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# The transdermal formulation of rivastigmine improves caregiver burden and treatment adherence of patients with Alzheimer's disease under daily practice conditions

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**SUMMARY**

**Background:** Rivastigmine is the only cholinesterase inhibitor (ChEI) available as transdermal patch. The patch was developed to improve gastrointestinal tolerability and treatment adherence to higher dosages as compared with oral medication. Preferences of patients and caregivers for the patch were reported; however, neither patient compliance nor caregiver burden has yet been measured under routine practice conditions. **Methods:** This was a prospective, multi-centre, observational study in patients with Alzheimer's disease treated with rivastigmine patch in Germany. To compare the transdermal with oral dosage forms, physicians were asked to enrol patients who recently switched from oral to transdermal medication. Beyond effectiveness and tolerability, outcome measures were drug adherence evaluated by the Morisky questionnaire, and caregiver burden, measured as the daily time expenditure for dressing the patient, controlling appearance and administration of medication. **Results:** In total, 1104 outpatients (57.5% female gender; mean age 77 $\pm$ 7 years) were enrolled in 220 sites. After 6 months of treatment, 67.5% of patients had an improved Clinical Global Impression and the Mini-Mental State Examination score increased from 19.0 $\pm$ 5.1 to 20.0 $\pm$ 5.2 ($p < 0.001$); 84.1% of patients were still on treatment, 64.6% on the target dose of 9.5 mg/day. Compliance and patient satisfaction with therapy continuously increased over the study period and average time savings of caregivers added up to 20 min/day. In general, tolerability was deemed good and there were no unexpected adverse events. **Conclusions:** Transdermal rivastigmine is an effective treatment alternative, which may improve adherence and treatment satisfaction of the patient and relieve the caregiver. Controlled parallel-group trials are warranted. Clinical trials registration: none (observational study).

**What's known**

Cholinesterase inhibitors (ChEIs) are a mainstay for the symptomatic treatment of mild-to-moderate Alzheimer's disease (AD). Rivastigmine is the only ChEI, which is available as transdermal patch. Controlled clinical trials demonstrated not only similar efficacy at superior gastrointestinal tolerability but also a clear preference of patients and caregivers for the patch vs. the capsule. Observational studies suggested more patients to reach and maintain optimal doses.

**What's new**

This was an observational study in an AD population with high proportion of patients having switched from oral to transdermal rivatigmine. It demonstrated a greater patient satisfaction and relief of caregivers through the patch under daily practice conditions. It confirmed existing data on its effectiveness, tolerability and patient acceptance. High treatment adherence and compliance was shown to persist for at least 6 months.

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## Introduction

Non-adherence to drug therapy is a major issue in elderly people with often multiple and chronic diseases. The problem may particularly worsen if the underlying disease is associated with dementia such as Alzheimer's disease (AD). Currently, for AD, no curative treatment is available. Symptomatic drug treatments need to be taken life-long and their efficacy depends on dose. A mainstay of symptomatic treatment of AD is acetyl cholinesterase inhibitors (ChEI). However, with oral dosage forms, particularly at high doses, gastrointestinal side effects are common and often result in suboptimal doses or discontinuation of treatment. Therefore, the development of alternative formulations to improve tolerability and adherence is of key importance (1).

In 2007, rivastigmine as the only ChEI became available as transdermal patch. The patch is to be applied to the skin and to be exchanged once daily. After a minimum of 4 weeks of treatment, the 4.6 mg/day patch should be up-titrated to the 9.5 mg/day patch, which is the currently recommended daily maintenance dose. Compared with the capsule, the patch at a dose of 9.5 mg/day demonstrated better tolerability and similar efficacy (2,3). In addition, a dose increase from 9.5 to 13.3 mg/day by use of a larger patch size was recently shown to further slow down cognitive and functional decline without increasing the incidence of serious or severe

adverse events (AE) (4). However, the patch may add benefit not only by improving general tolerability and as a consequence adherence but also increase patient compliance as attachment to the skin may act as a reminder for its regular use and change.

Controlled clinical trials and observational studies revealed better tolerability and patient acceptance (5–7), but also an improved treatment adherence (8) and a preference of caregivers for the patch over the capsule (9). However, detailed information on the impact of the patch formulation on patient compliance and caregiver burden in daily practice are still lacking. Therefore, this study aimed to evaluate compliance of Alzheimer patients to treatment with rivastigmine patch, its effectiveness and the caregiver burden in an unselected outpatient population in Germany.

