.8) with median equal to 28 (IQR: 25–33) at Visit 1 and a mean value of 31.6 (SD = 6.7) with median equal to 31 (IQR: 26–37) at Visit 2. The mean change in total scores of QOL-AD between Visit 1 and Visit 2 was 2.7 (SD = 6.2) according to patients’ reports and 2.5 (SD = 5.9) according to caregivers’ reports, indicating a significant increase in QOL scores (p < 0.001). Duration of treatment had a small but statistically significant positive correlation with changes in QOL-AD score of patients.

Table 1. Demographics and concomitant diseases.

|                      | N (%)       |
|----------------------|-------------|
| **Sex**              |             |
| Women                | 648 (43.0)  |
| Men                  | 858 (57.0)  |
| Missing              | 3           |
| **Age (years), mean (SD)** | 74.4 (6.9)  |
| **Weight (kg), mean (SD)** | 72.4 (10.4) |
| **Educational level (years)** |             |
| ⩽6                   | 961 (64.2)  |
| 6–12                 | 447 (29.9)  |
| >12                  | 89 (5.9)    |
| Missing              | 12          |
| **Living status**    |             |
| Living without partner | 229 (15.3)  |
| Living with family   | 1265 (84.7) |
| Missing              | 15          |
| **Caregiver status** |             |
| Professional         | 106 (7.4)   |
| Other                | 1334 (92.6) |
| Missing              | 69          |
| **Concomitant diseases** |           |
| Depression           | 571 (37.8)  |
| Anxiety disorder     | 225 (14.9)  |
| Panic disorder       | 123 (8.2)   |
| Balance and walking disorders | 259 (17.2)  |
| Delirium/Hallucinations | 166 (11)    |
| Weight loss          | 180 (11.9)  |
| Stroke               | 239 (15.8)  |
| Hypertension         | 646 (42.8)  |
| Coronary heart disease/ Myocardial infarction | 144 (9.5)  |
| Hyperlipidaemia      | 361 (23.9)  |
| Diabetes             | 343 (22.7)  |
| Cardiac arrhythmia   | 113 (7.5)   |

SD: standard deviation.
between Visit 1 and Visit 2 (r = 0.08, p = 0.013). QOL-AD score at Visits 1 and 2 was divided according to quartiles of the score at Visit 1. Based on caregivers’ reports, at Visit 2, in comparison with Visit 1, 538 patients (37.2%) belonged to a higher quartile range and 161 patients (11.1%) belonged to a lower quartile range. Based on patients’ reports, at Visit 2, in comparison with Visit 1, 512 patients (36.2%) belonged to a higher quartile range and 154 patients (10.9%) belonged to a lower quartile range.

Table 2. Proportion of caregivers and patients reporting Good/Excellent or Poor/Fair quality of life in the items of QOL-AD at Visit 1 and Visit 2, and statistical significance of differences between Visit 1 and Visit 2.

