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Original Research Article

Donepezil Adherence, Persistence and Time to First Discontinuation in a Three-Year Follow-Up of Older People

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Key Words

Donepezil · Geriatric epidemiology · Population-based study · Adherence · Discontinuation · Older people · Persistence

Abstract

Background: Donepezil is indicated for the management of mild to moderate dementia, particularly in Alzheimer's disease. Several studies have described low adherence rates with donepezil. ***Aim:*** To examine and measure donepezil adherence, persistence and time to first discontinuation in older New Zealanders. ***Methods:*** An inception cohort of 1,999 new users of donepezil, aged 65 years or older, were identified from the Pharmaceutical Collections and National Minimum Dataset from 1 November 2010 to 31 December 2013. Kaplan-Meier curves and Cox regression analysis were used to estimate the cumulative probability and risk of time to first discontinuation of donepezil therapy. ***Results:*** The mean age of the cohort was 79.5 ± 6.4 years and included 42.7% females. Adherence was high (89.0%), while the proportion of donepezil dispensings (81.0–32.5%) declined between 6 and 36 months. Persistence between the 1st and 6th dispensing visit decreased by 19.0%, and 11.0% of the total cohort had a gap of 31 days or more. The adjusted risk of time to first discontinuation in the non-adherent group was 2.2 times (95% CI 1.9–2.6) that of the adherent group. ***Conclusions:*** The non-adherent new donepezil users, on average, discontinued faster than the adherent group. Time to first discontinuation in this study was higher compared to discontinuation rates observed in clinical trials.

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Introduction

Clinical trials with cholinesterase inhibitors (ChEIs) have shown a short-term benefit in halting the progression of cognitive decline, enhanced ability to carry out activities of daily living and improved behaviour in mild to moderate dementia [1–3]. However, there has been minimal evidence supporting long-term use of ChEIs to improve cognition, physical function, challenging behaviours, admission to residential care and mortality [4–6].

Donepezil is the only subsidized acetylcholinesterase inhibitor approved for symptomatic management of dementia in Alzheimer's disease in New Zealand since 1 November, 2010 to date by the Pharmaceutical Management Agency (PHARMAC) [7]. The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of donepezil for mild to moderate dementia with assessment of cognitive function after the first 6 months [8]. In New Zealand, a psychiatric specialist or general practitioner working with mental health patients has to confirm the dementia diagnosis before treatment is initiated using either the Mini-Mental State Examination (MMSE; a score of 21–26 for mild dementia and of 10–20 for moderate dementia), the Addenbrooke's Cognitive Examination-Revised (ACE-R; scale of 0–100), or, in addition, the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; scale of 0–70) to indicate the need for treatment [1].

Donepezil discontinuation is calibrated depending on how effective the treatment is in halting cognitive decline [9–11]. Older people with dementia commonly experience a significant decline in cognitive function without the use of acetylcholinesterase inhibitors for the first 6 months [12]. Therefore, reassessing cognitive decline after donepezil initiation for a similar time frame would help determine if treatment was effective and beneficial or needs to be discontinued. The NICE and New Zealand Formulary have recommended discontinuation of donepezil in individuals with dementia who do not benefit from treatment within a 6-month exposure to the medicine and restarting treatment for those with a rapid decline in cognitive function after a trial withdrawal of the medicine [8, 12, 13]. In some individuals, a rapid decline in plasma levels of donepezil occurs during discontinuation and may not keep pace with the central nervous system readjustment leading to withdrawal symptoms and possible restarting of the treatment [14]. The donepezil starting dose is usually 5 mg daily in the first month and may be increased to 10 mg with caution, monitoring for dose-dependent adverse effects [15, 16].

The trend and characteristics of donepezil in new users (with no pre-exposure) and beyond 6 months have not been explored in New Zealand so far. Therefore, the objective of this study was to examine adherence, persistence and time to first discontinuation (TTFD) of donepezil in an inception cohort of new users over a 3-year follow-up period.

Methods

Study Design

An inception cohort of 1,999 de-identified new users of donepezil, who were aged 65 years or older, was followed for 3 years from 1 November 2010 (start of donepezil subsidy) to 31 December 2013. The inception cohort was chosen from the Pharmaceutical Collections (Pharms) maintained by the Ministry of Health in New Zealand. New users of donepezil, with pre-exposure for 12 months before the index date, were taken to mitigate the challenge of defining and delimiting exposure in the cohort; hence, the measured outcome can, to a large extent, be attributed to donepezil. The scope of our study covered all dispensing data claims for subsidized donepezil in older people aged 65 years or older in New Zealand. The Human Ethics Committee of the University of Otago, New Zealand, approved the study (approval No. H13/001).

