Are we over-estimating the effectiveness of dementia therapies? A Systematic Review of the use of Last-Observation-Carried-Forward in Dementia Drug Studies.

Frank J. Molnar MSc MDCM FRCPC[1,2,3]
Malcolm Man-Son-Hing MSc MD FRCPC[1,2,3]
Brian Hutton BSc, MSc [1]
Dean Fergusson MHA, PhD[1,4,5]

[1]Clinical Epidemiology Program, the University of Ottawa Health Research Institute, [2]Élisabeth-Bruyère Research Institute, Ottawa; [3]Division of Geriatric Medicine, Department of Internal Medicine, University of Ottawa; [4]Clinical Trials Research Group, Biomedical Ethics Unit, McGill University; [5]Department of Medicine, University of Ottawa.

Corresponding Author:
Dr. F. Molnar
Director of Research
University of Ottawa Division of Geriatric Medicine
The Ottawa Hospital, Civic Campus
1053 Carling Ave, Ottawa Ontario, Canada K1Y 4E9
Telephone: (613) 798-5555 ext 16486
Fax (613) 761-5334
email: fmolnar@ottawahospital.on.ca

Brian Hutton
Biostatistician
Research Coordinator, Age of Blood in Premature Infants **(ARIPI)** Study
Ottawa Health Research Institute
Ottawa University Center for Transfusion Research
E-mail: bhutton@ohri.ca
Phone: (613) 737-8122
Ottawa Hospital
501 Smyth Road
Ottawa, Ontario
K1H 8L6

Malcolm Man-Son-Hing
University of Ottawa Division of Geriatric Medicine
The Ottawa Hospital, Civic Campus
1053 Carling Ave, Ottawa Ontario, Canada K1Y 4E9
Telephone: (613) 798-5555 ext 16486
Fax (613) 761-5334
email: mhing@ohri.on.ca

Dean A. Fergusson, MHA, PhD
Director, The CEP Methods Centre, The Ottawa Hospital
Associate Director, Clinical Epidemiology Program
Scientist, Ottawa Health Research Institute
Phone #: 613-737-8899 Ext. 7-9216
Fax #: 613-739-6266
dafergusson@ottawahospital.on.ca

ABSTRACT

Objective: To examine the use of intent-to-treat (ITT) imputation of missing data techniques, such as Last-Observation-Carried-Forward, employed in cholinesterase inhibitor and memantine randomized-controlled trials (RCTs) in Alzheimer disease, Vascular dementia, Mixed dementia and Mild Cognitive Impairment.

Design: Systematic review of analytic methodology.

Data Sources: Systematic electronic search of Medline and Cochrane's RCT Register, supplemented by hand search of the reference lists of selected articles, meta-analyses and review articles.

Review Methods: Two reviewers independently reviewed selected RCT reports; extracted data using standardized forms and performed quality assessments using the Jadad scale (+ Schultz criteria). These reviewers then met to review discrepancies in extracted data, and to resolve these via a modified Delphi technique.

Results: Of the 57 studies selected, 12 did not report the results of ITT analyses and 35 employed Last-Observation-Carried-Forward as the only form of ITT analysis (with 24 of these studies reporting conditions that could promote bias favoring the drug under study in Last-Observation-Carried-Forward analyses).

Conclusions: The findings suggest that the published results of some dementia drug RCTs may be inaccurate (i.e. exaggerated effectiveness) or potentially invalid (i.e. false positive results). RCTs that either did not report the results of ITT analyses or employed Last-Observation-Carried-Forward while also demonstrating conditions that could introduce bias in favor of the drugs under study (e.g. greater dropout in treatment groups) should be reanalyzed to verify their results.

The potential problem uncovered may represent the 'tip of the iceberg'. Systematic reviews of the use of Last-Observation-Carried-Forward in other areas of research involving chronic progressive disorders (e.g. Osteoporosis, Parkinson's disease, Lewy Body disease, Stroke, Multiple Sclerosis, COPD, Congestive Heart Failure, Diabetes, Chronic Renal Insufficiency, AIDS etc.) are encouraged.

Given the potentially enormous scope of this problem, the CONSORT group (www.consort-statement.org) should consider incorporating additional guidelines regarding appropriate analyses for studies of medications used to treat chronic progressive disorders. Licensing authorities (e.g. U.S. Food & Drug Administration, European Agency for the Evaluation of Medicinal Products, Health Canada) should review the suitability of Last-Observation-Carried-Forward in drug research in chronic progressive diseases.

