

REPRESENTATION OF PATIENTS WITH DEMENTIA IN CLINICAL TRIALS OF DONEPEZIL



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ABSTRACT

Objectives

To evaluate the representation of frail older adults in randomized controlled trials (RCTs), and to assess consequences of under representation by analyzing drug discontinuation rates.

Methods

A cohort of older adults newly dispensed donepezil in Ontario between September 2001 and March 2002 was constructed using administrative data. A systematic review of the literature identified RCTs of donepezil. Patients dispensed donepezil were then compared to clinical trial subjects. Discontinuation rates were examined for patients with and without potential contraindications to this drug.

Results

There were 6,424 older adults in the Ontario cohort with new claims for donepezil. Ten RCTs evaluating the use of donepezil were identified (n = 3,423). Between 51% and 78% of the Ontario cohort would have been ineligible for RCT enrolment. Patient's dispensed donepezil were older (80.3 vs. 73.7 years, p<0.001) and more likely to be in long-term care (14.1 vs. 7.1%, p < 0.001) than RCT subjects. Overall, 27.8% of the Ontario cohort discontinued donepezil within seven months of initial prescription. Discontinuation rates were significantly higher for patients with a history of obstructive lung disease, active cardiovascular disease, or Parkinsonism.

Conclusions

Fewer than half of the older adults dispensed donepezil in Ontario would have been eligible to participate in the RCTs that established this drug's efficacy. Discontinuation rates were higher among patient groups not represented in the trials. Clinicians should carefully assess the potential risks and benefits of such drug therapies for older patients with dementia.

Key Words: Dementia; cholinesterase inhibitors; donepezil; clinical trials

Randomized controlled trials (RCTs) are generally considered to provide the best evidence for treatment efficacy, but studies have shown that the subjects they enrol often fail to represent patients who receive the treatment in practice. Exclusion criteria commonly restrict enrolment on the basis of age and co-morbidity.¹⁻³ This issue is especially relevant to

the study of Alzheimer's disease (AD) and related dementias, which are predominantly conditions of older adults.⁴ The population with dementia also carries a significant burden of co-morbid disease and functional dependence. Cholinesterase inhibitors have been widely adopted to manage the symptoms of AD.^{5,6}

Donepezil is the most widely studied agent in this drug class. In 1997, Schneider and colleagues documented that the restrictive selection criteria for early RCTs of cholinesterase inhibitors resulted in a demographically and clinically constrained subgroup that was not representative of patients typically presenting to memory clinics.⁷ Greenberg and colleagues⁸ subsequently conducted an independently funded RCT to see if the positive results of previous donepezil trials⁹⁻¹³ could be replicated in patients drawn from clinical practice. The Greenberg trial confirmed the modest benefits of donepezil on cognitive performance but found no evidence of improved global functioning.⁸ Since the Greenberg trial, several more RCTs of donepezil have been published.¹⁴⁻¹⁷ The exclusion criteria for these newer trials are still quite restrictive. Thus, concerns about adequate representation persist.¹⁸

We compared the use of donepezil in clinical practice with that in RCTs. The objectives were to determine how many older adults receiving donepezil in a population-based cohort would have been eligible for enrolment in RCTs, and to compare the profiles of these groups. To highlight the consequences of excluding certain patient groups from RCTs, we compared the donepezil discontinuation rates in patients with and without potential contraindications to cholinesterase inhibitors. Patients with these contraindications were largely excluded from the trials. The findings of this study underscore the divergence between representation in RCTs and prescribing patterns in actual practice.

METHODS

We first constructed a cohort containing all older adults newly dispensed donepezil in Ontario (the "Ontario cohort") using administrative data. A systematic review of the literature was next undertaken to identify all published RCTs of donepezil to treat AD. The demographic data and drug utilization characteristics of the Ontario cohort and the RCT subjects were then compared. In Ontario, a universally funded health program covers nearly all physician services, medications, and hospital services for people aged 65 and older. Encrypted unique identifiers that are common between databases were used to link anonymous information on demographics and

health services utilization for patients in the Ontario cohort. The linked databases included computerized pharmacy records of the Ontario Drug Benefit Program (ODB), which records prescription drugs dispensed to all Ontario residents aged 65 years or older.

