

# Drug Persistency Patterns for Patients Treated With Rivastigmine or Donepezil in Usual Care Settings

JOSEPHINE A. MAUSKOPF, PhD; CLARK PARAMORE, MSPH; WON CHAN LEE, PhD; and EDWARD H. SNYDER MBA, DrPH

## ABSTRACT

**OBJECTIVE:** To compare levels of persistency with 2 cholinesterase (ChE) inhibitors—rivastigmine and donepezil—for the treatment of Alzheimer's disease (AD) through the use of administrative claims data.

**METHODS:** This retrospective cohort study identified treatment-naïve community-based AD patients having an initial prescription (index event) for rivastigmine or donepezil between June and December 2000, in the United States, from pharmacy claims in a proprietary administrative claims database. Patients were excluded if they received either drug during the 180 days prior to their index prescription or if they did not have continuous plan enrollment during this period and for at least 90 days following the index date. The probability of treatment discontinuation within the first 60 days of treatment was estimated. Time to treatment discontinuation was analyzed for the cohort of patients that remained on therapy  $\geq 60$  days as well as for subgroups of the cohort reaching either approved or maximum recommended doses of donepezil or rivastigmine. Treatment discontinuation was defined as either a stop of therapy (no prescription refill within 60 days of estimated completion of prior prescription) or a switch to an alternative AD drug. Kaplan-Meier survival and proportional hazard model analyses were performed. Proportion of days covered (PDC) by an AD therapy was also evaluated in each quarter during the first year of follow-up.

**RESULTS:** Of the newly treated AD study population, 30.4% (171/563) of rivastigmine patients and 31.2% (583/1,871) of donepezil patients discontinued treatment within 60 days of starting therapy ( $P=0.72$ ). For the cohort of patients that remained on therapy 60 days, the mean time to treatment discontinuation was 331 days (95% confidence interval [CI], 307-355) for rivastigmine patients ( $n=392$ ) versus 337 days (95% CI, 322-352) for donepezil patients ( $n=1288$ ). The proportion of patients with a PDC  $\geq 80\%$  after 12 months of follow-up was 23% for the donepezil group and 19% for the rivastigmine group ( $P=0.34$ ). For the cohort subgroup that reached an approved dose, the mean time to treatment discontinuation was 346 days (95% CI, 318-374) for rivastigmine patients ( $n=282$ ) versus 338 days (95% CI, 323-353) for donepezil patients ( $n=1,283$ ). For the cohort subgroup that reached the maximum recommended dose, the mean time to treatment discontinuation was 396 days (95% CI, 343-449) for rivastigmine patients ( $n=61$ ) versus 364 days (95% CI, 344-384) for donepezil patients ( $n=712$ ).

**CONCLUSION:** Newly treated AD patients in a usual care setting who initiate therapy with either rivastigmine or donepezil have similar levels of persistency with treatment.

**KEYWORDS:** Alzheimer's disease, Cholinesterase inhibitors, Persistency

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**Note:** An editorial on the subject of this article, "Does Persistence With Drugs for Alzheimer's Disease Matter?" appears on pages 260-61 of this issue.

Alzheimer's disease (AD) is a degenerative disease of the brain and is the leading cause of dementia in the elderly in the United States, accounting for approximately 60% to 70% of all dementia cases.<sup>1</sup> In 2000, there were 4.5 million persons with AD in the United States, and due to the growing number of elderly in the population, this number is expected to increase to nearly 13 million by 2025.<sup>2</sup> The cost of treating AD in the United States has been estimated to exceed \$100 billion per year,<sup>3</sup> with the annual cost of caring for one AD patient ranging from \$18,400 for a patient with mild AD to \$36,000 for a patient with severe AD.<sup>4</sup>

Treatment with cholinesterase (ChE) inhibitors such as rivastigmine (Exelon) and donepezil (Aricept) can provide improvement in symptoms, temporary stabilization of cognition, or reduction in the rate of cognitive decline in some patients with mild to moderate AD.<sup>5-8</sup> However, patients who repeatedly experience troublesome side effects such as gastrointestinal symptoms, which commonly occur with ChE inhibitors, may discontinue therapy or switch to other ChE inhibitors.<sup>9-11</sup>

Persistence with treatment is critical if AD patients are to maintain the benefits of these drugs. As evidence, within 6 weeks after discontinuing their AD therapy, donepezil-treated patients' cognitive function dropped to a level similar to placebo-treated patients.<sup>12</sup> Furthermore, in the placebo-controlled studies involving rivastigmine, placebo-treated patients never matched the levels of cognitive functioning demonstrated by rivastigmine-treated patients even after the placebo-treated patients were switched to treatment with rivastigmine (Alzheimer Disease Assessment Scale-Cognitive Subscale [ADAS-Cog] mean  $\pm$  SD) change from baseline of  $-3.7 \pm 0.62$  for patients treated with placebo for 26 weeks followed by

