Received: 28 June 2019 | Revised: 31 December 2019 | Accepted: 3 January 2020

DOI: 10.1002/alz.12058

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Initiation of symptomatic medication in Alzheimer's disease clinical trials: Hypothetical versus treatment policy approach

Michael C. Donohue[1] | Fabian Model[2] | Paul Delmar[2] | Nicola Volye[2] | Hong Liu-Seifert[3] | Michael S. Rafii[1] | Paul S. Aisen[1] for the Alzheimer's Disease Neuroimaging Initiative

[1]Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, California

[2]F. Hoffmann - La Roche Ltd, Basel, Switzerland

[3]Eli Lilly, Indianapolis, Indiana

Correspondence
Michael C. Donohue, University of Southern California, San Diego, CA USA.
Email: mdonohue@usc.edu; mcdonohue@gmail.com

This work was supported by National Institute on Aging grant R01-AG049750.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

In clinical trials in populations with mild cognitive impairment, it is common for participants to initiate concurrent symptomatic medications for Alzheimer's disease after randomization to the experimental therapy. One strategy for addressing this occurrence is to exclude any observations that occur after the concurrent medication is initiated. The rationale for this approach is that these observations might reflect a symptomatic benefit of the concurrent medication that would adversely bias efficacy estimates for an effective experimental therapy. We interrogate the assumptions underlying such an approach by estimating the effect of newly prescribed concurrent medications in an observational study, the Alzheimer's Disease Neuroimaging Initiative.

KEYWORDS

Alzheimer's, clinical trials, concurrent medication, intercurrent events, symptomatic medication

The draft *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*[1] published recently by the U.S. Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) has sparked much debate among Alzheimer's disease (AD) clinical trialists on the appropriate handling of intercurrent events, such as initiation of concurrent medications (see Table 1 for the definitions of key terms *estimand* and *intercurrent event*). This is a common event in clinical trials in populations with mild cognitive impairment (MCI) in which many subjects are naïve to approved symptomatic AD drugs at randomization. Many patients will typically start concomitant symptomatic treatment after randomization. For example, in a recently reported Phase 3 study of 799 prodromal AD patients, 46 (5.8%) of the patients had initiated an acetylcholinesterase inhibitor (AChEI) or memantine treatment at the time of futility analysis.[2] If the study had completed 2-year follow-up as planned, we would expect up to 10% of placebo patients to have initiated symptomatic treatment during the trial. Symptomatic drugs used in clinical practice include donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), and memantine (Namenda).

The currently approved symptomatic drugs have demonstrated modest clinical efficacy in moderate-to-severe stages of AD dementia.[3] Prior studies in populations with mild-to-moderate or severe dementia have demonstrated that participants on the combination of AChEIs and memantine experience less decline on cognitive and functional measures than those on either AChEIs alone or neither medication.[4,5] In a randomized trial of donepezil over 24 weeks in N = 262 participants with MCI, a mean benefit compared to placebo of about 1.4 points

($p < .05$) on the Alzheimer's Disease Assessment Scale–13-item cognitive subscale (ADAS-Cog 13) was observed.[6] However, in a larger 3-year trial of donepezil, no effects on ADAS-Cog 11, ADAS-Cog 13, or Clinical Dementia Rating Sum of Boxes (CDR-SB) persisted beyond 18 months.[7] Given the potential short-term cognitive benefits, it remains unclear whether allowing the use of AChEIs, memantine, or combined therapy in randomized clinical trials can affect the assessment of efficacy of novel therapeutic agents.

The ICH E9 (R1) addendum discusses the handling of intercurrent events in the context of the construction of estimands, or targets of estimation. For example, under the "treatment policy strategy," we would attempt to collect and analyze data until the end of the planned observation period, irrespective of intercurrent events. But under a "hypothetical strategy," we might exclude data collected after the event to attempt to estimate what the effect might have been in absence of the intercurrent event.

One important intercurrent event in clinical trials in MCI populations is the initiation of symptomatic drugs. Historically, patients were often asked to discontinue from the study if they started a symptomatic treatment, excluding all post-intercurrent event observations and yielding a hypothetical estimand. The alternative treatment policy approach would include data after initiation of symptomatic drugs. One might be concerned that more subjects randomized to placebo might initiate symptomatic drugs compared to those randomized to an effective experimental therapy. And with the benefit of symptomatic drugs, the placebo group might appear closer to the active group, and power to detect the effect of the experimental drug will be reduced compared to a hypothetical strategy. For this reason, the EMA *Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease*[8] concedes that an appropriate target of estimation with regard to new or modified concomitant medication could be based on a hypothetical strategy, despite generally recommending a "treatment-policy" strategy for other intercurrent events.