Acute care hospitalization records were obtained from the Canadian Institute for Health Information Discharge Abstract Database (CIHI), which employs the International Classification of Diseases, Ninth Revision (ICD-9) nomenclature to provide detailed diagnostic records for all hospital admissions. The Ontario Health Insurance Plan (OHIP) provided physician billing information for inpatient and outpatient services, and the Registered Persons Database (RPDB) contained basic demographic information and vital statistics for each Ontario resident. The Ethics Review Board of Sunnybrook and Women's College Health Sciences Centre approved this study.

We identified a cohort of older adults who were newly dispensed donepezil between September 1, 2001 and March 31, 2002 using the ODB database. To restrict our cohort to new users, we looked back six months from the first date of dispensation to ensure subjects had not previously received donepezil. We considered donepezil had been stopped if no further dispensation was recorded in the ODB database in the six-month period after the end date of the last dispensation. We had access to information on the initial dispensation of donepezil only after September 2001. Prior to this time, patients newly started on donepezil received their first 12-week supply of the drug from a program administered by Caremark Limited, and paid for by Pfizer.¹⁹

We did not have data from Caremark on initial patient exposure to donepezil from this program. If patients tolerated donepezil for the initial 12-week period, further dispensations were administered through the ODB. After September 2001, all initial and subsequent dispensations of donepezil were administered through the ODB. Donepezil is listed on the ODB formulary as a Limited Use product, meaning that coverage is restricted to patients with probable AD of mild to moderate severity (Mini-Mental State Examination (MMSE) score between 10-26).

We searched MEDLINE (1966-September 2003), EMBASE (1980-September 2003), and the Cochrane Library (issue 1, 2003)²⁰ using the

medical subject heading (MeSH) terms Alzheimer disease and randomized controlled trials, and the text words donepezil and Aricept. Based on titles and abstracts, we retrieved the full publication of all potentially relevant English-language articles for review. We manually searched reference lists from these articles as well as previous systematic reviews of cholinesterase inhibitors^{6,21} to find additional relevant RCTs.

Articles were included if they contained original data on randomized, double-blinded, placebo-controlled trials of donepezil to manage the symptoms of AD. Papers that described primary open-label use of donepezil or open-label extensions of previously reported RCTs were excluded. Two trials were excluded because they were head-to-head comparisons of different cholinesterase inhibitors.^{22,23} One RCT pilot study was excluded because it examined the use of donepezil in subjects with AD associated with Down syndrome.²⁴ Finally, we excluded articles examining the use of other cholinesterase inhibitors (e.g., rivastigmine or galantamine); relatively few patients dispensed these drugs were available for analysis as they were only recently added to the ODB formulary.

We categorized the exclusion criteria explicitly reported in the RCTs as either “potential contraindications” or “potential complicating factors”. Potential contraindications were conditions for which the increased cholinergic tone induced by cholinesterase inhibitors might theoretically be harmful, such as bradycardia.²⁵

Potential complicating factors were conditions or medications that might mask the benefits of cholinesterase inhibitors on cognitive performance, or the assessment of such benefits. For example, psychotic features might mask modest cognitive gains, while significant visual or hearing impairment might preclude the cognitive assessments used in the RCTs to measure these gains.

We also generated a list of potential contraindications directly from the Warnings section in the 2001 Compendium of Pharmaceuticals and Specialties (CPS).²⁶ The CPS is a collection of monographs written by pharmaceutical companies according to guidelines published by the Health Protection Branch of Health Canada. Published annually, the CPS is

widely available and is consulted frequently by Canadian physicians.

We identified the presence of RCT exclusion criteria and CPS Warnings in the Ontario cohort using a combination of diagnostic coding in OHIP and CIHI, and drug dispensation using ODB. The databases and codes used to define individual exclusion criteria are listed in the Appendix A. We compared the percentage of subjects residing in long-term care (Ontario cohort vs. RCT) to indirectly reflect the burden of co-morbidity and/or functional dependence.²⁷ To summarize demographic characteristics for the aggregated RCT sample, we used means weighted by the sample size in individual RCTs when appropriate (e.g., age and MMSE scores). To compare proportions (e.g., percent residing in long-term care) we used the chi-square (χ^2) test. For the comparison of mean ages in the RCT sample and Ontario cohort, we used the two-sample t-test and assumed equal variances. The variance for mean age of the RCT cohort was unknown, as standard deviations of mean age were not reported in the individual RCTs.