Data Source

De-identified data from the Pharms database and National Minimum Dataset were collected for approximately 3 calendar years (2011–2013) from the Ministry of Health, New Zealand. The Pharms database is a national utilization claims database maintained by the Ministry of Health, which captures subsidized donepezil dispensings by all community pharmacies in New Zealand [17]. The Pharms database contained de-identified individual-level dispensing data used in the data analysis. The subsidized donepezil was categorized using the Anatomical Therapeutic and Chemical (ATC) classification for donepezil (N06DA02) developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology's Anatomical Therapeutic and Chemical (WHOCC) classification [18]. Deprivation scores used in this study are social indices derived as a composite variable of categorized basic social needs that include access to a phone or internet, subsidized benefits, income, employment, education, owning a house, or access to a car. The decile scores are a range of ordinal scores from 1 (least deprived) to 10 (most deprived) obtained from mesh blocks, which are the smallest geographical areas defined by Statistics New Zealand, with a population of 60–110 individuals [19].

Adherence and Persistence Measures

Adherence was defined as attaining a variable medication possession ratio (VMPR) of 85% or more. The VMPR served as a proxy to estimate compliance, i.e. following the dispensing interval for refills from the index to the final dispensed date plus the last days of receiving the medicine [20].

Persistence, on the other hand, was defined as the accumulation of time from initiation (first dispensing claim) to discontinuation (last claim plus days of last medicine supply) of treatment with a dispensing gap ≤31 days between refills, while non-adherence (discontinuation) was defined as a gap of more than 31 days, at any time during the 12-month period. The period allowed for the gap was sensitive to changes in measurement for donepezil discontinuation following the implementation of subsidy in New Zealand [7]. Those patients who continued until the end of the study were right censored, while patients who switched medicines were excluded from the study as there was no other subsidized medicine in this therapeutic class. Donepezil dispensings were usually issued or refilled as expected, between 28 days and up to 3 months all at once, and there were only few outliers to this range.

New users of donepezil were defined as not having used donepezil in the preceding 12 months before the index date. The selection of patients was made on the basis of adherence, with a VMPR ≥85% as cut-off, and a sum calculation for each patient on the medicine was done. The VMPR quantifies the accumulation of exposure time from the initial medicine use until the discontinuation of therapy, requiring one or more medicines. The formula below was used to compute the VMPR [20].

$$\text{VMPR} = \frac{\text{total days the medicine was supplied}}{\left(\text{first date dispensed} - \text{last date dispensed}\right) + \text{sum of last prescription days}}.$$

The VMPR can be used for patients who discontinued and/or restarted donepezil therapy and had their missing days accounted for in terms of quantity and daily dose (variables in the Pharms database). The VMPR measures medicine stockpile refills even when there are overlaps between gaps.

Statistical Analyses

Descriptive statistics were performed to generate frequencies and percentages of patient characteristics, adherence and persistence measures in the cohort. Kaplan-Meier curves and

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Table 1. Cohort baseline characteristics of new users of donepezil in the 3-year follow-up among older people (n = 1,999)

	Characteristics	n	%
Sex	Male	1,146	57.3
	Female	853	42.7
Age group	65–69 years	151	7.6
	70–74 years	318	15.9
	75–79 years	457	22.9
	80–84 years	609	30.5
	≥85 years	464	23.2
Ethnicity	Unknown	137	6.8
	Others	1	0.1
	New Zealand Europeans	1,739	86.9
	Maori	52	2.6
	Pacific	19	1.0
	Asian	40	2.0
	MELAA	11	0.6
DHB	Overseas and Unident	2	0.1
	Auckland	200	10.0
	Bay of Plenty	95	4.8
	Canterbury	324	16.2
	Capital and Coast	93	4.7
	Counties Manukau	140	7.0
	Hawkes Bay	68	3.4
	Hutt Valley	45	2.3
	Lakes	56	2.8
	MidCentral	96	4.8
	Nelson	24	1.2
	Northland	54	2.7
	South Canterbury	68	3.4
	Southern	140	7.0
	Tairawhiti	29	1.5
	Taranaki	49	2.5
	Waikato	153	7.7
	Wairarapa	21	1.1
	Waitemata	306	15.3
	West Coast	20	1.0
	Whanganui	16	0.8
NZDep	Unknown	296	14.8
	1 (least deprived)	190	9.5
	2	168	8.4
	3	172	8.6
	4	169	8.5
	5	190	9.5
	6	220	11.0
	7	191	9.6
	8	193	9.7
	9	145	7.3
	10 (most deprived)	65	3.3
VMPR discontinued	≥85%	1,465	73.3
	≤85%	209	10.4
VMPR censored	≥85%	313	15.7
	≤85%	12	0.6
VMPR overall	≥85%	1,778	89.0
	≤85%	221	11.0
	Total	1,999	100.0

DHB = District Health Board; MELAA = Middle East Latin America and Africa; Unident = unidentified; NZDep = New Zealand Index of Deprivation.