Key words: Alzheimer's disease, dementia, clinical trials, dropout, withdrawal, intent-to-treat, missing data

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INTRODUCTION:

Worldwide it is estimated that 24.3 million people suffer from dementia and that the annual costs for Alzheimer's disease (1996 $US dollars) range as high as $155 billion in the US.[1,2] It has been argued that one potential approach to decreasing the negative impact on patients, families and societies may be the optimal use of medications to treat dementia.[2]

Since its introduction in the 1960s, the principle of intention-to-treat (ITT), the inclusion of all patients in the analysis according to the group determined at randomization, has become the accepted standard for the analysis of controlled clinical trials.[3] The strength of ITT is that it promotes balance between treatment groups for both known and unknown confounders, thereby preserving the benefits of randomization. In order for ITT approaches to analyze all patients randomized, including dropouts, several methods to impute missing data have been developed.[3-10]

A commonly employed technique to impute missing data is Last-Observation-Carried-Forward, also known as 'endpoint analysis'. Last-Observation-Carried-Forward replaces subjects' missing outcomes with the last available measurement and requires that two basic conditions be met: [1] that the subjects' responses would have been constant (i.e. stable) from the last observed value (i.e. point of dropout) to the endpoint of the trial

rather than declining or improving further, and [2] that missing values are 'missing completely at random' (i.e. that the probability of dropout is not related in any way to variables such as disease severity, symptoms, group assignment or drug side-effects).[5-7]

Since 1998, researchers have expressed concern that the use of Last-Observation-Carried-Forward in dementia drug trials contravenes both assumptions and, hence, risks generating biased results.[2,11-21] It has been pointed out that since progression is the hallmark of dementia,[22,23] the first condition of stable values from the point of dropout to the end of a study cannot be guaranteed.[3,9,10]

It has also been pointed out that Last-Observation-Carried-Forward ignores the trajectory of a patient's clinical progress (i.e. whether the subject was improving or getting worse at the time of dropout).[8] It freezes outcome values at the last observation, thereby creating an apparent stabilization of disease and/or function in dropouts (Figure 1). Based on this effect, authors have highlighted three contraindications to the use of Last-Observation-Carried-Forward - factors that indicate the second condition (e.g. values are missing completely at random) has been breeched and that can bias results in favor of the drug under study relative to the placebo: [1] greater dropout rates in the treatment group, [2] earlier dropouts in the treatment group, and [3] more rapid progressors in the treatment dropout group.[3,4,9,10,11] These conditions result in more treatment group dropouts having their decline artificially frozen at an earlier stage of disease thereby inflating the measured efficacy of the drug under study. Researchers have not raised similar concerns regarding other imputation techniques.

It remains unclear how concerned we should be regarding the limitations of Last-Observation-Carried-Forward. If a drug study clearly ruled out or minimized the effect of the abovementioned contraindications or if Last-Observation-Carried-Forward were verified by a sensitivity analysis that included other ITT imputation of missing data techniques, then there would seem to be little to worry about. Conversely, if contraindications to the use of Last-Observation-Carried-Forward are present in a trial and Last-Observation-Carried-Forward based results are not verified by other ITT imputation of missing data techniques in a sensitivity analysis, then we should be more concerned regarding potential bias in such a study.

To better understand how significant these concerns might be in dementia research we examined not only the prevalence of use of Last-Observation-Carried-Forward but also the frequency with which the above contraindications were present in randomized trials employing Last-Observation-Carried-Forward to estimate the efficacy of cholinesterase inhibitors and memantine in the treatment of Alzheimer disease, Vascular dementia, Mixed dementia and Mild Cognitive Impairment.

METHODS:

This systematic review was conducted in accordance with the QUOROM guidelines [24] (adapted for a methodological systematic review).

Identification of Studies:

An electronic literature search of Medline and the Cochrane Register of Controlled Trials from 1989 to February 2008 was performed using the OVID search interface. The search strategy included the following terms, and the Medline search was augmented by the use of the Dickersin filter for identification of randomized controlled trials: *dementia, Alzheimer, vascular dementia, mixed dementia, donepezil, Aricept, rivastigmine, Exelon, galantamine, Reminyl, memantine, Ebixa, cholinesterase inhibitor*. This electronic search was supplemented by hand searching of the reference lists of selected articles, meta-analyses and review articles.