We demonstrate, using data from an observational study, the Alzheimer's Disease Neuroimaging Initiative (ADNI),[9] that this concern might be unwarranted. Although symptomatic drugs have demonstrated their modest benefits in randomized trials,[7,10] it is unclear how this benefit compares to the decline that precipitates their prescription in the course of typical clinical care. Schneider et al.[11] observed that use of cholinesterase inhibitors and memantine was associated with greater *decline* in ADNI. Han et al.[12] similarly found that individuals in the National Alzheimer's Coordinating Center's Uniform Data Set with MCI due to AD and mild AD dementia appeared to decline faster with cholinesterase inhibitors. We further interrogate this observation using updated data from ADNI and consider implications in the context of a treatment policy estimand. We emphasize that these analyses cannot be used to make any conclusions about the effectiveness or efficacy of the symptomatic drugs under consideration, as ADNI is not a randomized trial. Rather we aim to interrogate the effect of two alternative analysis approaches (ignoring observations after initiating symptomatic drugs vs not) on the mean change over time in a group given the standard of care.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature on the effect of approved symptomatic Alzheimer's medications using traditional (eg, PubMed) sources.
2. Interpretation: Our findings suggest that following a treatment policy approach and allowing data after the initiation of symptomatic medications to be included in analysis, is not likely to harm the power of clinical trials of novel interventions.
3. Future directions: The approach taken in the study, whereby data are analyzed including, versus excluding, data after the initiation of symptomatic medications can be applied retrospectively to any clinical trial that included these observations in the study database.

1 | METHODS

1.1 | Data

We use natural history data from the prospective observational cohort study ADNI.[13] The inclusion and exclusion criteria, schedule of assessments, and other details can be found at adni.loni.usc.edu. Data for this analysis were downloaded from adni.loni.usc.edu on April 8, 2019. We include all ADNI participants who began ADNI diagnosed with MCI, including early MCI (EMCI). No other criteria were applied to include or exclude participants, and all follow-up observations as of April 8, 2019, were included. Examination dates ranged from October 2005 to April 2019. Symptomatic medications include any reported prescriptions of donepezil, galantamine, rivastigmine, memantine, or tacrine. For longitudinal outcome measures, we considered the ADAS-Cog 13[14,15] (including Delayed Word Recall and Number Cancellation), CDR-SB,[16] and MMSE.[17]

1.2 | Statistical methods

We summarize the baseline characteristics of ADNI MCI participants who never initiated, those who did initiate, and those who began the study already taking symptomatic therapy with means, standard deviations (SDs), counts, and percentages. The three groups are compared at baseline using Pearson's χ^2 test or Kruskal-Wallis test. Longitudinal data for participants who were prescribed symptomatic medication are summarized with spaghetti plots with Locally Estimated Scatter Plot Smoothing in which the horizontal axis is the time since initiation of symptomatic medication in years (ie, time of first reported use of a symptomatic drug is time zero).

We apply the Mixed Model of Repeated Measures (MMRM)[18] to change scores with baseline score, apolipoprotein E gene (*APOE*) $\varepsilon 4$ status (0 if no $\varepsilon 4$ alleles, 1 otherwise), and age as covariates. We fit

TABLE 1 Definitions of key clinical trial terminology

Terminology	Definition
Estimand	The true target of an estimate for a particular clinical trial objective. It is defined by the subject population, the outcome, the handling of intercurrent events, and the statistical summary measure of effect. Estimates are produced by statistical estimation procedures applied to data and might depend on a variety of assumptions if the estimand of interest is not directly observable, eg, due to imperfect adherence of subjects to the protocol.
Treatment-policy estimand	The *effectiveness* of an intervention regardless of events that occur after intervention is administered (eg, compliance to intervention regime or attrition). The *intention-to-treat principle* (analyzing all available data from all randomized subjects) is applied when the treatment-policy estimand is desired. If all subjects are followed until the end of the trial the treatment-policy estimand can be estimated without assumptions.
Intercurrent event	An event that occurs after randomization to an intervention, which might interfere with the estimation or interpretation of the effect of the intervention (eg, initiation of a rescue therapy).
Hypothetical estimand	An alternative to the treatment-policy estimand under a particular hypothetical scenario (eg, the *efficacy* of an intervention had an intercurrent event, such as initiation of rescue therapy, not occurred). Estimation of hypothetical estimands generally relies on untestable assumptions.