Table 2. TTFD (months) of donepezil in a 3-year follow up of new users (n = 1,999)

Period, months	Probability of discontinuation, %	Probability of continuing treatment	Cumulative discontinuations, n	Patients discontinued, n	Proportion of donepezil dispensings
Single dispensings		–	–	124	–
6 months	35	0.65	699	699	81.0
12 months	49	0.51	980	281	69.3
18 months	59	0.41	1,178	198	55.4
24 months	77	0.33	1,328	150	45.9
36 months	93	0.17	1,674	222	32.5
≥36 months (censored)	>94	≤0.16	325		≤27.5
Total after study period			1,999	1,674	

Cox regression analysis were also used to estimate the cumulative probability and risk of TTFD of donepezil therapy. Data analyses were performed with IBM SPSS for Windows version 22, 2013 [21].

Results

Baseline Characteristics

The cohort of 1,999 patients consisted of 42.7% females, and the mean age of the population was 79.5 ± 6.4 years. The percentage of new donepezil users for the 65- to 69-year age group (7.6%) increased with age up to the ≥85-year age group (23.2%). New Zealand Europeans were the majority of donepezil users (87.0%), and the top new user of donepezil stratified by the District Health Board was Canterbury (16.2%). Only 3.3% of new users were least deprived with a score of 10 (table 1).

Time to First Discontinuation

After a 3-year follow-up, 124 patients discontinued treatment after a single (one-off) donepezil dispensing, and the Kaplan-Meier curve found that the probability of continuing donepezil treatment was 0.6 after the first 6 months of treatment. The median TTFD of donepezil was 12.4 months and only a fraction of patients who discontinued donepezil after 6 months declined faster in the non-adherent (57.0%) compared to the adherent group (30.0%) (fig. 1). TTFD of donepezil gave cumulative probabilities, which increased by 35.0% in 6 months, by 49.0% in 12 months and by 77.0% in 24 months from the index date (table 2). The percentage of people on donepezil dispensings after 6 months declined from 100.0 to 81.0%, and after 12 months, it declined from 81.0 to 69.3%, as expected (table 2). Findings from the Cox regression model showed that males had an adjusted risk of TTFD of donepezil that was 1.2 times (95% CI 1.1–1.4) higher than that of females. Furthermore, the risk of TTFD of donepezil in the non-adherent group was 2.2 times (95% CI 1.9–2.6) higher compared to that of the adherent group, while increasing age and deprivation scores were independent of TTFD of donepezil (online suppl. table S1; see www.karger.com/doi/10.1159/000441894 for all online suppl. material).

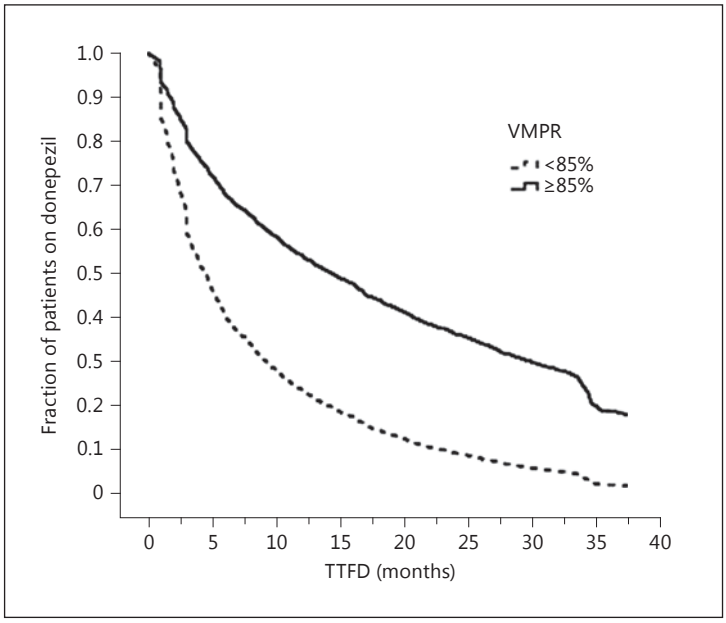

Fig. 1. TTFD of donepezil for 3 years of follow-up of new users by VMPR.