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26 weeks of treatment with rivastigmine [dose ranging from 1 mg to 6 mg twice a day (BID)] versus ADAS-Cog mean change from baseline of  $-2.3 \pm 0.62$  for patients treated with 6-12 mg per day rivastigmine for all 52 weeks).<sup>13</sup>

Persistence with AD treatment is also critical from an economic standpoint. Previous economic evaluations of ChE inhibitors in the treatment of AD demonstrate the need for long-term, efficacious treatment to achieve the full economic and patient benefits of AD therapy. In most patients, natural progression of the disease is slow and does not require significant use of health care resources in early stages.<sup>14,15</sup> One of the major potential economic benefits is a delay in placement of AD patients in nursing homes. An observational follow-up study of the patients in 1 of 3 randomized donepezil clinical trials found that when donepezil was taken at an effective dose (5 mg per day or more) for at least 9 to 12 months, time to first dementia-related nursing home placement and time to permanent nursing home placement were longer than in the group with minimal use (defined as less than 5 mg per day).<sup>16</sup> However several researchers questioned the findings from this study, including Karlawish,<sup>17</sup> and the AD2000 collaborative group study found no statistically significant delay in nursing home placement with donepezil.<sup>8</sup>

There is limited information regarding persistence with AD therapy outside the clinical trial setting; existing studies have focused solely on donepezil and have included small sample sizes. In a retrospective review of pharmacy claims data for 59 AD patients receiving treatment in a usual care setting (i.e., not in a randomized control trial), Roe et al.<sup>18</sup> found that the probability of a new user continuing donepezil at 90 days was  $79.7\% \pm 10.3\%$  and at 180 days was  $62.7\% \pm 12.4\%$ . Approximately 14% of those who continued therapy for at least 180 days showed gaps in treatment of 6 weeks or more.<sup>18</sup> The purpose of the current study was to assess drug persistence patterns for patients treated with either rivastigmine or donepezil in usual care settings, where conditions typically differ considerably from those in controlled clinical trials. There were 2 opposing reasons why a difference in persistence might be expected between rivastigmine and donepezil: the side-effect profile of rivastigmine compared with donepezil might result in lower persistence, and its dual mechanism of action might lead to better efficacy over the long term and thus better persistence.

## Methods

### Cohort Construction

This was a retrospective cohort study utilizing longitudinal, integrated medical and pharmacy claims data from the PharMetrics Anonymous Patient-Centric Database. The PharMetrics database includes patient-level medical and pharmaceutical claims histories of more than 27 million managed care patients belonging to 60 national and regional health plans in the United States. This database is representative of the national commercially

insured population on a variety of demographic measures, including geography, age, gender, and product type. This database also includes elderly patients (aged 65 years and older) who are enrolled in Medicare managed care plans (e.g., Medicare + Choice, now known as Medicare Advantage) that provide full medical benefits, including prescription drugs.

The database covered the period January 1, 2000, through December 31, 2001. The study population was selected for observation based on evidence of pharmacologic treatment for AD. Included were treatment-naïve AD patients aged >40 years who received their index (i.e., initial) prescription for either rivastigmine or donepezil during the 6-month period starting on or after June 1, 2000, when both products were available and ending on or before December 31, 2000. Treatment-naïve AD patients were defined as those who had not received a prescription for any AD medication in the 6 months prior to their index AD prescription. Newly treated AD patients were excluded if they did not have continuous enrollment in their health plan during the 6-month preindex period and for at least 90 days following the index date. Newly treated AD patients were followed until either disenrollment from their health plan or the end of the study period (i.e., December 31, 2001). Survival analysis techniques were used to adjust for any differences in follow-up between the 2 treatments.

Per the product information label, the dosages of donepezil shown to be effective in controlled clinical trials are 5 mg or 10 mg daily (QD), and treatment with 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. For rivastigmine, the dosages shown to be effective in controlled clinical trials are 3 mg to 6 mg BID. The starting dose is 1.5 mg BID. If this dose is well tolerated after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID or 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. Given these titration schedules, patients taking these drugs should reach their maintenance dose within 60 days following the initiation of therapy. Thus the study evaluated the distribution of dosing level for patients at 60 days following the initiation of AD therapy. The study also evaluated the maximum dose level achieved at any point during the study period.