the models to two data sets: (1) including all available observations (consistent with a "treatment policy" approach), or (2) all observations except those occurring after the initiation of symptomatic medication (consistent with a "hypothetical approach"). Although the data analyzed under these two rules are largely overlapping, they provide a clear comparison of the two approaches and allow us to assess the effect that excluding post-symptomatic medication observations has on estimates of placebo group change. We apply an autoregressive order 1 correlation structure with heterogeneous variance with respect to study visit. We apply the MMRM to the first 36 months of follow-up, and separately the first 132 months of follow-up.

We also apply a linear mixed-effect model treating time as continuous. Fixed effects in this model include time (in years) since ADNI baseline, age at baseline, *APOE* $\varepsilon 4$ status, an indicator for initiation of symptomatic medications at any time during follow-up (0 if never on symptomatic medications, 1 otherwise), years on symptomatic medication (0 until initiation of symptomatic medication), the interaction between time and *APOE* $\varepsilon 4$, the interaction between time and the indicator for symptomatic medication use, and the interaction between *APOE* $\varepsilon 4$ and years on symptomatic medication. Random effects included subject-specific random intercepts and slopes. We repeat all of the above analyses on the subgroup of participants who are deemed amyloid beta (Aβ) positive ("Aβ+") at baseline using florbetapir positron emission tomography (PET) cutoff of 1.10 standard uptake value ratio (SUVR) units, and a Roche Elecsys cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$ cutoff of 1065 pg/mL. Analyses were conducted using R version 3.5.2.[19]

2 | RESULTS

Table 2 shows the descriptive summaries of the ADNI population grouped according to when they were prescribed symptomatic medications: prior to ADNI baseline, during the course of ADNI follow-up, or never. The groups were different at the time of the participants' first ADNI visit in many respects. The group that initiated symptomatic medications prior to, or during, the course of ADNI were more advanced in terms of the diagnosis of late MCI (LMCI) versus EMCI, cognitive assessments, and hippocampal volume. Patients who received symptomatic medications exhibited a greater degree of amyloid pathology; and a greater rate of *APOE* $\varepsilon 4$ carriage. Those who never initiated symptomatic medications were younger.

Figure 1 shows spaghetti plots of ADAS-Cog 13, CDR-SB, and MMSE relative to the time of initiation of symptomatic medication (time 0). The average trend shows decline occurring in advance of the initiation of treatment (−2.5 to 0 years), as one might expect. However, this decline trend continues, rather than reverses, as one might expect, in the period after the initiation of symptomatic treatment. It is likely that the trend would show a greater degree of decline had participants not been prescribed symptomatic treatment, but the decline continued on average, nonetheless.

Similarly, Figure 2 demonstrates that MMRM estimates of the mean change from baseline in ADAS-Cog 13, CDR-SB, and MMSE that include post-symptomatic treatment observations (blue circles) are *worse* than estimates that exclude these data and are based on symptomatic medication-free observations only (red triangles). This suggests that a placebo group trend estimated under a treatment policy approach would be worse than a placebo group trend estimated under the naïve hypothetical approach of simply disregarding post-symptomatic treatment observations. Analyses restricted to the Aβ+ prodromal population were similar, but with a greater degree of decline under either rule (Supplemental Figure A2). Analyses on 132 months of follow-up (Supplemental Figures A3 and A4) show that the difference between approaches seen during the first 36 months of follow-up continue to grow over time.

The linear mixed-effect model results were consistent with the MMRM. These models confirmed that patients who eventually were prescribed medication, versus not, performed worse at baseline on the ADAS-Cog 13 (4.35 points, standard error [SE] 0.586, $p < .001$), CDR-SB (0.475 points, SE = 0.0813, $p < .001$), and MMSE (−0.92 points, SE = 0.0087, $p < .001$); and decline more after initiation of medication on the ADAS-Cog 13 (2.41 points per year on medication, SE = 0.302, $p < .001$), CDR-SB (0.642 points per year on medication, SE = 0.0704, $p < .001$), and MMSE (−0.91 points per year on medication, SE = 0.1269, $p < .001$).