Adherence and Persistence

Of the new users of donepezil during the study period, 89.0% of the adherent patients (both discontinued and censored) had attained a VMPR of 85% more, 10.4% were non-adherent (discontinued), and the remaining were right censored (table 1). After 6 months of treatment, the proportion of individuals who discontinued donepezil declined significantly (log-rank χ^2 statistics = 137.8; $p < 0.05$) in the non-adherent (60.0%) compared to the adherent group (30.0%) (fig. 1). Persistence was 17.0% after 3 years, donepezil utilization between the 1st and 6th dispensing visit decreased by 19.0% for the patients, and the probability to continue treatment was 0.6 (fig. 2). Persistence in donepezil dispensings after the 12th dispensing visit had declined by 30.7% and the probability had halved (0.5) for donepezil treatment follow-up.

Discussion

There is no pharmacoepidemiology study, to our knowledge, on the utilization of donepezil among new users in New Zealand published in the literature. The findings from this study showed the first TTFD population-based study of new donepezil users being older New Zealanders aged 65 years and above. In this study, the continuation rate for the cholinesterase inhibitor in the first 6 months was 65.0% and the finding was similar to a new user design study explored by Roe et al. [22] that reported a continuation rate for ChEI to be 62.7%, within the same study time frame. In contrast, other studies have reported higher continuation rates of 74.0 and 83.0%, respectively [23, 24]. Hollingworth and Byrne [25] found that in Australia, medicine subsidies influenced the prescribing trends of ChEIs and led to medicine stockpiling, though not observed in our cohort, towards the end of each calendar year.

In our study, 35.0% of the individuals discontinued donepezil 6 months after treatment, while 40.0–50.0% of patients had discontinued ChEI treatment within the same period in another population-based study [26]. Kogut et al. [23], in a cohort study, reported that 25.0%

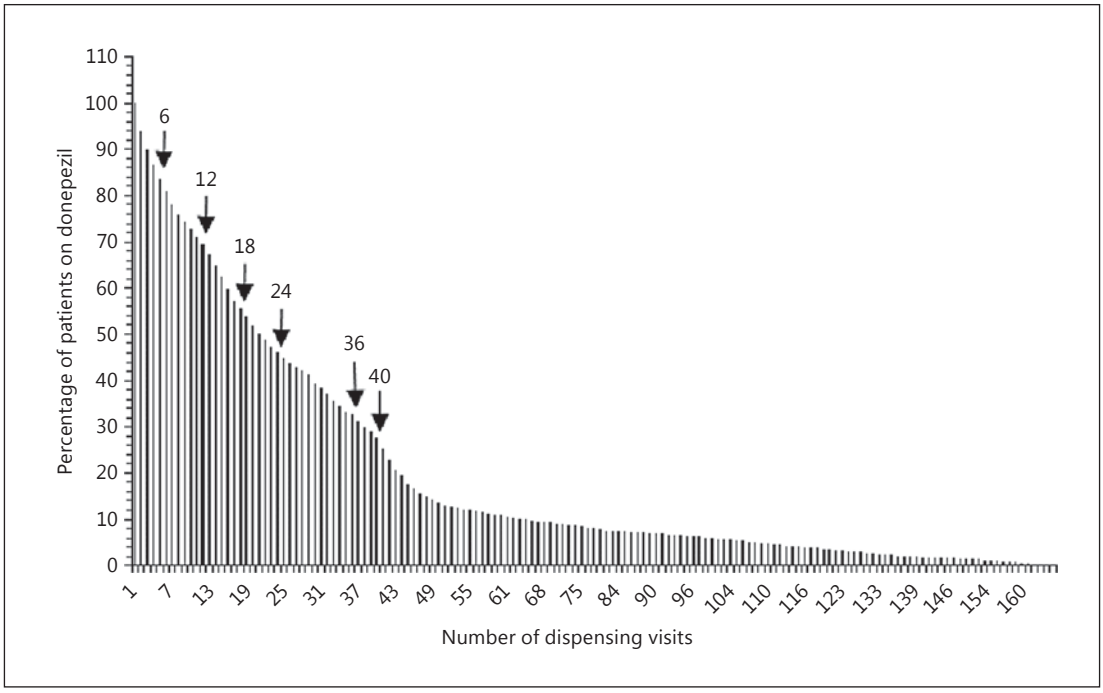

Fig. 2. Persistence in dispensing visits (between 1 and 3 months) for new users of donepezil in older people (n = 1,999).