### Study Definitions

Two approaches were utilized to determine persistence with AD treatment. With the first approach, patients were classified as remaining persistent with their index AD medication as long as they did not stop their index AD therapy or switch to a different AD medication. A stop of AD treatment was defined as a patient not receiving a refill for the index AD medication within 60 days after exhausting the drug supply from the prior prescription.<sup>19</sup> The supply extension period of 60 days was selected based on the typical 30-day supply for rivastigmine and donepezil prescriptions, and assuming a 33% adherence

rate (30 days/33% = 90 days total [30 days supplied + 60 additional days]).<sup>19</sup> As recommended by Dezii,<sup>19</sup> the 60-day supply extension was also used for AD prescriptions, with days supply exceeding 30 days (< 5% of all AD prescriptions had days supplied amounts > 45 days, including 90-day mail-order prescriptions). Switching was defined as a patient, at any time following the index date, filling a prescription for any AD medication other than the index medication, regardless of continued index drug use. "Time to treatment discontinuation" (i.e., the rate at which patients discontinue therapy over time), was calculated as the number of days from the index prescription fill date to either (1) the date of index medication supply exhaustion preceding a stop of treatment or (2) the date of the fill of a nonindex AD medication (i.e., switch), whichever occurred first.

Some patients may intend to persist with therapy and fill a prescription but end up not using any of the medication. Thus, a sensitivity analysis was conducted based on a more conservative definition of a stop of treatment. The stop date was changed from "date of end of days supply of last prescription + supply extension days" to "fill date of last prescription."

Because the reasons for switching or stopping treatment might be different in the early period of ChE-inhibitor treatment (e.g., side effects) compared with the later treatment period (e.g., lack of efficacy), the time to treatment discontinuation approach included 2 analytic components. First, the study estimated the probability of treatment discontinuation in the first 60 days for the entire study population, by index treatment group. Second, the study evaluated time to treatment discontinuation for the cohort of patients (designated the "study cohort") that remained on its index AD medication for at least 60 days. This was considered a reasonable minimum period of time under usual care conditions to observe either (1) titration or (2) dropout because of intolerance to side effects.

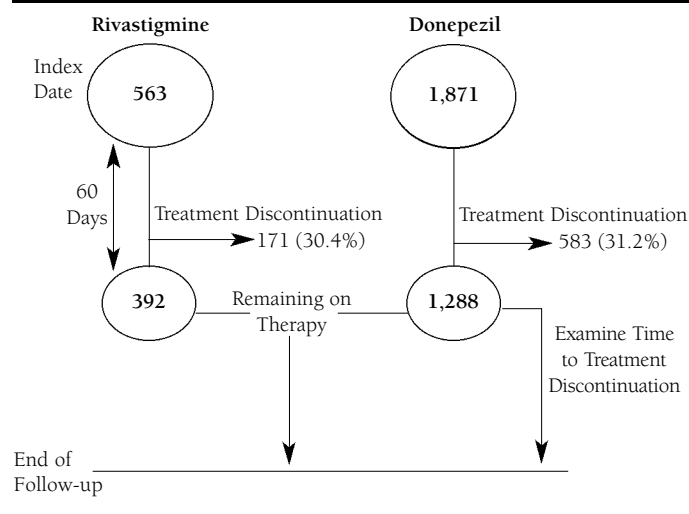
For the purpose of subgroup analyses, the study cohort was also classified based on whether or not patients reached the following dosing levels (per product prescribing information) for their index AD medication prior to either treatment discontinuation or the end of the study period:

1. approved dose (6-12 mg per day of rivastigmine or 5-10 mg per day of donepezil)
2. maximum recommended dose (12 mg per day rivastigmine or 10 mg per day donepezil).

The dosing level was determined from the pharmacy claims data by first taking the strength of dose into consideration (e.g., a 1.5 mg pill versus a 6 mg pill) and then dividing the quantity of drug dispensed by the days of drug supplied to determine the daily dose.

The second approach used to determine treatment persistence was the proportion of days covered (PDC).<sup>20</sup> The number of days supplied from each filled prescription was used to calculate the proportion of days on which a patient had an AD medication

**FIGURE 1** Disposition of Study Cohort During Follow-up Period



available in a given time interval. This analysis was conducted on the entire study population. Per Benner et al. (2002),<sup>20</sup> the cohort was divided into 3 groups: *adherent* patients were defined as those with a PDC  $\geq$  80%; *partially adherent* patients were those having a PDC of 20% to 79%; and patients with a PDC < 20% were considered *nonadherent*. Nonadherence or partial adherence in a given time interval were considered as *suboptimal persistence*. The PDC was evaluated at 3-month intervals (1-3, 4-6, 7-9, 10-12 months) following the index date for patients who had complete follow-up data at each time point.