TABLE 2 Characteristics of ADNI MCI participants grouped by whether or not the participant initiated a symptomatic medication during the course of follow-up

	N	On symptomatic medication at baseline (N = 351)	Initiated symptomatic medication (N = 147)	Never Initiated symptomatic medication (N = 479)	Combined (N = 977)	*P*-value
EMCI at baseline	977	74 (21%)	41 (28%)	240 (50%)	355 (36%)	<0.001
Age (years)	977	73.19 (7.18)	74.23 (6.98)	72.36 (8.12)	72.94 (7.65)	0.015
Sex (female)	977	129 (37%)	58 (39%)	214 (45%)	401 (41%)	0.066
Education (years)	977	15.91 (2.81)	15.80 (2.82)	16.03 (2.80)	15.95 (2.80)	0.607
Ethnicity	977					0.534
Not Hispanic/Latinx		338 (96%)	144 (98%)	457 (95%)	939 (96%)	
Hispanic/Latinx		12 (3%)	3 (2%)	18 (4%)	33 (3%)	
Unknown		1 (0%)	0 (0%)	4 (1%)	5 (1%)	
Race	977					0.046
Am. Indian/Alaskan		0 (0%)	0 (0%)	2 (0%)	2 (0%)	
Asian		5 (1%)	3 (2%)	8 (2%)	16 (2%)	
Hawaiian/Pacific Islander		0 (0%)	0 (0%)	2 (0%)	2 (0%)	
Black		5 (1%)	3 (2%)	27 (6%)	35 (4%)	
White		339 (97%)	139 (95%)	430 (90%)	908 (93%)	
>1		2 (1%)	2 (1%)	7 (1%)	11 (1%)	
Unknown		0 (0%)	0 (0%)	3 (1%)	3 (0%)	
Marital status	977					0.008
Divorced		19 (5%)	14 (10%)	57 (12%)	90 (9%)	
Married		294 (84%)	116 (79%)	345 (72%)	755 (77%)	
Never married		7 (2%)	1 (1%)	18 (4%)	26 (3%)	
Widowed		30 (9%)	15 (10%)	55 (11%)	100 (10%)	
Unknown		1 (0%)	1 (1%)	4 (1%)	6 (1%)	
APOE ε4 alleles	603					<0.001
0		136 (41%)	62 (42%)	272 (60%)	470 (50%)	
1		147 (44%)	67 (46%)	151 (33%)	365 (39%)	
2		52 (16%)	18 (12%)	32 (7%)	102 (11%)	
CSF A$\beta_{1\text{-}42}$ (pg/mL)	619	796 (372)	799 (375)	1145 (431)	961 (437)	<0.001
Florbetapir PET (SUVR)	488	1.313 (0.236)	1.295 (0.215)	1.150 (0.203)	1.215 (0.227)	<0.001
Aβ positive	743	154 (59%)	75 (64%)	204 (56%)	433 (58%)	0.300
CDR-SB	977	1.822 (0.944)	1.561 (0.817)	1.261 (0.768)	1.508 (0.880)	<0.001
ADAS-Cog 13	970	19.60 (6.47)	18.93 (6.19)	14.11 (5.98)	16.80 (6.73)	<0.001
MMSE	977	27.15 (1.84)	27.33 (1.80)	28.03 (1.71)	27.61 (1.82)	<0.001
Hippocampus (/ICVx1,000)	744	4.179 (0.736)	4.164 (0.746)	4.738 (0.772)	4.444 (0.805)	<0.001
Follow-up (years)	977	3.42 (2.68)	4.85 (2.15)	3.45 (2.94)	3.65 (2.78)	<0.001
Exposure to symptomatic medication (years)	977	-	2.913 (1.803)	-	-	-

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–13-item Cognitive subscale; CDR, Clinical Dementia Rating; EMCI, early mild cognitive impairment; ICV, intracranial volume; MMSE, Mini Mental State Exam; PET, positron emission tomography; SUVR, standard uptake value ratio.
P-values are from Pearson's χ^2 test or Kruskal-Wallis test.

