

Featured Article

# Persistence and adherence to rivastigmine in patients with dementia: Results from a noninterventional, retrospective study using the National Health Insurance research database of Taiwan

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## Abstract

**Introduction:** The objective of the study was to assess adherence and persistence of patients treated with rivastigmine versus donepezil.

**Methods:** Persistence was calculated as the time from the first prescription date of rivastigmine/donepezil until discontinuation/medication switch/end of available data, whichever occurred first. Adherence was calculated as proportion of days covered and medication possession ratio.

**Results:** A majority of patients persisted on 4.5 and 6 mg of rivastigmine for 429 and 468 days, respectively, versus 443 and 441 days for patients receiving 5 and 10 mg of donepezil daily, respectively. Patients who initially received 1.5 mg of oral rivastigmine required a shorter time to reach a stable dose compared with those who initiated treatment at a higher dose of rivastigmine. Patients at a stable dose of 4.5 or 6 mg of rivastigmine were observed to persist longer than those at a lower dose of rivastigmine and donepezil.

**Discussion:** Although results indicate significant difference in persistence between rivastigmine and donepezil groups, clinical significance remains undetermined.

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## Keywords:

National Health Insurance Research Database; Rivastigmine; Donepezil; Adherence; Persistence

## 1. Introduction

Dementia is a major health concern worldwide, and dementia of Alzheimer's type accounts for an estimated 60%–80% of the cases. The age-adjusted prevalence of all-cause dementia in a nationwide survey conducted in Taiwan was 8.04% [1]. In Taiwan, the projected number of people with dementia (aged  $\geq 65$  years) is 0.15 million, and this number is expected to reach 0.21 million by 2020 [2]. Current treatment options for Alzheimer's disease (AD) available in Taiwan include cholinesterase inhibitors (ChEIs), such as rivastigmine, donepezil, and galantamine, or the N-methyl-D-aspartate receptor antagonist, memantine [3].

Poor adherence and persistence to medication is a major challenge in treating patients, particularly those with chronic diseases [4]. Adherence and persistence to ChEIs is critical in patients with dementia to stabilize or improve cognitive function [5,6]. Adherence to ChEI therapy can also improve activities of daily living and may lessen behavioral disturbances that accompany AD [7]. However, the cognitive decline associated with disease progression leads to suboptimal treatment compliance in patients with AD. Older patients are particularly susceptible to treatment noncompliance [5,7,8]. Persistence to ChEI therapy has been reported to be affected by several other factors such as choice of drug, polypharmacy, increased risk of drug interactions, ease of administration, and reimbursement status of the drug [8–10]. Hence, this study aimed to assess adherence and persistence to rivastigmine versus donepezil using data from the Taiwan National Health Insurance Research Database.

## 2. Methods

### 2.1. Data source

In March 1995, a government-administered, insurance-based, national health-care system, that is, a single-payer National Health Insurance program, was launched in Taiwan. The database of this program contains registration files and original claims data for reimbursement. Large computerized de-identified data were derived from this system by the National Health Insurance Administration, Taiwan, and Ministry of Health and Welfare, Taiwan, and maintained by the Health and Welfare Data Center (HWDC), Taiwan. These data are provided to scientists in Taiwan for research purposes. The National Health Insurance Research Database collects and releases data annually [11]. The index date for the present study was defined as the first prescription of rivastigmine or donepezil.

### 2.2. Study population

The study population comprised patients with data available in the National Health Insurance Research Database from January 1, 2010 to December 31, 2012. Because the

index date was defined as the first prescription of rivastigmine (oral/transdermal patch) or donepezil, patients were required to have been continuously enrolled for a minimum of 1 year before the index date and at least 9 months after the index date. Thus, data were collected for subjects diagnosed with mild cognitive impairment or AD or Parkinson's disease dementia or dementia with Lewy bodies and prescribed with rivastigmine (oral/transdermal patch) or oral donepezil in 2011 and/or 2012.

Patients on any other ChEI or memantine during the pre-index period and/or during the study period were excluded from the study.

### 2.3. Treatment

Patients were prescribed 5-cm<sup>2</sup> rivastigmine patch, oral rivastigmine twice daily, or donepezil once daily.

### 2.4. Study design

This was an observational, retrospective database study of a population-based cohort to assess the adherence and persistence of rivastigmine versus donepezil.