### Statistical Analysis

All statistical and descriptive analyses were performed using SAS version 8.02 (Cary, North Carolina). Descriptive statistics, including means ( $\pm$ SD) for continuous data and relative frequencies for categorical data, were compared using *t* tests and chi-squared tests, respectively. Survival analysis methods were used to evaluate time to treatment discontinuation. Patients were followed until the first occurrence of one of the following events: discontinuation of index therapy, switch to different AD medication, disenrollment from health plan (censored), or end of study period (censored).<sup>21</sup> The primary reason to use survival analysis to measure drug persistence is that the analysis does not require follow-up to be identical for all patients. Because of potential selection bias associated with a retrospective design, Cox proportional hazards regression models were used to evaluate the risk of treatment discontinuation after adjusting for patients' baseline characteristics, including patient age (at index date) and gender, preindex period utilization (i.e., hospitalizations, office visits, prescription drugs), and level of comorbidity in the preindex period (including the use of a modified version of the

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**TABLE 1** Baseline Characteristics for Patients Remaining on Therapy 60 Days

Variable	Index AD Medication		P Value
	Rivastigmine (N = 392)	Donepezil (N = 1,288)	
Mean age in years (±SD)	74.29 (10.46)	74.11 (11.18)	0.778
Female (%)	59.95	61.49	0.584
Medicare + Choice members (%)	78.27	78.41	0.712
Mean follow-up after index date (±SD)	284.72* (126.73)	305.80 (138.20)	0.001
Median follow-up after index date	260	292	
<b>Preindex period utilization</b>			
Mean number of hospital admissions (±SD)	0.80 (1.55)	0.80 (1.64)	0.940
Mean length of hospital stay (±SD)	4.97 (12.41)	5.66 (16.80)	0.450
Mean number of office visits (±SD)	15.53 (18.37)	16.30 (20.39)	0.505
Mean number of prescription fills (±SD)	36.17* (37.13)	31.23 (32.15)	0.018
<b>Comorbidities in preindex period</b>			
Mean Charlson Comorbidity Index (±SD)	1.51 (1.56)	1.43 (1.59)	0.376
Hypertension (%)	35.71	36.49	0.780
Senile dementia (%)	8.42	7.69	0.637
Urinarytract infection (%)	9.18	9.16	0.989
Cancer (%)	15.82	15.22	0.773
Diabetes (%)	17.09	15.30	0.392
Stroke (%)	4.59	6.21	0.231
Congestive heart failure (%)	7.14	5.98	0.404
Chronic obstructive pulmonary disease (%)	9.44	7.38	0.184
Osteoarthritis (%)	8.42	9.32	0.588
Coronaryartery bypass (%)	13.01	10.71	0.208
Coronaryartery disease (%)	18.88	17.39	0.500

\*  $P < 0.05$ . AD = Alzheimer's disease.

Charlson Comorbidity Index<sup>22</sup> developed by researchers in a Dartmouth-Manitoba collaboration<sup>23</sup>). The cumulative probabilities of continuing therapy were plotted as a function of time using the Kaplan-Meier product-limit method (which results in graphical survival curves depicting the rate of treatment discontinuation over time). The a priori threshold level for statistical significance was  $P \leq 0.05$ .

### Results

The study population comprised 2,434 AD patients newly treated with either rivastigmine ( $n = 563$ ) or donepezil ( $n = 1,871$ ) who met all study eligibility criteria. Of this population, 30.4% (171/563) of rivastigmine patients and 31.2% (583/1,871) of donepezil patients discontinued treatment within 60 days of the index date ( $P = 0.72$ ) (Figure 1). There were no statistically significant differences in demographic characteristics (i.e., age, gender, comorbidity) or preindex period utilization between patients who discontinued treatment and those who continued treatment after 60 days.

The study cohort comprised the remaining patients who did not discontinue treatment within 60 days (Figure 1, Table 1). There was a statistically significant ( $P < 0.001$ ) difference between the 2 index treatment groups in terms of mean follow-up time after the index date (due to donepezil being first to market in the United States), but this difference did not impact the analysis since survival analysis methods were used to account for differential follow-up and the similarity in the range of follow-up times between the 2 groups.

The study cohort used a considerable amount of health care services in the preindex period (e.g., >15 office visits and 30 prescription fills in a 6-month period) (Table 1). Levels of preindex resource utilization and comorbidity were comparable between the 2 treatment groups (Table 1).