3 | DISCUSSION

Our goal was to assess the effect of concurrent symptomatic medications, when prescribed by physicians during a clinical trial, on likely placebo group trajectories. Counter to intuition fueled by an optimistic impression of symptomatic effects, placebo group trajectories estimated under a naïve hypothetical approach, excluding post-symptomatic treatment observations, might show *less decline*

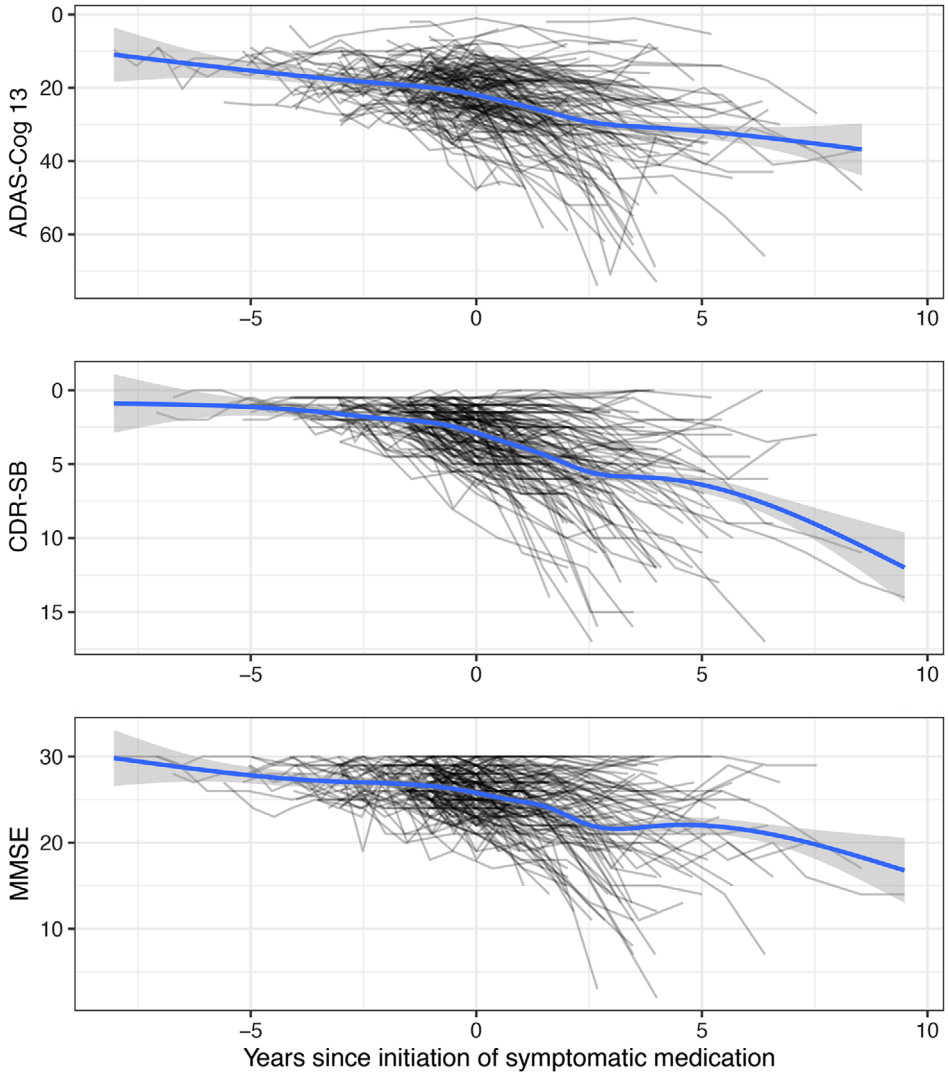

FIGURE 1 Spaghetti plots of ADAS-Cog 13, CDR-SB, and MMSE relative to time of initiation of symptomatic medication for ADNI participants who initiated symptomatic medication. The blue trend lines estimated by LOESS do not demonstrate a cognitive improvement soon after time 0, even though a benefit relative to no treatment cannot be ruled out. Shaded regions depict 95% confidence intervals, not accounting for repeated measures. ADAS-Cog 13, Alzheimer's Disease Assessment Scale–13-item cognitive subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes; LOESS, LOcally Estimated Scatterplot Smoothing; MMSE, Mini Mental State Exam

in cognitive and functional outcomes than trajectories estimated under a treatment policy approach including observations after symptomatic treatment. An effective disease-modifying therapy would be expected to reduce the incidence of symptomatic treatment initiation in the experimental as compared to the control arm. Excluding post-symptomatic treatment observations would therefore likely lead to a preferential underestimation of decline in the control arm. The implication is that the power to detect experimental treatment effects is likely improved, rather than diminished, by taking a treatment policy approach that aims to collect and analyze data observed after the initiation of symptomatic drugs rather than a naïve hypothetical approach. If a hypothetical estimand for the treatment effect in the absence of symptomatic treatment is desired, the statistical estimation would need to account for the likelihood that initiation of symptomatic treatment is predictive of more-severe future decline in cognitive and functional measures, and not simply ignore observations.

