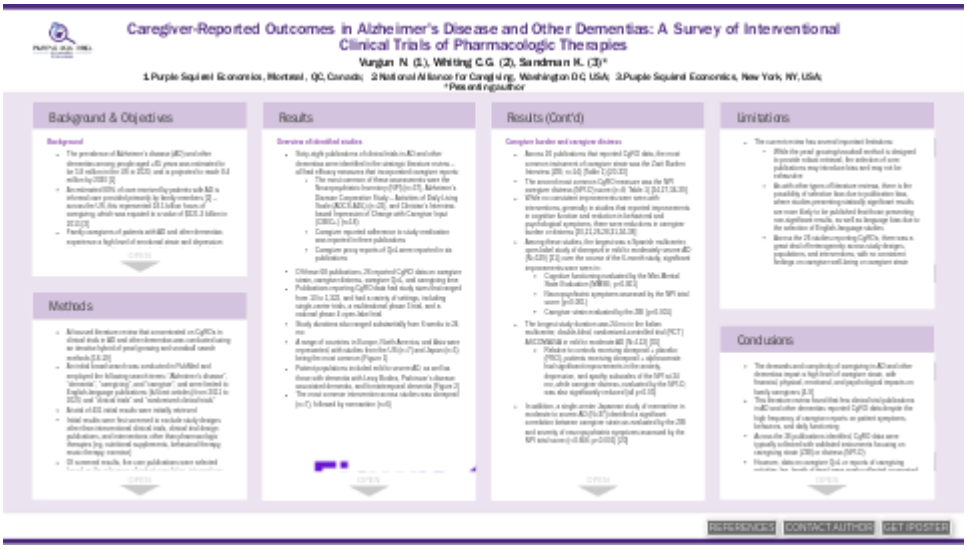
Caregiver-Reported Outcomes in Alzheimer's Disease and Other Dementias: A Survey of Interventional Clinical Trials of Pharmacologic Therapies



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PRESENTED AT:

BACKGROUND & OBJECTIVES

Background

- The prevalence of Alzheimer's disease (AD) and other dementias among people aged ≥65 years was estimated to be 5.8 million in the US in 2020, and is projected to reach 8.4 million by 2030 [1]
- An estimated 80% of care received by patients with AD is informal care provided primarily by family members [2] – across the US, this represented 18.1 billion hours of caregiving, which was equated to a value of $221.3 billion in 2015 [3]
- Family caregivers of patients with AD and other dementias experience a high level of emotional strain and depression that increases with greater levels of dependency for daily living activities and severity of behavioral problems and delirium [4-6]
- In order to accommodate caregiving activities, family caregivers experience disruptions in employment which augments financial strains associated with covering out-of-pocket medical expenses and daily living needs of patients [7-9]
- In clinical trials of AD and other dementias, family caregivers typically provide proxy reports on the patient's health status, daily functioning, or quality of life (QoL) using validated instruments such as Neuropsychiatric Inventory (NPI) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input Scale (CIBIC+) [10-13]
- Family caregivers can also provide distinct information on their own well-being and on caregiving strain via caregiver-reported outcomes (CgROs) [14-17]

Rationale & Objective

- The objective of this targeted review was to examine how CgROs were captured and reported in clinical trials of pharmacologic therapies in AD and other dementias in the past decade

METHODS

- A focused literature review that concentrated on CgROs in clinical trials in AD and other dementias was conducted using an iterative hybrid of pearl growing and snowball search methods [18-19]
- An initial broad search was conducted in PubMed and employed the following search terms: “Alzheimer’s disease”, “dementia”, “caregiving”, and ”caregiver”, and were limited to English-language publications (full-text articles) from 2011 to 2020, and “clinical trials” and “randomized clinical trials”
- A total of 431 initial results were initially retrieved
- Initial results were first screened to exclude study designs other than interventional clinical trials, clinical trial design publications, and interventions other than pharmacologic therapies (eg, nutritional supplements, behavioral therapy, music therapy, exercise)
- Of screened results, five core publications were selected based on the relevance of patient population, interventions, and outcomes to the research topic
- The core publications were then used for prospective searches (eg, cited by) and retrospective searches, as well as the identification of new search terms