Table 2 presents the distribution of the study cohort's daily dosing level at 60 days, and the maximum dose achieved at any point in the study period, following the initiation of AD therapy (based on daily dose calculation for the prescription refill with fill date closest to, but not sooner than, days 60 and 90 postindex date). Since the minimum dose of donepezil available on the market is 5 mg, it is not surprising that by day 60, 98% of donepezil-treated patients were taking doses shown to be effective in controlled clinical trials. It should be noted that both available strengths of donepezil, the 5 mg and 10 mg tablets, are considered to be clinically effective doses when taken once daily; however 2% of donepezil patients had prescription claims for the 5 mg tablet but with twice the number of days supplied as quantity dispensed. Therefore, based on our calculation for daily dose, these patients were not classified as receiving a minimum daily dose of 5 mg of donepezil.

Approximately one third of the rivastigmine-treated patients who had persisted with therapy for at least 60 days were not receiving a dose shown to be effective in controlled clinical trials

**TABLE 2** Distribution of Daily Dose for Study Population at 60 Days after Initiation of Therapy, and Maximum Dose at Any Point in Study Period

Daily Dose	At 60 Days (%)*	Maximum Dose	
		Any Point in Study Period (%)	
<b>Rivastigmine</b>			
1.5-4.5 mg	35		18
6.0-9.0 mg	55		67
12.0 mg	8		15
<b>Donepezil</b>			
5.0 mg	53		48
10.0 mg	45		52

\* Percents do not add to 100% due to exclusion of small proportion of patients with daily doses that were fractions of available doses.

(6 mg QD). Approximately 30% (117/392) of the rivastigmine-treated patients and 35% (456/1,288) of the donepezil-treated patients had at least 12 months of follow-up data following the index prescription. Of this subset of patients, 42% (49/117) of the rivastigmine group remained on their index therapy at 12 months postindex date, as compared with 37% (167/456) of the donepezil group ( $P = 0.30$ ). Of the rivastigmine patients not remaining on therapy, 72% (49/68) stopped treatment and 28% (19/68) switched to a different AD therapy; of the donepezil patients not remaining on therapy, 81% (235/289) stopped treatment and 19% (54/289) switched to a different AD therapy.

Based on results from the Cox regression model for the study cohort, the likelihood of treatment discontinuation for rivastigmine patients was not statistically significantly different from that of donepezil patients (RR [relative risk] = 0.98;  $P = 0.82$ ; 95% confidence interval [CI], 0.83-1.16). Adjusting for age, gender, preindex utilization, and concomitant disease did not significantly change the hazard ratio. The mean times to treatment discontinuation are provided in Table 3. The unadjusted Kaplan-Meier curves for time to treatment discontinuation are shown in Figure 2. The curves are flat for the first 60 days because, by definition, the study cohort could not discontinue or switch treatment during that time. The sensitivity analysis (i.e., changing the calculation for date of treatment discontinuation) did not significantly change the results. The mean time to treatment discontinuation was 318 days (95% CI, 293-343) for rivastigmine patients as compared with 315 days (95% CI, 301-329) for donepezil patients.

Analyses were repeated for the subgroup of patients in each index treatment group that reached an approved dose during the study period (282/392 rivastigmine patients; 1,283/1,288 donepezil patients). Similar to the results for the full study cohort, the likelihood of treatment discontinuation for rivastigmine patients reaching an approved dose was not statistically significantly different from that of the corresponding donepezil subgroup (RR=0.89;  $P = 0.24$ ; 95% CI, 0.73-1.08). Adjusting for age, gender, preindex utilization, and concomitant disease did not significantly change the hazard ratio. The mean times to treatment discontinuation for this subgroup are provided in Table 3. The unadjusted Kaplan-Meier curves for time to treatment discontinuation for this subgroup are shown in Figure 3.

Analyses were also repeated for the subgroup of patients in each index treatment group who reached the maximum recommended dose during the study period (61/392 [15.6%] rivastigmine patients; 712/1,288 [55.3%] donepezil patients). There was a trend toward a reduced likelihood of treatment discontinuation for this subgroup of rivastigmine patients (RR = 0.68, 95% CI 0.43 - 1.06) relative to the corresponding donepezil subgroup, but the difference was not statistically significant ( $P = 0.09$ ). Adjusting for age, gender, preindex utilization, and concomitant disease did not significantly change the hazard ratio. The mean times to treatment discontinuation for this

**TABLE 3** Kaplan-Meier Estimates Comparing Time (Days) With Treatment Discontinuation for Patients Treated With Rivastigmine or Donepezil