The analysis is limited in that ADNI might not be representative of all clinical trial populations. ADNI was designed to study a population similar to that of a therapeutic trial, and in general, it succeeds and has been the standard reference study for clinical trial design in MCI and mild AD dementia.[9,20] Though of course each trial varies in many details, ADNI is generally similar to North American trials in terms of its highly educated population. As shown in Table 2, mean (± SD) education is about 16 ± 3 years (regardless of reported symptomatic medication use). Recent relevant trials report mean education of about 13 or 14 years,[2,21] which suggests that ADNI indeed represents a slightly more educated sample than some trials. It is also true that ADNI includes a larger proportion of medication use (351/977 = 36% at baseline) than that reported in Ostrowitzki et al. We would

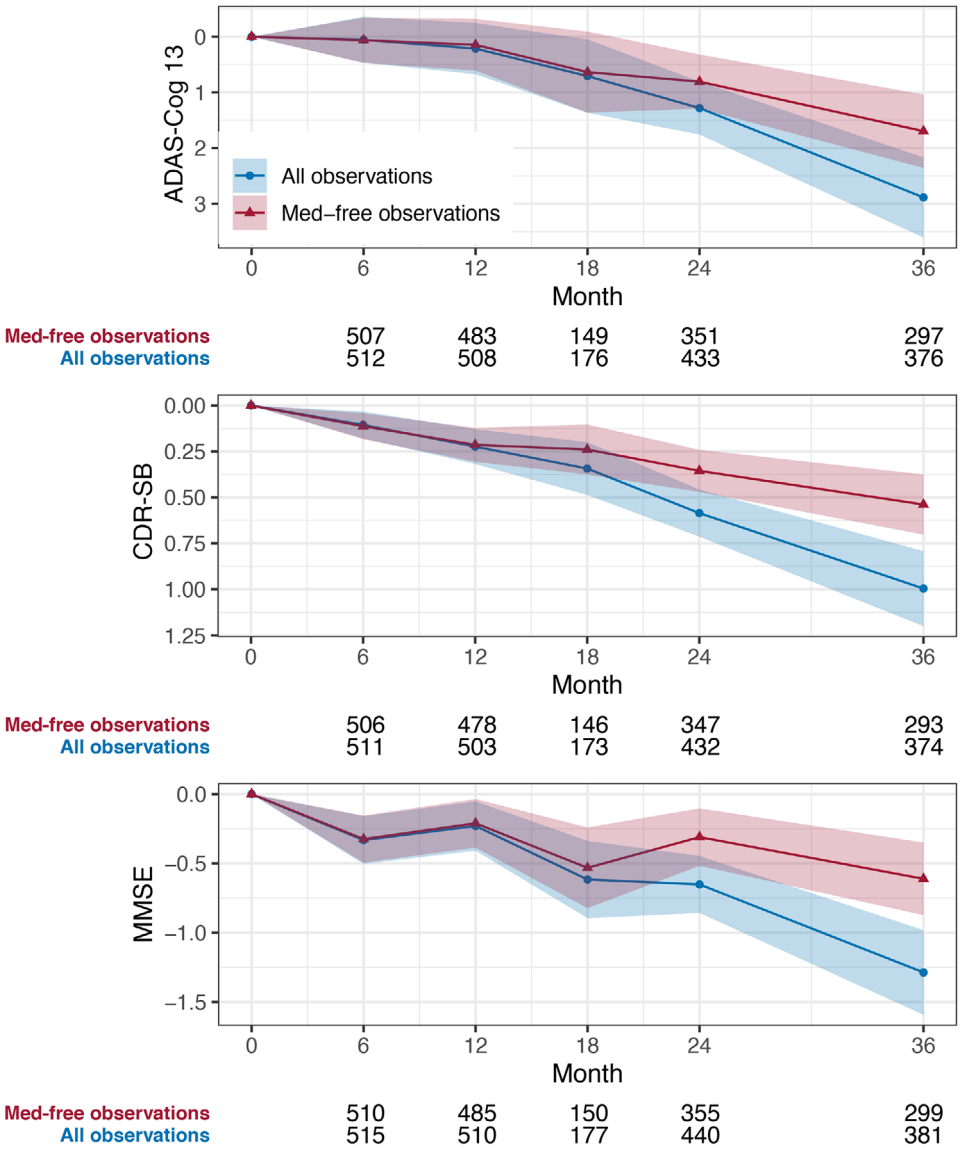

FIGURE 2 Plots of mean change in ADAS-Cog 13, CDR-SB, and MMSE among ADNI MCI participants estimated by including all observations (blue circles) or excluding observations after the initiation of symptomatic medication (red triangles) over the first 36 months of follow-up. Covariates include baseline score, *APOE* ε4 carriage, and age. Shaded regions depict 95% confidence intervals. Numbers below each plot are observation counts at each timepoint. ADAS-Cog 13, Alzheimer's Disease Assessment Scale–13-item cognitive subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMRM, Mixed Model of Repeated Measures; MMSE, Mini Mental State Exam

therefore expect that the effect of excluding observations after the initiation of symptomatic medications would be smaller in studies like Ostrowitzki et al. Nevertheless, the analyses provide no support for excluding observations, and therefore we would still recommend taking a treatment policy approach even in trials with sample characteristics like that reported in Ostrowitzki et al.

We note that retaining participants after they begin symptomatic medications will require careful assessment of adverse effects that may involve the interaction between the investigational product and the added therapy. Such interactions may not have been adequately assessed in prior trials and may be challenging to evaluate in the setting of the cognitive deterioration that precipitated starting symptomatic treatment. But because co-therapy of this sort is sure to occur following regulatory approval, this experience during the course of the trial may be valuable.

Consistent with prior findings,[11,12] our analysis suggests that the effects of symptomatic drugs are not as strong as we might hope, and are not able to compensate for the worsening cognition and function that triggered the treatment initiation. The reported results do not contradict the modest benefit that symptomatic treatments have demonstrated in randomized clinical trials, particularly in later, more symptomatic stages of AD. However, they underscore the need for more efficacious treatment options.