Adherence to treatment was measured as proportion of days covered (PDC) and medication possession ratio (MPR). For each index treatment, PDC and MPR were presented as a point estimate and as intervals of 20% (0%–19%, 20%–39%, 40%–59%, 60%–79%, and  $\geq 80\%$ ) and were provided for all patients and in those with at least two claims for the index therapy. Patients with PDC and MPR  $> 80\%$  were considered adherent, and those with PDC and MPR  $< 80\%$  as nonadherent. The methodology for calculating medication adherence is described in [Supplementary Figure 1](#).

Persistence to index therapy was calculated based on treatment practice patterns, that is, based on the time (in consecutive days) from index therapy initiation until discontinuation, medication switch, or end of available data, whichever occurred first.

### 2.5. Statistical analysis

Descriptive statistics, such as mean, median, standard deviation (SD), and percentiles, were summarized for continuous variables. Frequencies and proportions were derived for ordinal and nominal variables. Groups were compared for baseline characteristics and outcome measures using both parametric and nonparametric approaches such as the 2-sample *t* test and analysis of variance test for continuous variables and the chi-squared test and Fisher's exact test for categorical variables. In particular, analysis of variance was used for comparing the differences in PDC and MPR among oral rivastigmine, oral donepezil, and rivastigmine patch. SAS, version 9.4, was used for data management and statistical analysis; all tests were two-sided, and a *P* value  $< .05$  for a type-I error was considered statistically significant.

### 3. Results

A total of 385,097 patients were registered in the database between January 2010 and December 2012; 10,531 patients were first-time users of rivastigmine or donepezil. Of them, 3439 were treated with oral rivastigmine (mean age  $\pm$  SD: 77.14  $\pm$  7.93 years), 868 with 5-cm<sup>2</sup> rivastigmine patch (mean age  $\pm$  SD: 77.73  $\pm$  7.48 years), and 6224 with donepezil (mean age  $\pm$  SD: 77.79  $\pm$  7.95 years) (Fig. 1). Baseline characteristics of the study population are presented in Table 1.

Overall, the persistence duration in patients treated with oral rivastigmine, rivastigmine patch 5 cm<sup>2</sup>, and donepezil was 447  $\pm$  296, 375  $\pm$  262, and 481  $\pm$  287 days, respectively (Supplementary Table 1). The persistence duration for donepezil was statistically significant compared with oral rivastigmine ( $P = .001$ ). Overall, 72.06% of patients receiving 1.5 mg oral rivastigmine and 34.69% of patients receiving 3 mg oral rivastigmine at the index date were switched to higher doses (4.5 and 6 mg rivastigmine) to achieve a stable dose. Majority of patients achieved optimal treatment outcome at 3 mg (64.02%) or 4.5 mg (91.22%) oral rivastigmine. In the donepezil group, 29.02% of patients receiving 5 mg donepezil at the index date were switched to 10 mg donepezil to achieve a stable dose. Overall, 70.98% and 98.68% of patients were stable at 5 and 10 mg/day donepezil, respectively (Table 2).

#### 3.1. Persistence duration from initiation to discontinuation of the medication or end of available data

Unlike donepezil, the persistence duration of oral rivastigmine was longer at higher doses. Patients treated with 6 mg oral rivastigmine and 10 mg donepezil at the index

date had a persistence duration of 584  $\pm$  263 and 458  $\pm$  282 days, respectively (Fig. 2).

#### 3.2. Persistence duration of patients who switched dose during titration to stable dose

Patients in this study were found to initiate treatment with ChEIs at different doses. In this subgroup analysis, the persistence duration of patients receiving oral rivastigmine and donepezil was observed to be dose dependent. Patients who initially received 1.5 mg oral rivastigmine required a shorter time (72  $\pm$  83 days) to reach a stable dose compared with those who initiated treatment at a higher dose of rivastigmine (3 mg, 126  $\pm$  152 days [ $P < .0001$ ] and 4.5 mg, 124  $\pm$  154 days [ $P = .013$ ]). The average time to reach a maintenance dose of 3, 4.5, and 6 mg rivastigmine after initial treatment with 1.5 mg rivastigmine was 62  $\pm$  90, 76  $\pm$  76, and 149  $\pm$  89 days, respectively. For patients treated with donepezil, the persistence duration until dose adjustment was 174  $\pm$  153 and 184  $\pm$  204 days for donepezil 5 and 10 mg, respectively.