RESULTS

Overview of identified studies

- Sixty-eight publications of clinical trials in AD and other dementias were identified in the strategic literature review – all had efficacy measures that incorporated caregiver reports:
  - The most common of these assessments were the Neuropsychiatric Inventory (NPI) (n=37), Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) (n=22), and Clinician's Interview-based Impression of Change with Caregiver Input (CIBIC+) (n=18)
  - Caregiver reported adherence to study medication was reported in three publications
  - Caregiver proxy reports of QoL were reported in six publications
- Of these 68 publications, 26 reported CgRO data on caregiver strain, caregiver distress, caregiver QoL, and caregiving time
- Publications reporting CgRO data had study sizes that ranged from 10 to 1,322, and had a variety of settings, including single-center trials, a multinational phase 3 trial, and a national phase 4 open-label trial
- Study durations also ranged substantially from 6 weeks to 24 mo
- A range of countries in Europe, North America, and Asia were represented, with studies from the US (n=7) and Japan (n=5) being the most common (Figure 1)
- Patient populations included mild to severe AD, as well as those with dementia with Lewy Bodies, Parkinson's disease associated dementia, and frontotemporal dementia (Figure 2)
- The most common intervention across studies was donepezil (n=7), followed by memantine (n=6)

Figure 1: Geographic representation of studies reporting CgRO data

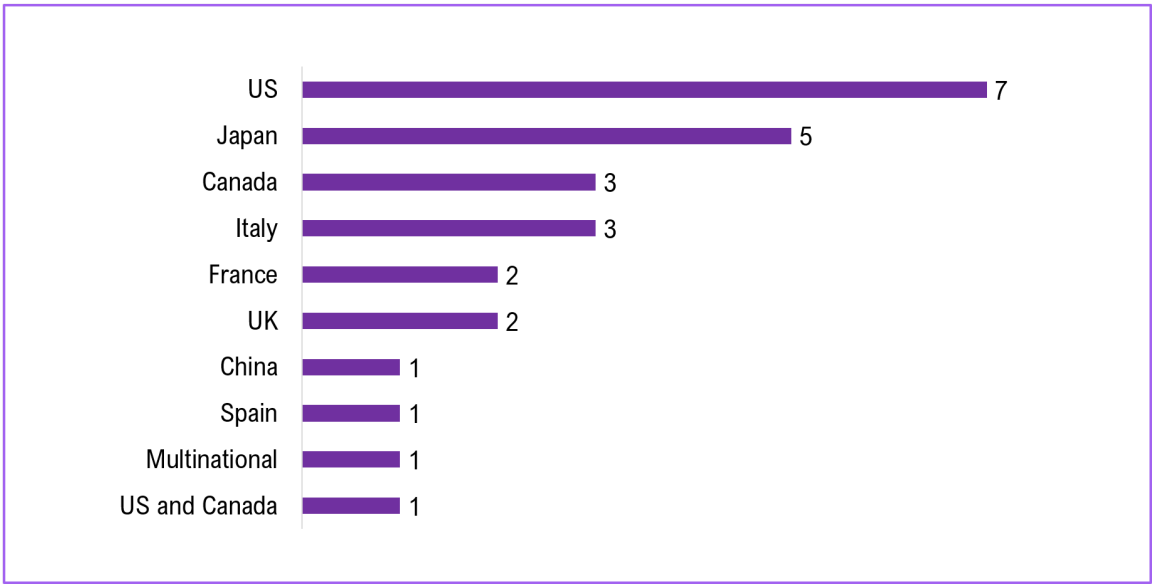
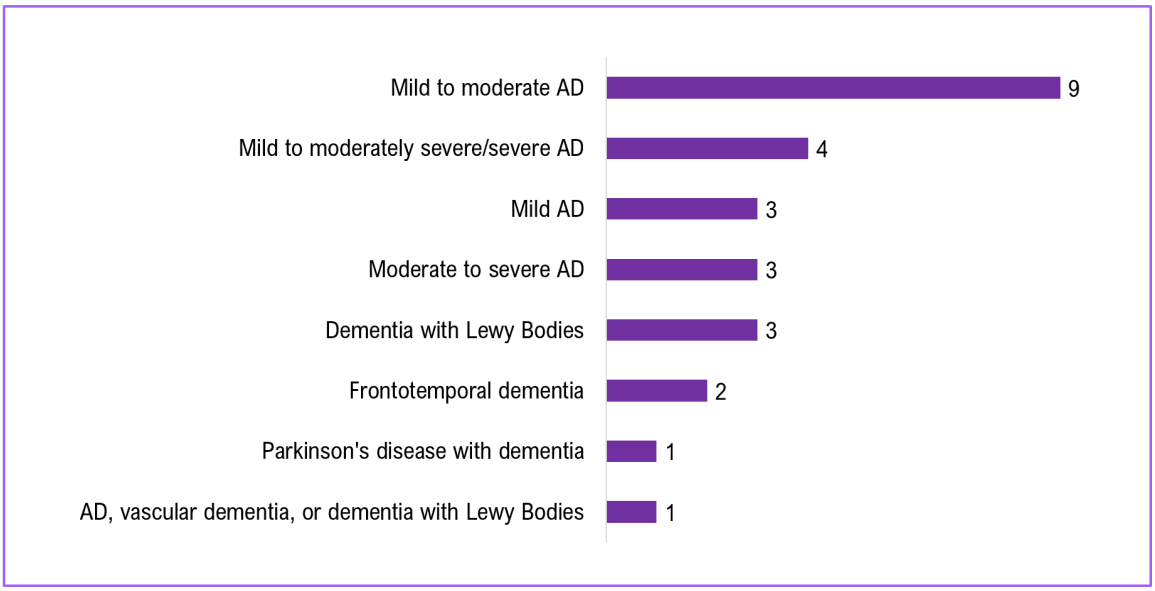