ORCID

Michael C. Donohue https://orcid.org/0000-0001-6026-2238

REFERENCES

1. Committee for Human Medicinal Products. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, Step 2b. In:2017.
2. Ostrowitzki S, Lasser RA, Dorflinger E, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimers Res Ther*. 2017;9(1):95.
3. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med*. 2008;148(5):379-397.
4. Gauthier S, Molinuevo JL. Benefits of combined cholinesterase inhibitor and memantine treatment in moderate-severe Alzheimer's disease. *Alzheimers Dement*. 2013;9(3):326-331.
5. Atri A, Hendrix SB, Pejovic V, et al. Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: a pooled area under the curve analysis. *Alzheimers Res Ther*. 2015;7(1):28.
6. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology*. 2004;63(4):651-657.
7. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352(23):2379-2388.
8. European Medicines Agency. Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementia. In: (CHMP) CfMPfHU, ed. Vol EMA/CHMP/539931/2014. London, United KIngdom, 2016.
9. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*. 2010;74(3):201.
10. Tariot PN, Solomon P, Morris J, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology*. 2000;54(12):2269-2276.
11. Schneider LS, Insel PS, Weiner MW. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. *Arch Neurol*. 2011;68(1):58-66.
12. Han JY, Besser LM, Xiong C, Kukull WA, Morris JC. Cholinesterase inhibitors may not benefit mild cognitive impairment and mild Alzheimer disease dementia. *Alzheimer Dis Assoc Disord*. 2019;33(2):87-94.
13. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*. 2010;74(3):201-209.
14. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S13-S21.
15. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
18. Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. *J Biopharm Stat*. 2001;11(1-2):9-21.
19. *R: A Language and Environment for Statistical Computing* [computer program]. Version 3.5.2. Vienna, Austria: R Foundation for Statistical Computing; 2018.
20. Aisen PS, Petersen RC, Donohue MC, et al. Clinical core of the Alzheimer's disease neuroimaging initiative: progress and plans. *Alzheimer's & Dementia*. 2010;6(3):239.
21. Coric V, van Dyck CH, Salloway S, et al. Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *JAMA Neurol*. 2012;69(11):1430-1440.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Donohue MC, Model F, Delmar P, et al. Initiation of symptomatic medication in Alzheimer's disease clinical trials: Hypothetical versus treatment policy approach. *Alzheimer's Dement*. 2020;16:797–803. https://doi.org/10.1002/alz.12058