## Material and methods

This was a prospective, multi-centre, open-label, uncontrolled, observational study in Alzheimer outpatients decided by the investigator to be treated with rivastigmine patch. The study was conducted in 220 outpatient clinics across Germany from May 2009 to November 2010, in compliance with the Declaration of Helsinki, the principles of Good Clinical Practice and all applicable legal requirements.

To compare transdermal with oral dosage forms, investigators were asked to enrol patients who were to switch or had recently switched from any oral medication to rivastigmine transdermal patch. However, to reflect daily practice conditions, the protocol neither stipulated any inclusion/exclusion criteria nor any dosing instructions. Both were to be decided by the investigator, based on the drug label. Observational data were requested to be collected at baseline prior to the start of treatment with the patch and after 1 month $\pm$ 1 week, 4 $\pm$ 1 months and 6 $\pm$ 1 months from treatment initiation.

Data to be collected comprised the Mini-Mental State Examination (MMSE) score and the Clinical Global Impression (CGI), drug tolerability as assessed by the physician and the incidence of AE. Treatment persistence was measured as the percentages of patients still on patch treatment and on the scheduled dose. Patients' treatment adherence was measured using the original four-item Morisky questionnaire (10) with an additional question on whether patients took their medicine all days at the same time. For an estimation of the caregiver burden, they were asked how much time during the last 24 h they had spent on (i) dressing the patient, (ii) controlling appearance (including personal hygiene) and (iii) the administration of medication. Patient satisfaction with their current antidementia therapy was rated at baseline prior to the start of treatment with the patch and on every visit after treatment initiation, using a 4-point scale. After treatment initiation, patients were also asked if they would prefer the patch over the oral treatment.

The statistical analysis was mostly descriptive; inferential statistics were applied to comparisons over time only. For this, depending on the distribution of data, paired *t*-test and Wilcoxon-test were used at a significance level of 0.05.

## Results

### Patient population

Overall, 1104 patients, 635 women (57.5%) and 469 men (42.4%), with a mean age of 77.2 $\pm$ 7.1 years were enrolled in 220 outpatient clinics; 753 patients (68.2%) lived with their family, 176 (15.9%) solitarily and 173 (15.7%) in a nursing home. AD was on average diagnosed 19.5 $\pm$ 26.7 months (median: 10.8 months) before the start of the observation period, and the appearance of first symptoms had been documented 31.6 $\pm$ 38.3 months ago (median: 20.7 months). Based on the International Classification of Diseases (ICD-10) of the WHO, 33 patients (3.0%) had early-onset AD, 847 (76.7%) late-onset AD, for 166 patients (15.0%), onset was not specified and 58 patients (5.3%) were suffering from 'other' types of dementia, but nevertheless were included in the analysis. Almost one third of patients (31.2%) were treated with a ChEI for the first time, while 768 (69.5%) changed antidementia therapy, most of them resulting from lack of effectiveness (46.0%) or poor tolerability (16.8%) of the previous treatment.

Patients' caregivers were primarily family members. About 40.8% of the patients were attended by their spouse, 30.9% were supported by another relative, whereas 21.1% of patients visited their doctor without attendant.

### Effectiveness and adherence

Over the whole observation period, CGI improved in 67.5% of patients (Figure 1) and MMSE significantly increased from 19.0 $\pm$ 5.1 to 20.0 $\pm$ 5.2 ($p < 0.001$). Six months after treatment initiation, 929 patients (84.1%) were still on patch treatment and 714 (64.7%) on the target dose of 9.5 mg/day. Among the 218 patients who discontinued patch treatment, the most common reasons for discontinuation were AEs, lost to follow-up, lack of compliance or lack of effectiveness (Table 1).

Preference for the patch along with patient satisfaction with therapy (Figure 2), as well as