Figure 2: Patient population in studies reporting CgRO data



RESULTS (CONT'D)

Caregiver burden and caregiver distress

- Across 26 publications that reported CgRO data, the most common instrument of caregiver strain was the Zarit Burden Interview (ZBI; n=14) (Table 1) [20-33]
- The second most common CgRO measure was the NPI caregiver distress (NPI-D) score (n=8; Table 1) [24,27,34-39]
- While no consistent improvements were seen with interventions, generally in studies that reported improvements in cognitive function and reduction in behavioral and psychological symptoms, there were reductions in caregiver burden or distress [20,21,26-28,31,34-38]
- Among these studies, the largest was a Spanish multicenter, open-label study of donepezil in mild to moderately severe AD (N=529) [21]; over the course of the 6-month study, significant improvements were seen in:
  - Cognitive functioning evaluated by the Mini-Mental State Evaluation (MMSE; $p<0.001$)
  - Neuropsychiatric symptoms assessed by the NPI total score ($p<0.001$)
  - Caregiver strain evaluated by the ZBI ($p<0.001$)
- The longest study duration was 24 mo in the Italian multicenter, double-blind, randomized-controlled trial (RCT) ASCOMALVA in mild to moderate AD (N=113) [35]
  - Relative to controls receiving donepezil + placebo (PBO), patients receiving donepezil + alphoscerate had significant improvements in the anxiety, depression, and apathy subscales of the NPI at 24 mo, while caregiver distress, evaluated by the NPI-D, was also significantly reduced (all $p<0.05$)
- In addition, a single-center Japanese study of memantine in moderate to severe AD (N=37) identified a significant correlation between caregiver strain as evaluated by the ZBI and severity of neuropsychiatric symptoms assessed by the NPI total score ($r=0.666$; $p<0.001$) [20]