|                         | Caregivers |         |         | p*       | Patients |         |         | p*       |
|-------------------------|------------|---------|---------|----------|----------|---------|---------|----------|
|                         | Visit 1    | Visit 2 |         |          | Visit 1  | Visit 2 |         |          |
|                         | N (%)      | N (%)   |         |          | N (%)    | N (%)   |         |          |
| Physical health         |            |         |         |          |          |         |         |          |
| Poor/fair               | 1026 (68.4)| 907 (60.4)| <0.001|          | 1067 (72)| 916 (62.1)| <0.001|          |
| Good/excellent          | 475 (31.6) | 594 (39.6)|         |          | 415 (28.0)| 558 (37.9)|         |          |
| Energy                  |            |         |         |          |          |         |         |          |
| Poor/fair               | 1105 (73.6)| 907 (60.5)| <0.001|          | 1099 (74.2)| 907 (61.5)| <0.001|          |
| Good/excellent          | 396 (26.4) | 593 (39.5)|         |          | 383 (25.8)| 568 (38.5)|         |          |
| Mood                    |            |         |         |          |          |         |         |          |
| Poor/fair               | 1089 (72.6)| 897 (59.8)| <0.001|          | 1097 (74.0)| 873 (59.3)| <0.001|          |
| Good/excellent          | 411 (27.4) | 604 (40.2)|         |          | 385 (26.0)| 600 (40.7)|         |          |
| Living situation        |            |         |         |          |          |         |         |          |
| Poor/fair               | 615 (41)  | 537 (35.8)| 0.003  |          | 703 (47.4)| 590 (40.1)| <0.001|          |
| Good/excellent          | 885 (59)  | 963 (64.2)|         |          | 779 (52.6)| 883 (59.9)|         |          |
| Memory                  |            |         |         |          |          |         |         |          |
| Poor/fair               | 1255 (83.6)| 1020 (68.0)| <0.001|          | 1207 (81.5)| 982 (66.6)| <0.001|          |
| Good/excellent          | 246 (16.4) | 480 (32.0)|         |          | 274 (18.5)| 492 (33.4)|         |          |
| Family                  |            |         |         |          |          |         |         |          |
| Poor/fair               | 736 (49.1)| 628 (41.9)| <0.001|          | 711 (48.0)| 622 (42.3)| 0.002  |          |
| Good/excellent          | 764 (50.9)| 872 (58.1)|         |          | 770 (52.0)| 849 (57.7)|         |          |
| Marriage                |            |         |         |          |          |         |         |          |
| Poor/fair               | 749 (50.7)| 665 (45.0)| 0.002  |          | 765 (52.5)| 678 (46.9)| 0.003  |          |
| Good/excellent          | 727 (49.3)| 812 (55.0)|         |          | 693 (47.5)| 767 (53.1)|         |          |
| Friends                 |            |         |         |          |          |         |         |          |
| Poor/fair               | 899 (59.9)| 769 (51.4)| <0.001|          | 904 (61.1)| 755 (51.4)| <0.001|          |
| Good/excellent          | 602 (40.1)| 728 (48.6)|         |          | 576 (38.9)| 713 (48.6)|         |          |
| Self as a whole         |            |         |         |          |          |         |         |          |
| Poor/fair               | 1008 (67.2)| 866 (57.8)| <0.001|          | 1023 (69.1)| 858 (58.3)| <0.001|          |
| Good/excellent          | 493 (32.8)| 633 (42.2)|         |          | 457 (30.9)| 613 (41.7)|         |          |
| Ability to do chores around the house | | | | | | | | |
| Poor/fair               | 1179 (78.6)| 991 (66.2)| <0.001|          | 1148 (77.7)| 969 (66.1)| <0.001|          |
| Good/excellent          | 321 (21.4)| 507 (33.8)|         |          | 330 (22.3)| 498 (33.9)|         |          |
| Ability to do things for fun | | | | | | | | |
| Poor/fair               | 1191 (79.5)| 1012 (67.5)| <0.001|          | 1167 (79.1)| 1000 (68.3)| <0.001|          |
| Good/excellent          | 308 (20.5)| 487 (32.5)|         |          | 309 (20.9)| 464 (31.7)|         |          |
| Money                   |            |         |         |          |          |         |         |          |
| Poor/fair               | 859 (57.2)| 771 (51.4)| <0.001|          | 910 (61.4)| 801 (54.3)| <0.001|          |
| Good/excellent          | 643 (42.8)| 729 (48.6)|         |          | 572 (38.6)| 673 (45.7)|         |          |
| Life as a whole         |            |         |         |          |          |         |         |          |
| Poor/fair               | 1016 (67.6)| 832 (55.5)| <0.001|          | 1031 (69.6)| 834 (56.6)| <0.001|          |
| Good/excellent          | 486 (32.4)| 668 (44.5)|         |          | 450 (30.4)| 639 (43.4)|         |          |

QOL-AD: Quality of Life in Alzheimer’s disease: Patient and Caregiver Report.