Eligibility Criteria:

Double-blinded, randomized controlled trials of cholinesterase inhibitors or memantine examining progressive symptoms (e.g. cognition, function) in Alzheimer disease, Vascular dementia, Mixed dementia or Mild Cognitive Impairment employing DSM (Diagnostic and Statistical Manual of Mental Disorders)[22] or NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association)[23] criteria for Alzheimer's disease or NINDS-AIREN (National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences) criteria for Vascular Dementia were eligible for this review. Trials of cholinesterase inhibitors not currently licensed in Canada (tacrine, metrifonate) were not reviewed. The systematic review was restricted to studies with full trial reports published in English language peer-reviewed journals. The diagnostic criteria for Mild Cognitive Impairment were not

specified, as they were still in development when the relevant studies were being published.

Open label studies, reviews, meta-analyses, commentaries, editorials, studies of pooled data from previous studies, tolerability and safety studies were not included. Subgroup analyses, secondary or retrospective analyses were also excluded.

Data Collection:

Data collected included publication details, investigative site locations, funding, drug comparators, drug doses, diagnostic criteria employed, type(s) of analysis employed, discussion of the limitations of the forms of analysis employed, dropout characteristics (e.g. number, timing, patient characteristics, reasons for dropout), , contraindications to the use of Last-Observation-Carried-Forward, and the results of each primary and secondary outcome measure employed.

Two certified specialists in Geriatric Medicine with clinical expertise in dementia, with formal research methodological training and with recognized expertise in the review of dementia drug trials independently extracted data from all included studies. The two reviewers resolved discrepancies in extracted data using a modified Delphi technique.

Quality Assessment of Included Trials:

Study report quality was assessed using the validated, 3-item Jadad scale (with the addition of the 1 point Schultz criteria).[25] This scale assigns points for randomization (0-2 points), double-blinding (0-2 points) and account for withdrawals (1 point).

RESULTS:

Of the 1146 articles identified by the search strategies, 191 were selected for full text review. Of these, 57 articles met the eligibility criteria for systematic review (Figure 2).[2,14,20,21,26-79]

Trial Characteristics (Tables 1 & 2):

Details of the 57 included trials are provided in Tables 1 and 2. Forty-five studies enrolled patients with Alzheimer disease (21 donepezil, 11 rivastigmine [1was a donepezil-rivastigmine comparison study], 7 galantamine, 6 memantine), 8 enrolled patients with vascular dementia or mixed dementia (3 donepezil, 3 galantamine, 2 memantine) and 4 enrolled patients with MCI (2 donepezil, 1 rivastigmine, 1 galantamine).

Forty trials explicitly indicated they were funded by industry, 6 implied industry funding (the authors were industry employees but the source of funding was not explicitly stated), 3 were funded by industry in partnership with public funders and four studies reported being entirely publicly funded (Table 1). The source of funding for 4 studies could not be determined.

All 57 study reports were rated as demonstrating high quality methodology with a Jadad / Schultz score ≥ 3 (Table 1).

Reporting of Dropouts (Tables 3 & 4):

Ten studies (18%) discussed potential bias secondary to dropouts (Table 3). Dropouts were described in 94% of cholinesterase inhibitor studies and 100% of memantine trials (Table 4). The descriptions were often incomplete with respect to timing and reasons for dropout. Seven of the 49 cholinesterase inhibitor trials (14%) and none of the memantine trials reported data on timing of dropouts. The reasons for dropout were often difficult to discern, as many were described as 'adverse events' that might be due to drug side effects, but were not reported as such. Cholinesterase inhibitor studies were more likely to demonstrate greater dropout in the treatment group (73% of studies) compared to memantine studies (25% of studies). Table 4 demonstrates that when cholinesterase inhibitor studies were combined, there was a higher dropout rate in the treatment group (23.3%) than in the control group (16.8%). When memantine trials were combined the opposite pattern was noted with fewer dropouts in the treatment group (14.6%) than in the control group (18.5%).

Types of non-ITT Analyses Conducted (Tables 2 & 3):

The most common non-ITT analysis (employed in 35 trials) was Observed Case analysis (Tables 2 & 3). Other forms of non-ITT analysis included Fully Evaluable Population analysis (FEP), Treatment Per Protocol analysis (TPP) and Completer analysis (CA). These were rarely described as non-ITT analyses.

Types of ITT Analyses Conducted (Tables 2 & 3):

The results demonstrate that 12 (21%) of the 57 studies did not identify the type of ITT analysis performed or performed only non-ITT analysis. Of the remaining 45 studies that did perform an identifiable form of ITT analysis, 42 (93%) employed Last-Observation-Carried-Forward. Thirty-five of the trials that performed ITT analysis (78 %) relied on Last-Observation-Carried-Forward as the only form of ITT analysis.