Table 1: Studies reporting ZBI or NPI-D outcomes

Study reference	Country	Study population	Study design and duration	Intervention(s)	ZBI outcomes*	NPI-D outcomes*
Nakayama 2017	Japan	Mild AD (N=50)	SC, prospective, 12 wk	Galantamine	No significant change in strain ($p>0.05$)	–
Padala 2018	US	Mild AD (N=60)	SC, DB, RCT, PBO-controlled, prospective, 12 wk	Methylphenidate vs PBO	Significant reduction in strain ($p=0.011$)	–
Amenta 2012 **Rea 2015** **Carotenuto 2017**	Italy	Mild to moderate AD (N=113)	MC, RCT, PBO-controlled, DB, 24 mo	Donepezil + alphoscerate vs donepezil + PBO	–	Significant reduction in distress ($p<0.05$)
Carrasco 2011	Spain	Mild to moderate AD (N=529)	MC, open-label, noncomparative, prospective, 6 mo	Donepezil	Significant reduction in strain ($p<0.0001$)	–
Frakey 2012	US	Mild to moderate AD (N=23)	SC, RCT, DB, PBO-controlled, 8 wk	Modafinil vs PBO	Reduction in strain did not reach statistical significance	–
Henderson 2015	US	Mild to moderate AD (N=42)	Two centers, RCT, DB, PBO-controlled, 12 mo	Raloxifene vs PBO	No significant difference in strain	No significant difference in distress
Vellas 2011	France	Mild to moderate AD (N=159)	MC, RCT, DB, PBO-controlled, parallel group, phase 2A, 3 mo	Etazolate hydrochloride vs PBO	No significant difference in strain ($p=0.61$)	–
Flynn Longmire 2014**	US	Caregivers of patients with mild to moderate AD (N=131)	MC, RCT, DB, PBO-controlled, 24 wk	Sertraline + psychosocial treatment vs PBO + psychosocial treatment	No difference in strain ($p=0.71$)	–
Porsteinsson 2014	US and Canada	Mild to moderately severe AD (N=186)	MC, RCT, PBO-controlled, DB, 9 wk	Citalopram vs PBO	–	Significant reduction in distress ($p=0.018$)
Trzepacz 2013	US	Mild to severe AD (N=132)	MC, RCT, DB, PBO-controlled, phase 2, 12 wk	Mibampator vs PBO	–	No significant difference in distress ($p=0.716$)
Mohamed 2012**	US	Caregivers of patients with mild to severe AD (N=361)	MC, RCT (CATIE-AD), 9 mo	Olanzapine, quetiapine, risperidone, or PBO	Significant reduction in strain ($p=0.009$)	Significant reduction in distress ($p=0.0209$)
Araki 2014	Japan	Moderate to severe AD (N=37)	SC, RCT, 24 wk	Memantine + donepezil vs donepezil	Significant reduction in strain ($p<0.001$)	–
Hermann 2019	Canada	Moderate to severe AD (N=39)	MC, RCT, DB, crossover, 6 wk	Nabilone vs PBO	–	Significant reduction in distress ($p=0.041$)
Ikeda 2013	Japan	Dementia with Lewy Bodies (N=108)	Open-label extension, 52 wk	Donepezil	Similar strain at baseline and week 52	–
Murata 2018	Japan	Dementia with Lewy Bodies (N=158)	MC, phase 2, PBO-controlled, RCT, DB, 12 wk	Zonisamide vs PBO	No significant change in strain	–
Mori 2012	Japan	Dementia with Lewy Bodies (N=140)	MC, RCT, PBO-controlled, 12 wk	Donepezil vs PBO	Significant reduction in strain ($p=0.004$)	–
Verceletto 2011	France	Frontotemporal dementia (N=52)	MC, RCT, DB, PBO-controlled, phase 2, 52 wk	Memantine vs PBO	No significant difference in strain ($p=0.43$)	–
Leroi 2014	UK	Parkinson's disease with dementia (N=25)	DB, PBO-controlled, RCT, parallel group, fixed dose, 16 wk	Memantine vs PBO	Significant reduction in strain ($p<0.04$)	–