AEs and compliance to treatment

Two patients (0.13%) discontinued treatment due to AEs. One patient reported diarrhoea, and treatment was discontinued.
Another patient developed erythema at the site of patch adhesion, and treatment was switched to rivastigmine caps. AEs were reported in only 14 out of 1509 (0.93%) cases. No severe AE or death was reported. Gastrointestinal AEs of mild to moderate severity were reported in 2 (0.13%) patients and skin-related AEs of mild to moderate severity in 12 (0.79%) patients. All AEs reported were considered as possibly related to the study drug by treating physicians. Duration of treatment for patients with AEs had a mean value of 7.6 weeks (SD = 6.7 weeks) and a median of 7 weeks (IQR: 3–9).

Compliance with rivastigmine patch treatment was very good for the vast majority of patients. The percentage of patients fully complying with treatment (thus, not missing a single dose) at Visit 1 was 84.8% and at Visit 2, 89.6% as shown in Figure 1. Compliance showed a trend to improve between Visit 1 and Visit 2, not reaching statistical significance.

**Discussion**

The findings of this study demonstrate that there is improvement in QOL of patients with AD having started treatment with rivastigmine patch relatively recently, as assessed by patients and caregivers over 2 months, with excellent tolerability and compliance. QOL was assessed by using the ‘QOL-AD’ scale.5 Patients ‘relatively recently treated’ with rivastigmine were defined as patients that were already being treated with rivastigmine patch at the time of enrolment (a mean duration of 5.9 weeks (median = 4) for rivastigmine patch 4.6 mg/24 h and 12.5 weeks (median = 8) for rivastigmine patch 9.5 mg/24 h). No patient had been treated for more than 24 weeks. Rivastigmine patch delivering 13.3 mg/24 h had not yet been approved by the European Medicines Agency at the time of study execution.

In the recent past, there has been much controversy regarding the cost-benefit ratio of AChEIs; the British National Institute for Health and Clinical Excellence (NICE) concluded in 2006 that drugs for AD should only be prescribed to those in the moderate stage of the disease, due to the fact that cost savings associated with reduction of the mean time spent in full-time care did not sufficiently offset the cost of treatment with AChEIs. The aim was to bring estimated cost-effectiveness to levels generally considered acceptable by the British National Health System’s (NHS) policy makers.7 However, in a more recent appraisal from NICE, rivastigmine and other AChEIs are recommended as options for managing mild as well as moderate AD, as there has been a change in the evidence base between 2004 and 2010.8 In that review, it is also noted that ‘current estimates of time to institutionalization and the benefits which flow from this in terms of improved QOL and reduced cost are based almost wholly on predictions made by models’; therefore, additional research on this topic could shed more light on this area, especially in the real-life clinical setting.

This study attempts to evaluate QOL changes as perceived by both AD patients on transdermal rivastigmine and their caregivers in a purely observational, real-life clinical scenario that reflects actual prescription and use of this formulation in Greece. Although the duration of the study was short, improvements in QOL that reached statistical significance for patients as well as caregivers were noted in the overall scores and in individual scale items.

Since even the most efficacious drug will not yield its full benefit unless properly taken by the patient, non-compliance is an issue of utmost importance for patients and their families; it also places a huge economic burden on health-care systems. According to a press notice by the Committee of Public Accounts of the UK Department of Health, ‘Unused and wasted drugs cost the NHS at least £100 million a year and almost certainly a lot more’ (http://www.parliament.uk/business/committees/committees-archive/committee-of-public-accounts/pacpn070117/). Additional treatments, hospitalization or nursing home admission resulting from non-compliance incur additional expenses. The results of this study indicate that compliance to rivastigmine patch was excellent, possibly reflecting its favourable profile of AEs, as well as ease of use. A remarkable near 90% adhered to prescribed medication totally.