We were concerned that observed differences in mean age might be biased by missing data in the Ontario cohort for subjects < 66 years. (The lower age cut-off for ODB eligibility is 65 years, and we examined the group 66 years and older in order to review the previous year’s drug utilization.) However, when we examined the age distribution of the Ontario cohort, it appeared normally distributed with most of the curve represented within our age range (> 66 years). This distribution corresponds to the known epidemiology of dementia: the mean age at the onset of dementia is approximately 80 years, and onset below age 65 is uncommon.⁴ To compare donepezil discontinuation rates for subjects in the Ontario cohort with and without potential contraindications, we used Fisher’s exact test because of the small sample sizes involved.

RESULTS

We identified 6,424 older adults with new ODB claims for donepezil between September 1, 2001 and March 31, 2002. The literature search strategy identified a total of ten published RCTs of donepezil that met the inclusion criteria.⁸⁻¹⁷ A total

of 3,423 subjects were involved in these trials, 2,070 of whom received donepezil (the remainder received placebo).

The RCTs and the demographics of their participants are detailed in Table 1. Among the nine trials for which sources of financial support were reported, eight (89%) received support from Eisai and/or Pfizer, the manufacturers of Aricept® (donepezil hydrochloride). Table 2 outlines the demographic comparisons between the RCT subjects and the Ontario cohort. In the Ontario cohort the mean age was 80.3 years, while in the RCTs the weighted mean age was 73.7 years ($p < 0.001$). Sex distributions were similar, with 35.7% of the Ontario cohort and 36.2% of RCT subjects being male. Compared to subjects in the RCTs, nearly twice as many people in the Ontario cohort were residing in long-term care facilities (14.1% vs. 7.1%, $p < 0.001$). Note that these patients were

being given donepezil for the first time after they had been placed in long-term care.

The exclusion criteria from the RCTs are listed in Table 3, categorized as potential contraindications and potential complicating factors. Individual trials used different subsets of these exclusion criteria. Column 3 in Table 3 lists the percentage of patients in the Ontario cohort with any of these exclusion criteria. Detailed data on eligibility for two trials is provided in columns 4 and 5. These two trials were chosen to illustrate the full range of ineligibility, from 51.0% for the Greenberg trial⁸ to 78.1% for the first published donepezil trial by Rogers et al.⁹ Column 6 indicates that 31.9% of donepezil recipients had potential contraindications to donepezil use, based on the Warnings section of the CPS.²⁶ The percentage of subjects in the Ontario cohort who would have been ineligible for the RCTs differed from trial to trial (Fig.1).

TABLE 1 Randomized controlled trials of donepezil: study design characteristics and study subject demographics

Study	Number of subjects	Study duration (weeks)*	Mean age (range) in years	Sex (% male)	Mean MMSE score (/ 30)
Rogers, Dementia 1996 ⁹	161 total (40 placebo) (121 donepezil)	12	71.4 (54-85)	16.0	18.6
Rogers, Arch Intern Med 1998 ¹⁰	468 total (153 placebo) (315 donepezil)	12	73.7 (50-94)	36.3	19.5
Rogers, Neurology 1998 ¹¹	473 total (162 placebo) (311 donepezil)	24	73.4 (51-94)	38.0	19.0
Burns, Dement Geriatr Cogn Disord 1999 ¹²	818 total (274 placebo) (544 donepezil)	24	71.7 (50-93)	42.3	20.0
Homma, Dement Geriatr Cogn Disord 2000 ¹³	228 total (112 placebo) (116 donepezil)	24	69.8 (48-90)	33	17.2
Greenberg, Arch Neurol 2000 ⁸	60 total†	6	75.0 (N/A)	50	21.8
Winblad, Neurology 2001 ¹⁴	286 total (144 placebo) (142 donepezil)	52	72.5 (49-88)	35.7	19.3
Mohs, Neurology 2001 ¹⁵	431 total (217 placebo) (214 donepezil)	54	75.3 (49-94)	37.2	17.1
Feldman, Neurology 2001 ¹⁶	290 total (146 placebo) (144 donepezil)	24	73.7 (48-92)	39	11.9

Tariot, J Am Geriatr Soc 2001 ¹⁷	208 total (105 placebo) (103 donepezil)	24	85.7 (64-102)	18	14.4
Totals	3, 423 total 2, 070 on active drug treatment	Range 6-54 weeks	73.7‡	36.2‡	18.1‡

Note: N/A = not available.