#### 3.3. Persistence duration from stable dose to treatment discontinuation or end of available data

Patients at a stable dose of 4.5 or 6 mg rivastigmine were observed to persist longer than those at a lower dose of rivastigmine and donepezil (Fig. 3).

#### 3.4. PDC and MPR

Patients receiving oral rivastigmine had the highest PDC and MPR and had a significantly higher PDC compared with those receiving rivastigmine patch ( $P < .001$ ). Patients

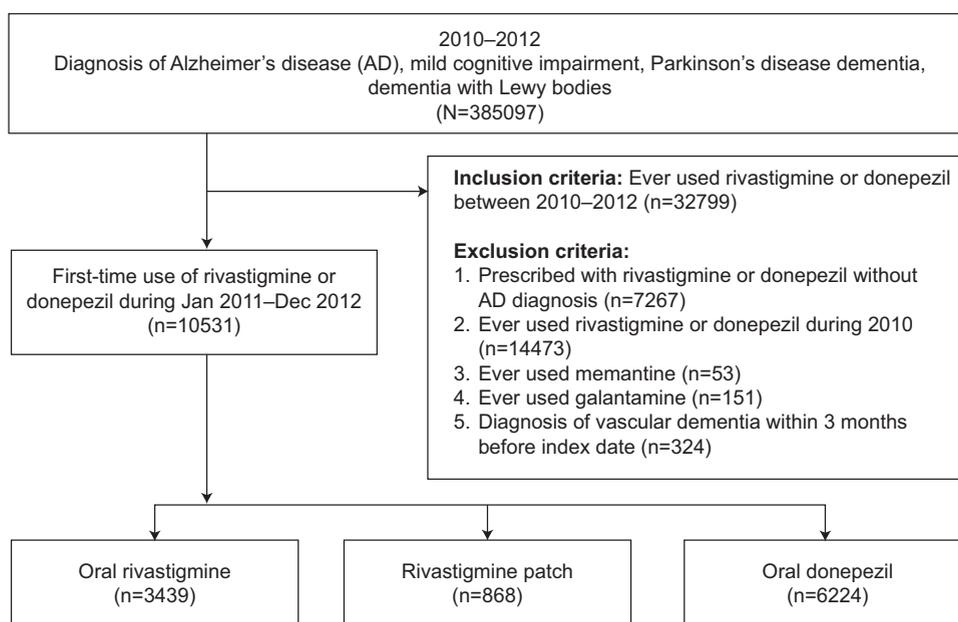


Fig. 1. Patient disposition.

Table 1  
Baseline characteristics

Characteristics	Rivastigmine patch (5 cm <sup>2</sup> )	Oral rivastigmine	Donepezil
N	868	3439	6224
Age, years	77.73 (7.48)	77.14 (7.93)	77.79 (7.95)
Gender			
Female	515 (59.33)	2048 (59.55)	3894 (62.56)
Male	353 (40.67)	1391 (40.45)	2330 (37.44)

NOTE. Values are presented as mean (standard deviation) unless otherwise stated.

receiving donepezil had a significantly higher PDC compared with those receiving rivastigmine patch ( $P = .001$ ), whereas no significant difference was observed between the oral rivastigmine and donepezil groups ( $P = .195$ ). A similar pattern was observed for MPR in the oral rivastigmine group compared with the rivastigmine patch group ( $P < .001$ ), in the rivastigmine patch group compared with the donepezil group ( $P = .001$ ), and in the oral rivastigmine group compared with the donepezil group ( $P = .079$ ) (Table 3).

#### 4. Discussion

The results of this study suggest that patients with dementia receiving a stable dose of 4.5 or 6 mg rivastigmine continued treatment for more days and were more likely to remain on therapy for a longer duration. Majority of patients receiving stable dose achieved optimal treatment outcome at higher doses of rivastigmine and donepezil. On the other hand, while similar pattern was reported when the persistence duration of oral rivastigmine was observed from the index date until discontinuation of the medication or end of available data, patients receiving donepezil 5 mg reported longer persistence duration than those receiving donepezil 10 mg. This indicates that patients receiving higher doses of rivastigmine may achieve better treatment outcomes with regard to slowing cognitive decline. Although, the reasons for discontinuation were not recorded, it may include the following: lack of efficacy;