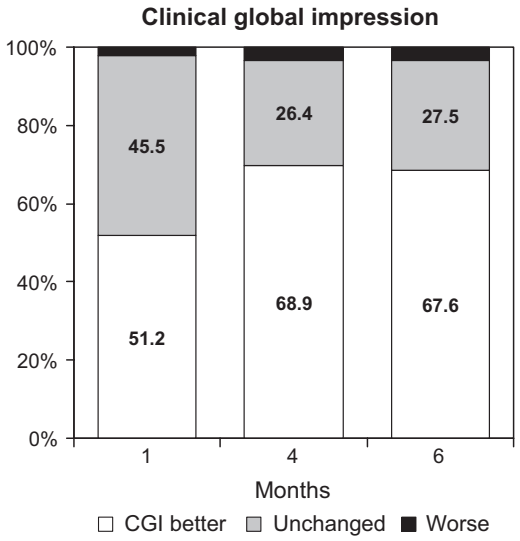


**Figure 1** Effectiveness: change in CGI over 6 months

compliance evaluated by the Morisky questionnaire (Figure 3A), consistently improved over the 6-month observation period; the percentage of patients taking the medication at regular times also increased from 58.8% to 76% within 4 months. Already after 4 weeks, 87% of patients tended to prefer the patch over the oral medication. Over 6 months, average time savings of caregivers added up to 20 min/day (dressing the patient from 56 ± 102 to 49 ± 89 min/day; control of appearance from 50 ± 104 to 43 ± 89 min/day; dispense of medication from 23 ± 76 to 16 ± 59 min/day; all $p < 0.001$; Figure 3B).

### Tolerability and safety

Of 1104 enrolled patients, 135 (12.2%) had in total 179 AEs, which in 21 patients (1.9%) were serious; 3 patients died. The majority of patients had one single AE ($n = 100$), 27 patients were affected by two and 8 patients by 3 or 4. Most AEs were of mild or moderate severity; 31 of 179 were considered severe; 20 AEs continued beyond the observation period. Causality with patch treatment was deemed unrelated or improbable in 24.0% of AEs, possible in 15.6%, and probable or even definite in 48.6% of AEs; in 11.7% of AEs, no causality assessment was available. Most affected organ system was the skin and subcutaneous tissue; the most frequent single AEs were erythema and contact dermatitis (in total 6.5%). Nausea and vomiting accounted for less than 2% of all AEs (Table 2).

## Discussion

Five years ago, the first and yet only transdermal ChEI (rivastigmine patch) has been marketed. Controlled clinical trials demonstrated similar efficacy for the treatment of AD with superior gastrointestinal tolerability of transdermal vs. oral rivastigmine at equivalent doses (3,7,11). In addition, they revealed a clear preference of both patients (7) and caregivers

**Table 1** Treatment adherence over 6 months

| | 0 | | 1 (± 1 week) | | 4 (± 1 month) | | 6 (± 1 month) | |
|---|---|---|---|---|---|---|---|---|
| **Month:** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Patients observed | 1104 | 100 | 1092 | 98.9 | 1028 | 93.1 | 949 | 86.0 |
| Missing | – | | – | | 1 | | 1 | |
| **Dose** | | | | | | | | |
| Not specified | 4 | 0.4 | 8 | 0.7 | 8 | 0.8 | 20 | 2.1 |
| 4.6 mg/day | 1018 | 92.2 | 649 | 59.4 | 299 | 29.1 | 215 | 22.7 |
| 9.5 mg/day | 82 | 7.4 | 435 | 39.8 | 721 | 70.1 | 714 | 75.2 |
| **Persistence** | | | | | | | | |
| Continued patch after visit | 1104 | 100 | 1034 | 93.7 | 952 | 86.2 | 888 | 80.4 |
| Discontinued patch after visit | 0 | 0 | 58 | 5.3 | 75 | 6.8 | 60 | 5.4 |
| **Reason for discontinuation*** | | | | | | | | |
| AE | | | 37 | | 38 | | 25 | |
| Insufficient effectiveness | | | 2 | | 15 | | 8 | |
| Insufficient compliance | | | 9 | | 14 | | 9 | |
| Patient did not return | | | 8 | | 9 | | 19 | |
| Withdrawn | | | 1 | | 2 | | 2 | |
| Other | | | 7 | | 9 | | 5 | |

*Multiple responses.