*Study duration excludes placebo washout period.

†Crossover trial – all subjects received donepezil for 6 weeks, then placebo for 6 weeks (or vice versa).

‡Mean weighted by study sample size

TABLE 2 Demographic features of randomized controlled trial subjects and the Ontario cohort

Randomized trials (n = 3,423)		Ontario Cohort (n = 6,424)	P value*
Mean age (years)	73.7	80.3	<0.001
Sex (% male)	36.2	35.7	0.4
N (%) in long-term care	244† (7.1)	904 (14.1)	<0.001

*Two-sample t test (equal variances assumed) or chi-square (χ^2) test.

†36 subjects from the Feldman trial¹⁶ and all 208 subjects from the Tariot trial¹⁷ were recruited from long-term care facilities

TABLE 3 Exclusion criteria listed in randomized controlled trials of donepezil, the warnings listed in the CPS, and their prevalence in the Ontario cohort

Exclusion criterion or CPS warning*	Number of trials with this exclusion (of 10)	Percentage of Ontario cohort with this exclusion	Exclusion in Greenberg 2000 trial⁶ (fewest exclusions)	Exclusion in Rogers 1996 trial⁷ (most exclusions)	Exclusion as a CPS warning
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A. POTENTIAL CONTRAINDICATIONS

Asthma or COPD	10	21.2	Yes	Yes	Yes
Active GI bleeding	10	0.6	Yes	Yes	Yes
Active Cardiovascular Disease (a-d)		(3.3% total)			
(a) Congestive heart failure	9	1.4	-	Yes	Yes
(b) Acute myocardial infarction	9	1.0	-	Yes	Yes
(c) Bradycardia	10	0.2	Yes	Yes	Yes
(d) Syncope	9	0.8	-	Yes	Yes
Parkinsonism†	9	7.3	-	Yes	Yes
Seizures†	9	4.0	-	Yes	Yes

B. POTENTIAL COMPLICATING FACTORS

Hearing impairment	10	17.1	Yes	Yes	-
Visual impairment	10	2.9	Yes	Yes	-
Stroke	10	18.3	Yes	Yes	-

Diabetes mellitus	1	19.7	-	Yes	-
Insulin use	4	3.0	-	-	-
Schizophrenia/major psychosis	10	9.8	Yes	Yes	-
Neuroleptic drug use	7	17.3	-	Yes	-
Alcohol or drug dependence	6	4.5	-	Yes	-
Any antidepressant use	6	28.5	-	Yes	-
TCA use	3	5.1	-	-	-
Benzodiazepine use	5	22.0	-	Yes	-
NSAID Use	1	19.4	-	-	-
Any hospitalization in the previous 3 months	1	15.3	-	-	-

Subtotal A (% excluded for any potential contraindication)	-	-	21.7	31.9	31.9
Subtotal B (% excluded for any potential complicating factor)	-	-	39.3	71.7%	-
Total % Excluded	-	-	51.0	78.1	31.9

Note: CPS = Compendium of Pharmaceuticals and Specialties, COPD = chronic obstructive pulmonary disease, GI = gastrointestinal, TCA = tricyclic antidepressant, NSAID = non-steroidal anti-inflammatory drug, - = not applicable to this trial or to the CPS list of Warnings.

*See the Appendix for definitions of exclusion criteria.