lack of safety and tolerability e.g., patients experiencing more cholinergic side effects such as nausea and vomiting; and cognitive decline of  $\geq 2$  points on the Mini-Mental State Examination (MMSE) scale, which may pose a challenge in reapplication of the drugs. Per the reimbursement criteria in Taiwan, patients have to be reevaluated for treatment response every year and are required to stop the treatment following a cognitive decline of  $\geq 2$  points on the MMSE scale or  $\geq 1$  point on the clinical dementia rating scale compared with the previous treatment year. In Taiwan, the 5-cm<sup>2</sup> rivastigmine patch was reimbursed since March 2011, whereas the 10- and 15-cm<sup>2</sup> rivastigmine patches were not available in the timeframe during which this study was conducted. Considering that titration is critical in optimizing the disease treatment outcome, the study simply presents the analysis results of the 5-cm<sup>2</sup> rivastigmine patch but does not compare it with oral rivastigmine and donepezil, for which the titration doses were available.

The results from an observational administrative health database study ( $N = 5622$ ) in patients aged  $\geq 65$  years who received a new prescription of an oral ChEI between February and May 2006 showed that the 1-year persistence of treatment with donepezil and rivastigmine was 45.9% (95% confidence interval [CI]: 43%–48.8%) and 40.2% (95% CI: 37.3%–43.1%), respectively. The average periods of rivastigmine and donepezil therapies were 272 and 287 days, respectively [9]. Results from a 12-month retrospective analysis of longitudinal research databases of patients (aged  $\geq 65$  years) with newly diagnosed AD and a filled prescription for rivastigmine or donepezil between January 1, 1999 and December 31, 2002 showed that the persistence durations of rivastigmine and donepezil were 234 days (median: 312) and 235 days (median: 315), respectively [12]. An analysis of the administrative health-care database in Québec, Canada ( $N = 28,405$ ) showed that in patients aged  $\geq 50$  years and new users of oral ChEIs from 1997 to 2006, treatment adherence to donepezil ( $n = 19,031$ ) and rivastigmine ( $n = 3791$ ) was 94.5% (95% CI: 94.1%–95.0%) and 99.2% (95% CI: 97.8%–100.6%), respectively [13].

Clinical trials and open-label extension studies have reported the long-term treatment benefits of ChEIs in patients

Table 2  
Dose titration up to stable dose

Dose at index date (mg)	No. of patients who switched dose/total no. of patients	Dose at stable dose period (oral rivastigmine) (mg)				Donepezil (mg)	
		1.5	3	4.5	6	5	10
Oral rivastigmine							
1.5	1736/2409	673 (27.94%)	716 (29.72%)	980 (40.68%)	40 (1.66%)	-	-
3	249/692	9 (1.3%)	443 (64.02%)	192 (27.75%)	48 (6.94%)	-	-
4.5	28/319	6 (1.88%)	6 (1.88%)	291 (91.22%)	16 (5.02%)	-	-
6	0/15	0 (0%)	0 (0%)	0 (0%)	15 (100%)	-	-
Donepezil							
5	1146/3949	-	-	-	-	2803 (70.98%)	1146 (29.02%)
10	30/2275	-	-	-	-	30 (1.32%)	2245 (98.68%)

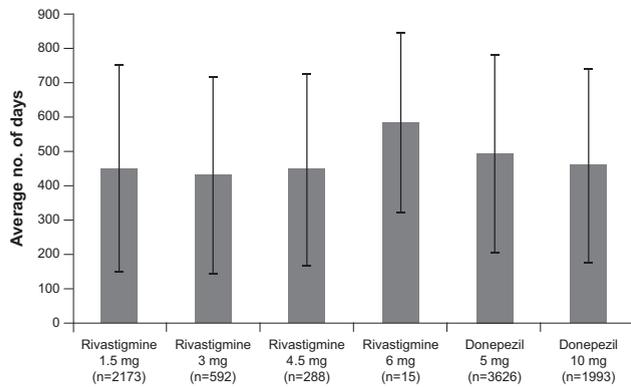


Fig. 2. Persistence duration from initiation to discontinuation of the medication or end of available data (grouped by initiation dose).