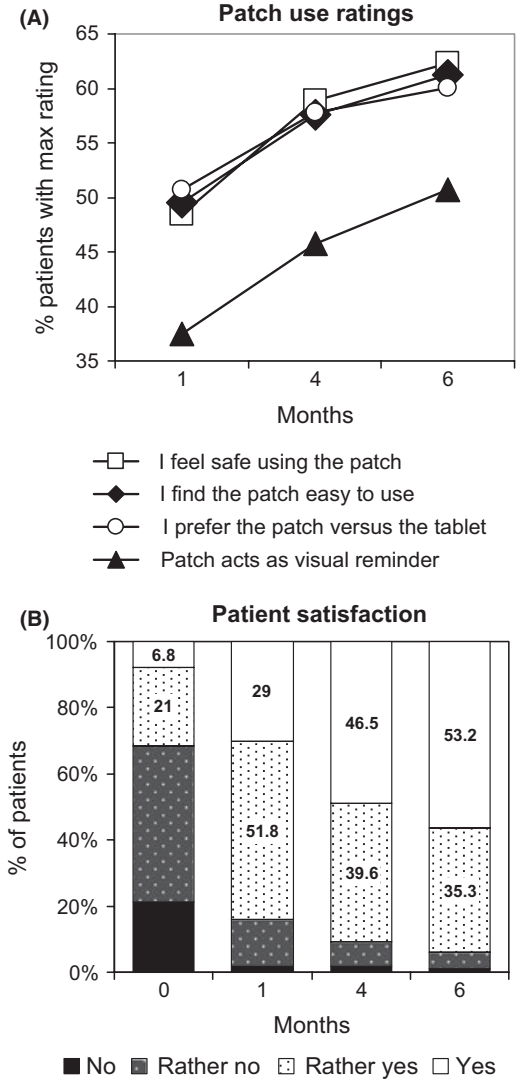


**Figure 2** Patient satisfaction: (A) reasons for preference of the patch and (B) patient satisfaction with current antidementia therapy

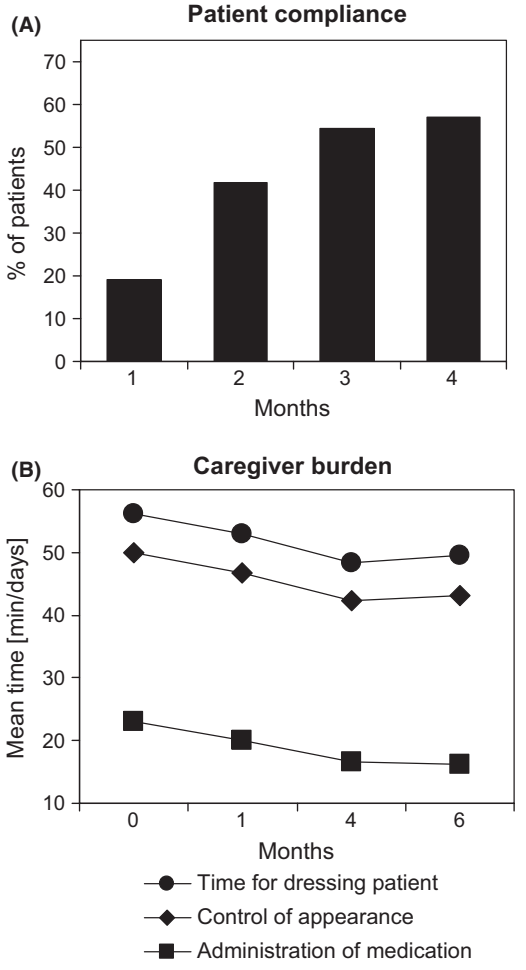


**Figure 3** (A) Patient compliance, based on the Morisky Questionnaire (10) and (B) caregiver burden

(9) for the patch over the capsule, primarily because of ease of its use. The observational study described here not only confirmed the effectiveness and tolerability of the patch but also the increasing patient satisfaction and relief of caregivers with its use under daily practice conditions in Germany. In addition, the study demonstrated high treatment adherence as expected, based on tolerability and acceptance data from clinical trials.

## Effectiveness

Over 6 months of treatment with rivastigmine patch, two thirds of AD patients clinically improved and the mean MMSE score significantly increased from 19.0 ± 5.1 to 20.0 ± 5.2. These effectiveness data are fully in line with results from other observational studies. In the very similar German patient cohort of the EXPECT study, 61% of 1113 patients clinically improved and MMSE also increased on average by about 1 unit (0.9 ± 3.4) over 4 months (12). In the smaller ADEPT study, the mean MMSE increase over 6 months was only slightly higher (1.3 ± 3.8), whereas the percentage of patients with clinical improvement was only half of that in our trial (13). However, in this study, clinical improvement was rated differently and not by the physician, but by patients and caregivers.