†Parkinsonism or seizures: subject was considered to have this condition if either a diagnosis or drug use was coded in the appropriate administrative database (CIHI, OHIP or ODB)

Among the RCTs published after the Greenberg trial, the percentages ineligible were: 59.8% for the Winblad trial,¹⁴ 63.9% for the Mohs trial¹⁵ 66.6% for the Feldman trial,¹⁶ and 66.4% for the Tariot trial.¹⁷

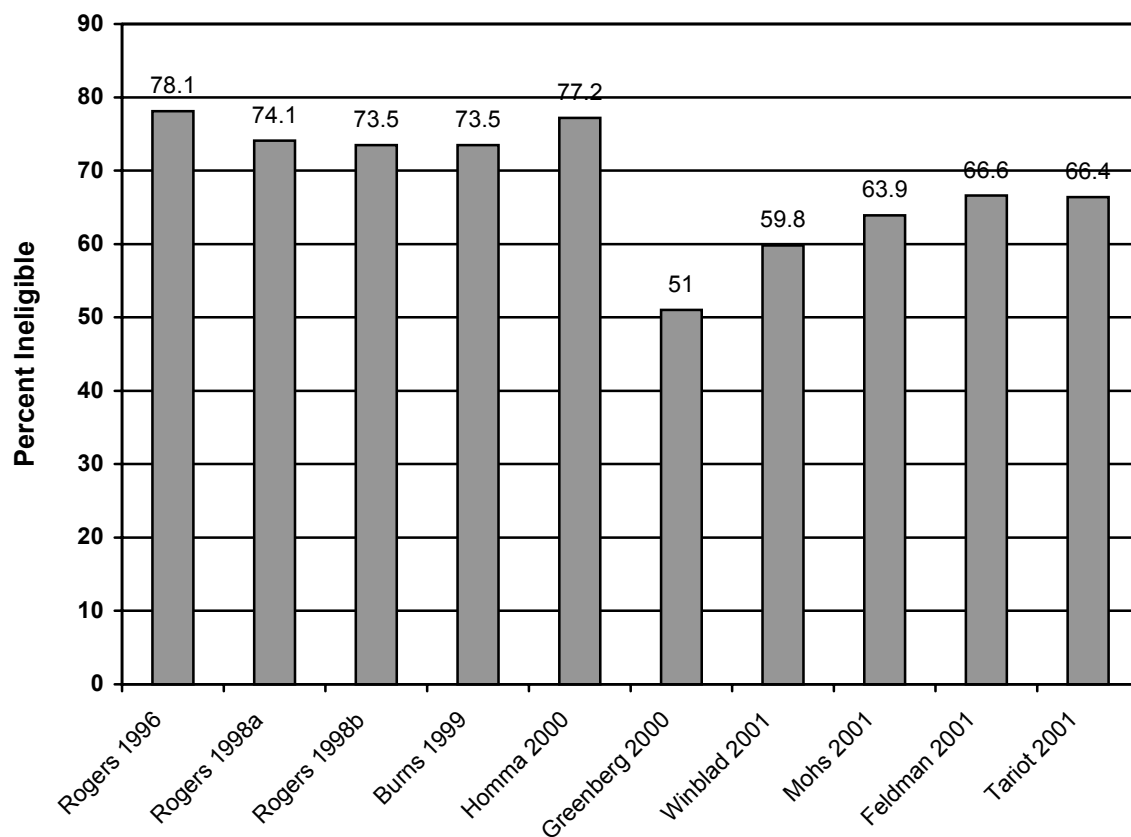
Overall, 27.8% of the Ontario cohort discontinued treatment with donepezil within seven months of their initial prescription (September 2001-March 2002). Table 4 lists the discontinuation rates for subjects in the Ontario cohort with and without potential contraindications to donepezil as defined using the Warnings listed in the CPS. The discontinuation rate was always higher among those with potential contraindications, but did not reach statistical significance for those with

active gastrointestinal bleeding or a history of seizures. Discontinuation rates were significantly higher for those subjects with a history of obstructive lung disease ($p = 0.002$), active cardiovascular disease ($p = 0.001$), or Parkinsonism ($p = 0.009$).

DISCUSSION

Fewer than half of the patients receiving donepezil in Ontario would have qualified for the RCTs that established this drug's efficacy. Despite the publication of studies that emphasized the importance of adequate representation in trials of cholinesterase inhibitors,^{7, 8} ineligibility rates for even the most recently published donepezil RCTs were still over 50% (Fig. 1).

Fig. 1 Percentage of Ontario cohort ineligible for entry into randomized controlled trials of donepezil, based on exclusion criteria in individual trials.