AD: Alzheimer's disease; DB: double-blind; mo: month; MC: multicenter; NPI-D: Neuropsychiatric Inventory caregiver distress; SC: single-center; UK: United Kingdom; US: United States; wk: week; ZBI: Zarit Burden Interview

**Results with treatment are presented relative to the control arm in RCTs or relative to baseline in single-arm studies*

***These publications were secondary analyses that specifically examined CgRO data captured in clinical trials*

Caregiving activities and time commitments

- Two publications reported the impact of interventions on time taken to perform caregiving activities:
  - In the TEAM-AD VA cooperative RCT (N=613; mild to moderate AD), median time to perform six types of activities (communicating with care recipient, using transportation, eating, dressing, looking after recipient's appearance, and supervising) ranged from 2.7 to 3.2 hours per day across treatment groups at baseline [40]
    - No statistically significant differences in caregiving time were seen between treatment arms (vitamin E, memantine, or vitamin E + memantine) vs PBO over the mean follow-up of 2.27 years
    - Over the duration of the study, the mean annual rate of increased caregiving time ranged from +1.48 hours to +2.26 hours per day across treatments
  - In the second study, which was a single center, double-blind, PBO-controlled cross-over RCT (N=10; AD, vascular dementia, or frontotemporal dementia), incobotulinumtoxin A treatment for paratonic rigidity was not found to significantly impact time needed for cleaning and dressing [41]

Caregiver depression

- Two publications reported the impact of interventions on caregiver depression:
  - In an analysis of the DIADS-2 study (N=131 caregivers), patient treatment with sertraline over 24 weeks was not associated with significant reduction in caregiver depression as evaluated by the Beck Depression Inventory (BDI) (p=0.02 favoring PBO) – caregiver distress or strain were also not reduced with treatment [22]
  - In an analysis of the CATIE-AD study (N=361), treatment of patients with atypical antipsychotics (olanzapine, risperidone, quetiapine) over 9 mo was not associated with reduction in caregiver depression (BDI; p=0.5185), despite significant reductions in caregiver strain (ZBI; p=0.0090) and distress (NPI-D; p=0.0209) relative to PBO [27]

Caregiver QoL

- Only one publication reported the impact of intervention on caregiver QoL:
  - In the analysis of the DIADS-2 study, there was no significant impact on the QoL of caregivers as evaluated by the Short Form-12 (SF-12 physical component score: p=0.64; SF-12 mental component score: p=0.70) [22]

LIMITATIONS

- The current review has several important limitations:
  - While the pearl growing/snowball method is designed to provide robust retrieval, the selection of core publications may introduce bias and may not be exhaustive
  - As with other types of literature reviews, there is the possibility of selection bias due to publication bias, where studies presenting statically significant results are more likely to be published that those presenting non-significant results, as well as language bias due to the selection of English-language studies
  - Across the 26 studies reporting CgROs, there was a great deal of heterogeneity across study designs, populations, and interventions, with no consistent findings on caregiver well-being or caregiver strain

CONCLUSIONS

- The demands and complexity of caregiving in AD and other dementias impart a high level of caregiver strain, with financial, physical, emotional, and psychological impacts on family caregivers [4-9]
- This literature review found that few clinical trial publications in AD and other dementias reported CgRO data despite the high frequency of caregiver reports on patient symptoms, behaviors, and daily functioning
- Across the 26 publications identified, CgRO data were typically collected with validated instruments focusing on caregiving strain (ZBI) or distress (NPI-D)
- However, data on caregiver QoL or reports of caregiving activities (eg, length of time) were rarely collected or reported
- Across studies, CgRO data generally complemented efficacy outcomes, whereby treatments that led to improvements in cognitive, behavioral and psychiatric symptoms also reduced caregiver burden or distress
- Collectively, findings of the review suggest that there is an opportunity to recognize and promote collection of CgRO data in clinical trials as a distinct form of information that can contribute to a more holistic understanding of the impact and value of new therapies in AD and other dementias

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