## Adherence

This study demonstrated persistence to treatment with the patch to be high: 84.1% of patients were still on treatment and 64.6% on the target dose of 9.5 mg/day after 6 months. Again, this is well in line with other studies depicting daily practice conditions. In the German EXPECT study, 89.2% were still on transdermal rivastigmine treatment and 67.4% on

**Table 2** Safety of the patch: most affected organ systems and most frequent AEs (incidence ≥ 0.5%)

| MedDRA | | | | Non-serious | | | | Serious | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | All | | Unrelated | | Related | | Unrelated | | Related | |
| System organ class | Preferred term | n* | % | n* | % | n* | % | n* | % | n* | % |
| Total | | 1104 | 100 | 1104 | 100 | 1104 | 100 | 1104 | 100 | 1104 | 100 |
| Gastrointestinal disorders | Total | 21 | 1.9 | 5 | 0.5 | 13 | 1.2 | 1 | 0.1 | 2 | 0.2 |
| | Nausea | 8 | 0.7 | 2 | 0.2 | 5 | 0.5 | 0 | – | 1 | 0.1 |
| | Vomiting | 6 | 0.5 | 1 | 0.1 | 5 | 0.5 | 0 | – | 0 | – |
| General and administration site | Total | 15 | 1.4 | 8 | 0.7 | 5 | 0.5 | 2 | 0.2 | 0 | – |
| Nervous system | Total | 19 | 1.7 | 7 | 0.6 | 8 | 0.7 | 3 | 0.3 | 1 | 0.1 |
| | Cognitive disorder | 6 | 0.5 | 4 | 0.4 | 1 | 0.1 | 0 | – | 1 | 0.1 |
| Psychiatric disorders | Total | 28 | 2.5 | 8 | 0.7 | 15 | 1.4 | 1 | 0.1 | 5 | 0.5 |
| | Confusional state | 5 | 0.5 | 2 | 0.2 | 2 | 0.2 | 0 | – | 1 | 0.1 |
| | Restlessness | 7 | 0.6 | 1 | 0.1 | 5 | 0.5 | 0 | – | 1 | 0.1 |
| Skin and subcutaneous tissue | Total | 72 | 6.5 | 1 | 0.1 | 71 | 6.4 | 0 | – | 0 | – |
| | Dermatitis allergic | 10 | 0.9 | 0 | – | 10 | 0.9 | 0 | – | 0 | – |
| | Dermatitis contact | 12 | 1.1 | 0 | – | 12 | 1.1 | 0 | – | 0 | – |
| | Erythema | 19 | 1.7 | 0 | – | 19 | 1.7 | 0 | – | 0 | – |
| | Pruritus | 8 | 0.7 | 0 | – | 8 | 0.7 | 0 | – | 0 | – |
| | Skin reaction | 9 | 0.8 | 0 | – | 9 | 0.8 | 0 | – | 0 | – |

*n, number of patients.

the target dose after 4 months. In a Spanish cohort of 649 AD patients, adherence to therapy as instructed by the physician was even 85.9% after 6 months, without, however, specifying whether instructions complied with dosing recommendations given in the label (8). The latter study also revealed forgetfulness, avoidance of AEs, refusal of treatment and the caregiver burden to be the major reasons for non-compliance in AD patients. The risk of non-compliance attributable to any of these reasons was shown to be lower with the patch as compared with capsules, but the difference missed significance for the avoidance of AEs. This corresponds well with our data on compliance (Figure 3A), patient satisfaction (Figure 2B) and on time savings of the caregiver (Figure 3B).

### Caregiver burden

As mentioned, the caregiver burden associated with treatment has not only major impact on his or her personal satisfaction but in about 25% of AD patients also on adherence to treatment (8). In the IDEAL trial (3,11), a majority of caregivers preferred the patch over the capsule primarily because of ease of use and of following the dosing schedule (9). However, to our knowledge, this is the first study that examined the impact of the formulation on the caregiver burden in daily routine by examining time expenditure for certain activities of daily care. This significantly decreased over time and savings accumulated to 20 min/day during the course of the trial. Although this appears highly relevant and might be of interest to public health, data should be interpreted with caution as times were not measured, but estimated by the unblinded caregivers and comparative data for the capsule are lacking. Controlled studies on this aspect might be warranted.

### Safety and tolerability

There were no new findings on safety and tolerability. AEs did not account for differences in adherence to treatment with capsules and patches in a Spanish cohort (8) and still remained the most common reason for treatment discontinuation in our study. Thus, one may raise the question whether the apparently better adherence to the patch might be rather linked to factors other than tolerability. As we did not collect comparative data for the capsule in parallel, our data cannot contribute to the clarification of this question.

## Conclusion

Transdermal rivastigmine proved to be an effective treatment alternative, which may improve adherence, compliance and treatment satisfaction of the patient, and relieve the caregiver.

## Acknowledgement

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## Author contributions

All authors contributed to the content, drafting, critical revision and approval of this manuscript.

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