These ineligibility rates have important implications. Selection of clinical trial participants who are younger and fitter may lead to overestimates of effectiveness and/or underestimates of adverse drug event rates that are eventually observed in clinical practice.³ Patients with potential contraindications to donepezil were excluded from the trials. We have shown that patients with these contraindications are more likely to discontinue donepezil than patients actually represented by RCT subjects (Table 4). The higher discontinuation rates in patients with contraindications may reflect more adverse drug

events in this group as compared to RCT subjects.

Although it is possible that differences in discontinuation rates reflect a higher risk of disease progression or death among patients with contraindications, this is unlikely given the short period of follow-up (seven months). Our findings therefore suggest that the presence of common comorbid diseases (e.g., obstructive lung disease, active cardiovascular disease, Parkinsonism) may influence drug tolerability. We found that nearly one-third of the Ontario cohort was dispensed donepezil despite having one or more of these conditions (Table 2, column 6).

TABLE 4 Donepezil discontinuation rates for subjects in the Ontario cohort with and without potential contraindications to donepezil use.

Potential contraindication	Number (%) of total Ontario cohort with this potential contraindication	Discontinuation rate among those with potential contraindication (%)	Discontinuation rate among those without potential contraindication (%)	P value*
Asthma or COPD	1359 (21.2)	31.1	26.9	0.002
Active GI bleeding	40 (0.6)	35.0	27.7	0.3
Active cardiovascular disease	214 (3.3)	37.9	27.4	0.001
Parkinsonism	468 (7.3)	33.1	27.4	0.009
Seizures	255 (4.0)	32.9	27.6	0.06

Note: COPD = chronic obstructive pulmonary disease, GI = gastrointestinal.

*Fisher's exact test

We have also identified important demographic differences. The Ontario cohort was significantly older than the RCT group, with a difference in mean age of greater than six years. As AD is predominantly a disease of the elderly,⁴ older age groups should be represented in RCTs evaluating medications for this condition.

We found that a larger proportion of the Ontario cohort resided in the long-term care setting (14.1% vs. 7.1% for RCTs). Some authors have raised concerns about the use of cholinesterase inhibitors in the vulnerable nursing home population.^{28, 29} The widespread use of

donepezil among patients who were not represented in RCTs is due in part to the absence of effective alternative treatments for AD. RCTs evaluating cholinesterase inhibitors have generally been well designed and conducted; a recent meta-analysis found most trials had good methodological quality as rated using the Jadad scale.⁶ The clinical importance of the RCTs' findings, however, has been subject to debate.²⁸⁻³² A significant component of this debate centres on representation and generalizability. Why is it that RCTs of new drug therapies are often not representative of their eventual target population?

The first aim of clinical trials is to ensure internal validity, and this is often achieved at the expense of external validity (i.e., generalizability).³³

It may be reasonable for early RCTs evaluating a drug to have extensive exclusion criteria in order to ensure the safety of participants. Once these early trials have established efficacy, however, further RCTs must begin to address the practical question of the drug's effectiveness in the target clinical population. If they do not, we lose confidence in our ability to generalize efficacy and safety data from trials to our patients who would not have qualified for trial entry. The impact of our findings can be illustrated by examining the trial by Tariot and colleagues.¹⁷ Subjects enrolled in this study were long-term care residents with a mean age of 85.7 years. In this frail older population, investigators found no significant benefit with donepezil relative to placebo in slowing cognitive decline (measured using the MMSE). Earlier studies with younger outpatients have documented benefits using the MMSE. Furthermore, weight loss was significantly more common among subjects assigned donepezil as compared to those on placebo in the Tariot trial.^{17,28}

Potential limitations of our study should be noted. First, we could not make direct comparisons of co-morbidity, as most RCTs do not publish detailed co-morbidity data. Nonetheless, the differences in age distribution and long-term care status would suggest that the Ontario cohort carried a higher burden of co-morbid disease than subjects enrolled in the RCTs. A second potential limitation was the fact that we had limited clinical information about the Ontario cohort because we used administrative data. Third, we could not directly determine reasons for drug discontinuation; although we suspect discontinuation rates primarily reflect drug tolerability, it is possible that other factors might explain differences in these rates. Finally, recent evidence suggests some of the exclusion criteria in the donepezil RCTs we examined may not preclude the use of cholinesterase inhibitors (e.g., co-morbid cerebrovascular disease).^{34, 35}

In summary, future clinical trials evaluating dementia therapies should attempt to adequately represent the frail older adults who carry the burden of this disease. Until such trials are available, clinicians should carefully weigh the potential risks and benefits of such drug therapies for their most vulnerable older patients with dementia.