Overall incidence of AEs with rivastigmine patch in the study at hand was relatively low in comparison with previous reports in existing literature; discontinuation rate due to AEs was as low as 0.13%. Regarding application site reactions, which are of particular interest here, according to a recently published report on all strengths of rivastigmine transdermal patch in the double blind ACTION and OPTIMA trials, such reactions led to treatment discontinuation in 1.7%–3.5% of patients, without a notable effect of dose.4 Due to the nature of our study, the vast majority of patients had already been on treatment with rivastigmine patch for a sufficiently long period of time (>4 weeks); therefore, one could argue that perhaps patients who had discontinued their medication due to early AEs were filtered out, as it has been observed that AEs in the OPTIMA study decreased over time.9 In addition, physicians outside the interventional clinical trial setting may have the tendency to underreport...
common and/or relatively innocuous AEs, especially if they consider them unrelated to the study drug. Nevertheless, even after taking the above factors into account, it can be argued that the tolerability profile of rivastigmine patch was excellent throughout the study period, in accordance with what has been shown in interventional studies.

Similar considerations may apply to compliance to treatment; the high adherence rates we recorded are similar to those previously reported in observational real-life studies. It is also of interest that adherence rates have shown a trend to improve with time, a finding replicated in our cohort. Regarding caregiver preference, it has previously been shown in a double blind fashion that caregivers of AD patients prefer the patch over rivastigmine capsules in terms of ease of use, greater satisfaction and less interference with daily life, a finding that was corroborated later in the real-life clinical scenario. It is rational to assume that favourable caregiver preference plays a significant role in the all-important compliance to treatment.

This prospective, non-interventional study has of course certain limitations inherent to its design. A control group receiving placebo was a priori not included. However, we used a very large sample of ‘real world’ patients in order to extend the validity of our study, focusing on results with the highest clinical relevance in the setting of routine clinical practice in different parts of Greece. This kind of research takes into account different diagnostic algorithms and prescribing principles between various territories and is essential in providing estimations for any rare and serious adverse effects, as well as in establishing ‘real-life’ drug effectiveness regarding variables such as QOL, which have substantial impact on patients’ and caregivers’ lives but are not routinely assessed during regulatory research in AD. Of course, as a consequence of the ‘real-life’ nature of this study, a wash-out period from any previous treatment could not be applied; on the other hand, it should be noted that most enrolled patients had already been on transdermal rivastigmine for >1 month, and therefore, any effects of past therapies should have been insignificant at this point. Moreover, because of the non-interventional design of the study, a significant proportion of patients were depressed and possibly on antidepressant medication, a positive effect of which on QOL cannot be safely ruled out. One should also note the relatively short follow-up period, which was selected to be 2 months, as this was considered by participating investigators to be the average follow-up interval in their usual practice for the patient population of this study (e.g. patients relatively recently treated with an AChEI, as described above). Bearing these considerations in mind, we consider our findings as highly relevant for routine treatment of AD; real-life experience with the transdermal route of administration has been shown to be efficacious and tolerable and, as such, tends to be preferred by physicians as well as patients and their caregivers.

A recent post hoc analysis of a randomized controlled trial evaluated QOL by using the Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) measure and showed significant improvements from baseline to weeks 16, 24, 32 and 48 on rivastigmine with the high (13.3 mg/24h) versus medium (9.5 mg/24h) dose transdermal patch, including autonomy and higher level functioning factors. In another recent post hoc analysis, the high and medium rivastigmine transdermal doses were compared regarding their effect on cognition. The greater cognitive efficacy of 13.3 mg/24h versus 9.5 mg/24h rivastigmine patch was attributed primarily to effects on memory, particularly in the areas of following commands, orientation, and word recognition. With these results in mind, it seems reasonable that the advantages of transdermal delivery can lead to the administration of higher dosages and hence to increased efficacy, since AChEI actions have long been considered to have a dose-dependent effect on cognition, but also dose-related – and dose-limiting – gastrointestinal side effects, which appear to be mitigated by the transdermal route.

Additional research should focus on head-to-head comparisons among different formulations of AChEIs regarding QOL and cost-effectiveness; the latter parameter emerges as an increasingly important factor in the current economic environment.

Conclusion
QOL, as perceived by both patients with AD and their caregivers, improved over 2 months in patients having started treatment with rivastigmine transdermal patch recently. Moreover, compliance was excellent, possibly due to the convenient transdermal delivery and the absence of severe AEs.

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