(compared to 35.0% in the present study) of patients discontinued ChEI treatment within the first 6 months. Le Couteur et al. [4], in a long-term Australian study, found consistent measures after 12 months; 54.7% (compared to 51.0% in the current study) of those were initiated with ChEI treatment and continued on it. After 36 months, only 32.9% (compared to 32.5%) remained on treatment. In a real-world population-level study of Alzheimer's disease patients conducted in Canada, discontinuation rates for donepezil were up to 66.4% at 12 months [26]. Herrmann et al. [27], using administrative health databases, reported discontinuation rates for ChEI of 40.0–50.0% at 12 months. Similarly, Dybicz et al. [9], in a 12-month nursing home population-based study, found 43.1% discontinuations, and Umegaki et al. [28], in a retrospective chart review, found 53.1% (compared to 33.0%) discontinuations at 24 months.

The discontinuation rates of donepezil in our study at 6 months (35.0%) and 12 months (49.0%) were higher compared to the clinical trial discontinuation rate of 10–28.0% reported by Rogers et al. [29]. Access to specialist psychogeriatric and mental health services varied from one jurisdiction to another, and may have contributed to higher donepezil utilization rates found in Canterbury, Waitemata and Auckland compared to other District Health Boards [30].

Persistence was directly influenced by adherence, while age was independent of TTFD of donepezil. The adjusted risk of TTFD of donepezil in the non-adherent group was more than twice that of the adherent group in our findings. However, Kogut et al. [23] found that those aged 85 years or older were more persistent than younger patients. After adjusting for race and institutional setting, they found that patients who were taking medicines that impair cognition were more likely to have discontinued ChEI treatment over 6 months compared to those who did not use such medicines. The continuation rate in the present study had declined

to 65.0% after the first 6 months and to 17.0% after 36 months. In a similar long-term study, Le Couteur et al. [4] measured 70.3% persistence at 6 months and retained 26.0% of patients who, at the end of their study, were still on treatment. Courtney et al. [31] found, in a randomized controlled trial study on donepezil, that a persistence of 60.0% (compared to 51.0% in our study) was reached at 12 months and 23.0% (compared to 33.0%) after 24 months of donepezil treatment, which indicated longer persistence in our 'as-treated' design. Furthermore, Winblad et al. [10] observed donepezil persistence rates of 66.9% in a randomized controlled trial, which retained similar rates in the placebo group (67.4%) after 12 months of exposure. Dispensing visits (1–3 monthly) for new users of donepezil was a useful indicator for assessing persistence in relation to time, as well as the refill trend. Patients with more dispensing visits were less likely to discontinue donepezil treatment, and this finding was consistent with a similar study by Suh et al. [32].

There is very little meaningful information to derive about persistence from clinical trials in relation to donepezil new users in older people; hence, real-world observational data are important to examine persistence patterns, as strictly controlled trial data are often short-term, suffer from selection bias and deviate from real-world clinical practice [31]. Persistence to donepezil is also important for demonstrating efficacy and tolerability, and could have economic implications [26]. Previous studies have demonstrated that improved persistence to donepezil can delay residential care admissions [6]. Single dispensings were observed for some patients during follow-up, and this finding may likely be due to misdiagnosis, switching of medicines or loss to follow-up.

This study has some limitations. The VMPR was used as a proxy for adherence with the assumption that everyone consumed the medicine. Individuals lost during the follow-up were not individually investigated to find out the reasons for their discontinuation. MMSE scores or other cognitive measures were not available to be included as variables in this study. The new users were identified based on the use of donepezil rather than a diagnosis of dementia. Previous studies have identified the underreporting of dementia in national claims data [33]. The clinical reasons for discontinuation of donepezil, including dementia severity, tolerability and adverse effects, were not ascertained. However, the study highlights the initial use and TTFD of donepezil as being consistent, based on population-level data for each patient, within the first 6 months in relation to clinical recommendations for patient characteristics, adherence and persistence in new users.

In conclusion, donepezil adherence, persistence and TTFD beyond the first 6 months in older people were consistent with current clinical practice recommendations. Non-adherence to donepezil treatment reduced persistence and increased the risk of discontinuation. However, the rate of TTFD was high compared to clinical trial discontinuation rates. Future studies should examine the clinical correlates for donepezil discontinuation.

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Disclosure Statement

No potential conflicts of interest were disclosed.

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