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Contributors

Drs. Gill, Bronskill, Mamdani, Li, Anderson, and Rochon, Ms. Sykora and Mr. Hillmer conceived and designed the study and contributed substantially to the acquisition, analysis and interpretation of data. Drs. Shulman and Wodchis contributed substantially to the analysis and interpretation of data. All authors critically revised the manuscript for important intellectual content and gave approval of the final manuscript. Dr. Gill is guarantor of the study.

Conflict of Interest

None of the authors have a conflict of interest to declare in connection with this manuscript.

APPENDIX A Databases and codes used to define exclusion criteria ICD-9 categories (from CIHI), OHIP diagnosis codes, and drug dispensation recorded in the ODB were used to identify the presence of the exclusion criteria from the randomized controlled trials. Consistency between individual randomized trials in applying these codes were used for exclusion criteria. The presence of all exclusions listed in the trials for the Ontario cohort (e.g., ability to ambulate independently, presence of a caregiver) could not be identified. Thus, the estimates of eligibility may overestimate eligibility for enrolment in the randomized trials.

Exclusion Criterion	Administrative Data Code(s) and Time Frame*
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A. Potential Contraindications

Asthma	ICD 493.0, 493.1, 493.2, 493.9 or OHIP 493 within 5 years
Chronic obstructive pulmonary disease	ICD 491.2, 491.20, 491.21, 492.0-492.8, 496 or OHIP 491, 492, 496 within 5 years
Upper gastrointestinal hemorrhage	Most responsible diagnosis of ICD 531, 532, 534, 578.0, 578.1, or 578.9 within 3 months
Congestive heart failure	Most responsible diagnosis of ICD 428 within 3 months
Acute myocardial infarct	Most responsible diagnosis of ICD 410 within 3 months
Bradycardia	Most responsible diagnosis of ICD 426 within 3 months
Syncope	Most responsible diagnosis of ICD 780.2 within 3 months
Parkinsonism	Defined using either disease codes (ICD 332 or OHIP 332 within 5 years) or drug use (anti-Parkinsonian drug dispensed in last 120 days)
Seizures	Defined using either disease codes (ICD 345 or OHIP 345 within 5 years) or drug use (anticonvulsant drug dispensed in last 120 days)

B. Potential Complicating Factors

Hearing impairment	ICD 389 or OHIP 389 within 5 years
Visual impairment	ICD 369 or OHIP 369 within 5 years
Stroke	ICD 431, 434, 436 or OHIP 432, 436 within 5 years
Diabetes mellitus	Identified using the Ontario Diabetes Database algorithm, including both incident and prevalent cases of diabetes within 5 years
Insulin	Any use listed in ODB in last 120 days
Schizophrenia or other major psychosis	ICD 295 to 299 or OHIP 295 within 5 years
Neuroleptics	Any use listed in ODB in last 120 days
Alcohol abuse	ICD 291.4, 291.9, 303.0, 303.9, 305.0, V11.3 or OHIP 291, 303 within 5 years
Drug dependence	ICD 304 or OHIP 304 within 5 years
Antidepressants	Any use listed in ODB in last 120 days
Tricyclic antidepressants (TCAs)	Any use listed in ODB in last 120 days
Benzodiazepines	Any use listed in ODB in last 120 days
Non-steroidal anti-inflammatory drugs (NSAIDs)	Any use listed in ODB in last 120 days
Any hospitalization	Any CIHI discharge abstract in last 3 months (time frame as given in Tariot trial ¹⁷)

Note: ICD = International Classification of Diseases, Ninth Revision (CIHI database code), ODB = Ontario Drug Benefit database, OHIP = Ontario Health Insurance Plan, CIHI = Canadian Institute for Health Information Discharge Abstract Database.

*Time frames given as periods preceding the index donepezil claim in the ODB database

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