with AD [14–17]. Doody et al. reported a rapid decline in cognition and function when a 6-week placebo washout was given to patients who had been receiving donepezil [18]. A study examining the effect of persistent treatment with anti-dementia drugs reported less decline on multiple cognitive, functional, and global outcome measures with persistent drug treatment [19]. Maintaining ChEI therapy may provide a greater chance of slowing/delaying symptomatic disease progression and delaying nursing home placement [20,21]. Therefore, as long as ChEI treatment is tolerated and patients benefit, the treatment gap should be monitored carefully [22,23]. The National Health Insurance reimbursement criteria for mild-to-moderate dementia include an MMSE score of 10–26 or a clinical dementia rating score of 1–2. Per the reimbursement criteria in Taiwan, patients can switch to other ChEIs within 3 months as a result of any side effect(s), and there is no need to resubmit for approval. However, it is imperative to record the reasons for switching medication to avoid frequent switching. Patients have to be reevaluated for treatment response every year, and the treatment should be stopped if MMSE scores decrease by  $\geq 2$  points or clinical dementia rating scores by  $\geq 1$  point compared with the previous treatment year.

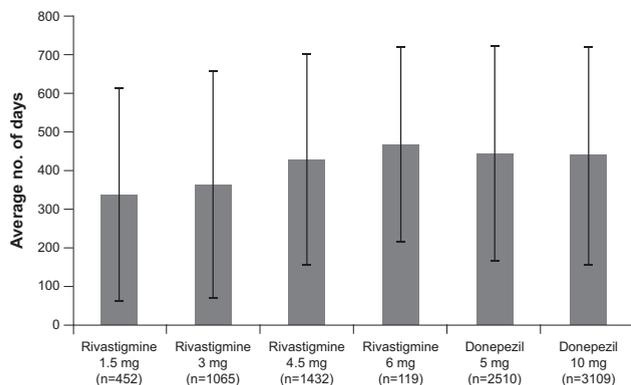


Fig. 3. Persistence duration from stable dose to discontinuation of treatment or end of available data (grouped by prescription dose at stable stage).

Table 3  
Comparison of PDC and MPR for AD medications

	Oral rivastigmine	Rivastigmine patch 5 cm <sup>2</sup>	Donepezil
PDC	0.9227 $\pm$ 0.1429	0.8956 $\pm$ 0.1692	0.9166 $\pm$ 0.1467
MPR	0.9404 $\pm$ 0.1385	0.9074 $\pm$ 0.1687	0.9332 $\pm$ 0.1438

Abbreviations: AD, Alzheimer's disease; MPR, medication possession ratio; PDC, proportion of days covered; SD, standard deviation.

NOTE. All values are mean  $\pm$  SD unless specified.

NOTE. n = 9468; 1063 samples are excluded from the analysis due to only one record of therapy initiation but without following medication.

The major strength of this study is the use of nationwide population-based data which provides with a large sample size. However, there are certain limitations of this study. First, the reasons of discontinuation were not recorded which is important to understand the differences in the duration of the use of medications. In addition, the sample size of high dose of rivastigmine (6 mg) group is small; hence, generalizing the findings should be done with caution. Further research is needed to ascertain the findings from this study.

## 5. Conclusion

Although the difference in persistence and adherence to treatment between patients on a stable dose of 4.5 or 6 mg rivastigmine twice daily and donepezil was statistically significant, the clinical significance is yet to be determined. Results from this study add onto the existing evidence of dose-dependent efficacy, that is, patients receiving rivastigmine should be titrated to the maximum possible dose before switching to another drug is considered.

## Acknowledgments

The study was funded by Novartis (Taiwan) Co., Ltd. This study was based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the HWDC. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Department of Health, or National Health Research Institutes. The authors wish to thank Preetinder Kaur from Novartis Healthcare Pvt. Ltd., Hyderabad, India, for providing medical writing support for development of the manuscript. All authors reviewed the draft and provided critical comments and approved the final submitted version.

Disclosures: Winco Hsu was employee of Novartis (Taiwan) Co., Ltd. at the time of conduct of the study.

## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.trci.2018.06.013>.

## RESEARCH IN CONTEXT

1. Systematic review: Based on the review of literature available on PubMed on adherence and persistence to cholinesterase inhibitors in patients with dementia, and to the best of our knowledge, this is the first study on adherence and persistence to rivastigmine in an Asian population.
2. Interpretation: We suggest that patients receiving rivastigmine should be titrated to the highest possible dose before switching to any other cholinesterase inhibitor or memantine; switching should only be encouraged when treatment response is considered insufficient at the maximum tolerated dose.
3. Future directions: Use of currently available cholinesterase inhibitors needs optimization until new therapies are introduced. Findings of this study will add on to the existing knowledge of dementia management, and the data can be extrapolated to other Asian countries.

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