Patient Population	Mean Time to Discontinuation (Days)	95% Confidence Interval (Mean)	Median Time to Discontinuation (Days)	95% Confidence Interval (Median)
<b>Full study cohort ( 60 days on drug)</b>				
Rivastigmine (n = 392)	331	307-355	288	238-408
Donepezil (n = 1,288)	337	322-352	283	256-310
<b>Patients receiving approved dose at some point in study period*</b>				
Rivastigmine (n = 282)	346	318-374	322	261-N/A
Donepezil (n = 1,283)	338	323-353	283	256-312
<b>Patients receiving maximum recommended dose at some point in study period†</b>				
Rivastigmine (n = 61)	396	343-449	N/A	239-N/A
Donepezil (n = 712)	364	344-384	332	286-396

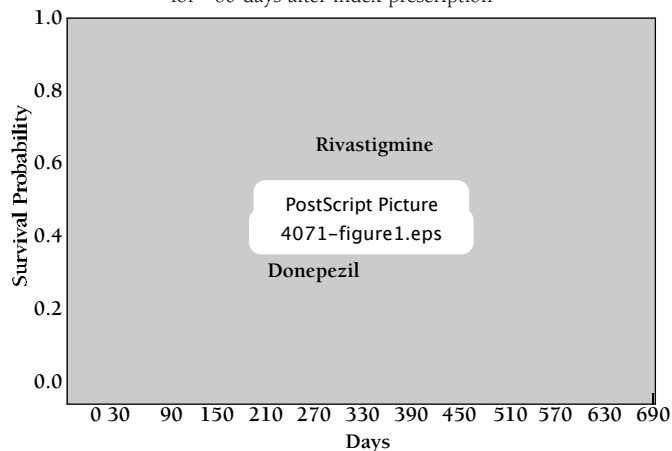
\* 6-12 mg per day rivastigmine; 5-10 mg per day donepezil.

† 12 mg per day rivastigmine; 10 mg per day donepezil.

N/A = SAS did not compute due to large number of censored observations.

**FIGURE 2** Kaplan Meier Curves for Time to Treatment Discontinuation (Full Study Cohort)

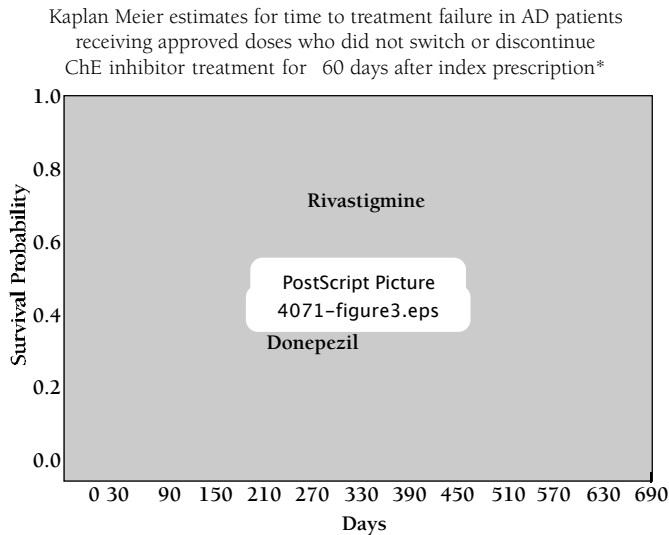
Kaplan Meier estimates for time to treatment failure in AD patients who did not switch or discontinue ChE inhibitor treatment for 60 days after index prescription\*



\* Results are not statistically significant.

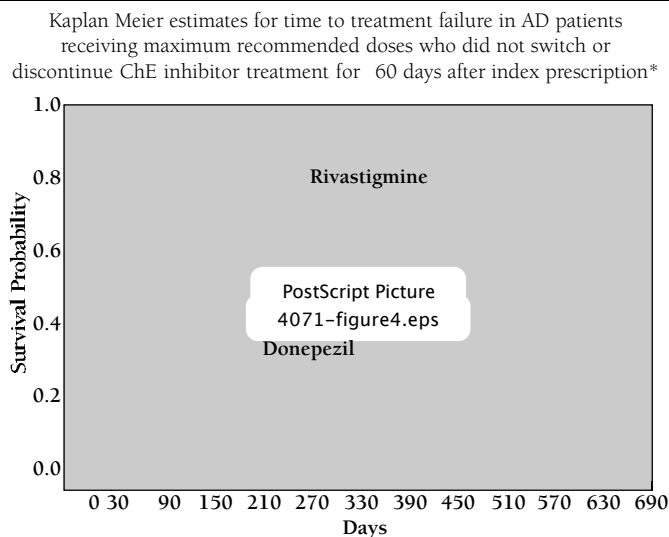
AD = Alzheimer's disease; ChE = cholinesterase.

**FIGURE 3** Kaplan Meier Curves for Time to Treatment Discontinuation (Patient Subgroup Reaching Approved Dose)



\* Results are not statistically significant.  
AD=Alzheimer's disease; ChE=cholinesterase.

**FIGURE 4** Kaplan Meier Curves for Time to Treatment Discontinuation (Patient Subgroup Reaching Maximum Effective Dose)



\* Results are not statistically significant.  
AD=Alzheimer's disease; ChE=cholinesterase.

subgroup are provided in Table 3. The unadjusted Kaplan-Meier curves for time to treatment discontinuation for this subgroup are shown in Figure 4.

The results of the PDC analysis (Table 4) indicated that the proportion of patients persisting with AD therapy (i.e., maintaining a PDC  $\geq 80\%$ ) declined over time. In the first 3-month interval following the index date, a significantly higher percentage ( $P < 0.01$ ) of donepezil patients (44%) versus rivastigmine patients (35%) maintained a PDC  $\geq 80\%$ . However, there were no statistically significant differences for the 3-6 month, 7-9 month, and 10-12 month intervals following the index date. The mean PDC at 12 months was 33% in both treatment groups, and the proportion of patients with a PDC  $\geq 80\%$  after 12 months of follow-up was 23% for the donepezil group and 19% for the rivastigmine group ( $P = 0.34$ ).

### Discussion

Treatment with ChE inhibitors has been proven to slow the decline in cognitive and functional abilities for patients with AD,<sup>5,8</sup> and persistence with therapy is critical for long-term effectiveness. Reasons for lack of persistence with ChE therapy are numerous. Patients or physicians may perceive that the therapy is no longer effective, patients may become intolerant of side effects, or the dosing system may be inconvenient. The present study assessed persistence with patients' initial AD therapy by evaluating longitudinal, patient-level prescription claims data from real-world practice settings. The results indicated that levels of persistence with treatment were similar for newly treated AD patients receiving either rivastigmine or donepezil in a real-world setting.

These persistence results from real-world data are in contrast to those from a recent randomized open-label study that directly compared treatment outcomes and persistency after 12 weeks for patients receiving either rivastigmine or donepezil.<sup>24</sup> The results of this short-term trial indicated that both groups showed comparable cognitive improvements, but more donepezil-treated patients (89.3%) completed the study than rivastigmine-treated patients (69.1%).<sup>24</sup> Given the differences in study design between the published clinical trial by Wilkinson et al. and the current study, it is difficult to compare the persistence findings.

The short-term trial results<sup>24</sup> also indicated that fewer rivastigmine-treated patients (60%) than donepezil-treated patients (98.2%) reached the maximum recommended dose at some point in the 12-week study. In comparison, the real-world results from the current study indicated that only 11% of rivastigmine-treated patients and 55% of donepezil-treated patients received the maximum recommended dose at some point in the 12-month follow-up period.

Delays in cognitive decline associated with persistence with AD therapy may have important personal, social, and economic implications. For example, a recent study has demonstrated that when donepezil was taken for at least 9 to 12 months,

**TABLE 4** Proportion of Days Covered for Rivastigmine and Donepezil Patients

	3 Months		6 Months		9 Months		12 Months	
	Donepezil	Rivastigmine	Donepezil	Rivastigmine	Donepezil	Rivastigmine	Donepezil	Rivastigmine
Number	1,871	563	1,414	412	998	271	641	161
Mean PDC (%)	69	65*	43	42	37	35	33	33
Median	70	68	35	34	24	27	0	0
25th percentile	34	34	0	0	0	0	0	0
75th percentile	96	90	84	82	78	73	74	70
Percent with PDC >80%	44	35*	28	27	24	22	23	19

\*  $P < 0.05$ . PDC = proportion of days covered.

delays to nursing home placement were longer than when it was taken for a shorter time period.<sup>16</sup> In our study, similar rates of persistence were shown for both rivastigmine (42%) and donepezil (35%) at 9 months. A database study has shown that, in a large managed Medicare plan, AD patients receiving donepezil for  $\geq 270$  days had health care costs that were \$4,921 lower than control AD patients not being treated, while costs for those receiving donepezil for less than 270 days were only \$3,579 lower than untreated control AD patients.<sup>25</sup>

It should be noted that a recently published study (AD2000) calls into question the long-term (2-year) clinical benefit of donepezil.<sup>8</sup> Over a 3-year period, the study enrolled patients who were referred to memory clinics with a diagnosis of AD and were not already taking a ChE inhibitor. After a 12-week pretreatment period, 486 patients were randomized to receive 5 mg per day of donepezil, 10 mg of donepezil, or placebo. The results indicated that the groups taking donepezil showed minor improvements in cognitive and functional abilities, which persisted over 2 years. There were no statistically significant differences in the time to nursing home placement or progression to disability among the 3 treatment groups. In addition, there were no significant differences between donepezil and placebo for behavioral and psychological changes, psychological well-being of the primary caregiver, and death from AD. The long-term effectiveness data for rivastigmine are not yet available.

The division of the patient population into those who stop treatment within 60 days and those who continue for longer allows us to estimate the impact of acute side effects separately from the impact of long-term side effects and efficacy on persistence with therapy. These estimates have the potential to give a more accurate picture of patient persistence than a single measure.

The 2 methodological approaches utilized in the study to examine treatment persistence provided dissimilar results. Based on time to treatment discontinuation, approximately 50% of AD patients were persistent with AD therapy after 9 months of treatment. In contrast, the proportion of patients deemed persistent after 9 months of treatment based on the PDC

approach was 32%. The difference may be due to the less restrictive definition of persistence used in the time to treatment discontinuation approach (i.e., allows for a supply extension of 60 days). The advantage of the PDC is its ease of calculation and explanation. The advantage of the survival analysis approach is that it can be used to determine the percentage of patients who are persistent on each day of follow-up, thereby revealing subtle trends.

The persistence findings from this study are based on AD prescription drug fills that were recorded in an administrative claims database. There are 2 principal benefits associated with the use of this type of data source. First, claims databases offer access to large populations of patients that are typical of routine clinical practice, including patients that might be excluded from controlled clinical trials. Second, these data permit the conduct of longer-term analyses than can generally be conducted with clinical trial data.

### Limitations

It is important to recognize some study limitations related to the use of claims data. First, the prescription refill rates estimated from the claims data serve as a proxy for persistence with therapy; we cannot be sure that patients actually took the medications that they received. However, studies in other disease areas have shown that pharmacy dispensing records correlate well with patient drug exposure.<sup>26,27</sup>

Second, claims data contain no direct clinical information, especially as related to treatment side effects and the study cohort's level of AD disease severity. It is possible that treatment side effects may explain, in part, why some rivastigmine patients were not receiving a dose shown to be effective in controlled clinical trials ( $\geq 6$  mg daily). However, other factors could also be involved, including the dosage instructions given by physicians to AD patients. A concern about the impact of varying disease severity across treatment groups was offset to some extent in the study by the inclusion of only "newly treated" AD patients.

Third, it is possible that the prescription records contained

errors in the values for days supply or for quantity dispensed.

Fourth, the relatively recent market launch of rivastigmine in the United States limited our sample size. A larger sample size for the rivastigmine group would enhance the power of the study to detect differences in persistence between the 2 AD treatments. Finally, the claims data do not provide the reasons for patients either stopping or switching from their index AD treatment.

Another study limitation is related to the introduction of rivastigmine in mid-2000, which was near the time frame of the patient identification period of our study (July-December 2000). The introduction of rivastigmine may have been associated with some physicians switching patients from donepezil to rivastigmine simply because a new product (rivastigmine) was available, thus biasing the treatment discontinuation results against donepezil. On the other hand, the limited prescriber experience with rivastigmine may also have led some physicians to switch patients from rivastigmine to another therapy sooner than might have occurred with more prescriber experience with rivastigmine. Longer-term studies focusing on later time periods may avoid both of these sources of potential bias.

It should be noted that nearly 80% of the AD patients in the study had Medicare + Choice as their health insurance coverage. This program provides drug coverage for enrollees but typically has annual drug expenditure caps of \$750 to \$1,000 per patient.<sup>28</sup> Given that the annual cost of AD therapy is more than \$1,500 per year of therapy at discounted prices with either rivastigmine or donepezil, many AD patients likely face increasing out-of-pocket costs the longer they remain on AD therapy. These increased out-of-pocket costs may have a negative impact on treatment persistence and may explain some of the reduction in treatment persistence over time that was found in our study. On the other hand, it can be hypothesized that Medicare patients who enrolled in the Medicare + Choice program did so for the prescription drug benefit and, therefore, may be more persistent with treatment than other Medicare patients. Thus, while these 2 factors would appear to counterbalance each other, the results of the study may not be applicable to the full Medicare population.

### Conclusion

When choosing drug therapy for a chronic illness such as AD, AD patients and their physicians must select an initial drug therapy that is both effective and well tolerated. The results of this study indicate that starting AD patients on either rivastigmine or donepezil, regardless of the daily dosage, results in similar levels of persistence with treatment for patients who remain on therapy for at least 60 days. When the dosage level is taken into consideration (i.e., patients reaching an approved dose or using the maximum recommended dose), levels of persistence remain similar. In light of the findings of AD2000, further research is warranted, especially to evaluate the

effectiveness and cost-effectiveness of longer-term use of these drugs.

### DISCLOSURES

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