Ten of the 57 studies (17.5%) reported employing ITT techniques other than Last-Observation-Carried-Forward (Tables 2 and 3). Breaking this down by drug class demonstrates that 6 of 49 cholinesterase studies (12%) and 4 of 8 memantine studies (50%) employed ITT techniques other than Last-Observation-Carried-Forward. The alternate ITT imputation of missing data techniques included: replacement of missing values with the mean changes observed in the placebo group,[42, 58] time response relationship for ADAScog/11 analyzed using generalized linear modeling,[50, 52] mixed effects modeling,[56, 63] mixed models repeated measures (MMRM),[78,79] replacement of missing data with worst ranks,[57] and sensitivity analyses consisting of a number of simulations.[68]

Eight of these 10 studies performed both Last-Observation-Carried-Forward and a confirmatory ITT technique other than Last-Observation-Carried-Forward. Put differently, of the 42 studies that employed Last-Observation-Carried-Forward, only 8 reported performing another type of ITT analysis. Three of these 8 studies did not

comment on the results of the alternate non- Last-Observation-Carried-Forward analysis. Of the 5 studies that commented on the results of the alternate ITT analysis, 4 did not report the values of the outcomes calculated by the alternate ITT analysis but did indicate that the direction of results was unchanged. This would indicate that the direction of the findings of the 6 positive outcomes in these 4 studies was unchanged when Last-Observation-Carried-Forward analysis was verified by another ITT analysis (i.e. no false positive findings were generated by Last-Observation-Carried-Forward).

Only 1 study verified the point estimates of outcomes measuring drug efficacy generated by Last-Observation-Carried-Forward with point estimates of an alternate form of ITT analysis.[42] The study verified the values of 3 positive outcomes.

Contraindications to the use of Last-Observation-Carried-Forward as the only form of ITT analysis:

Of the 35 studies employing Last-Observation-Carried-Forward as the only form of ITT analysis, 23 (66 %) explicitly demonstrated contraindications (factors that could introduce bias) to the use of Last-Observation-Carried-Forward. It was unclear if the remaining 12 studies were free of contraindications as most studies failed to report adequate data regarding the timing and severity of disease of dropouts to permit a precise estimate of the number of contraindications to the use of Last-Observation-Carried-Forward. Consequently, Table 2 provides a range of potential contraindications to the use of Last-Observation-Carried-Forward for each study. Seven trials (12%) discussed the limitations of Last-Observation-Carried-Forward or non-ITT approaches (Table 3).

DISCUSSION:

This study set out to determine whether the coexistence of Last-Observation-Carried-Forward and contraindications to the use of this form of analysis (i.e. conditions that would increase the probability of bias) were relatively infrequent occurrences of minor significance or whether these were highly prevalent occurrences suggesting the need for further study to rule out the possibility of widespread bias in this field of research. The study also examined whether confirmatory ITT analyses (e.g. Sensitivity Analyses) were published to rule out the possibility of '*Last-Observation-Carried-Forward bias*'.

The results demonstrate that Last-Observation-Carried-Forward has been the primary approach employed for imputation of missing values in ITT analyses in dementia and MCI drug trials. Despite previously published cautions that this form of analysis may introduce bias into research on dementia, the results are rarely verified by other forms of ITT analysis. This is particularly concerning in cholinesterase inhibitor research as most of the cholinesterase inhibitor studies reviewed violated the conditions required for valid (i.e. unbiased) Last-Observation-Carried-Forward analyses (Table 2): [1] the assumption that missing values are 'missing completely at random' is unlikely given the frequently reported gastrointestinal side-effects of the cholinesterase inhibitors; [2] differential dropout (e.g. greater dropout in the treatment group) is widely prevalent in cholinesterase inhibitor research; and [3] given the fact that progression is the hallmark of dementia and is incorporated into the definitions of dementia[22] and of Alzheimer disease[23], the assumption that subjects' outcome measures would remain constant from the time of

dropout until completion of the trial (rather than declining further) is not guaranteed to be correct. The latter concern is supported by the fact that the reviewed studies often include graphs demonstrating continued decline in outcome measures throughout the study. Conditions that may lead to bias in favor of the drugs under study when employing Last-Observation-Carried-Forward analysis are frequently present in cholinesterase inhibitor studies that rely on Last-Observation-Carried-Forward as the sole form of ITT analysis. Due to lack of data on timing of dropouts and severity of disease in dropouts, our results may underestimate the true extent of the problem uncovered. Until completion and reporting of studies that verify the point estimates of drug efficacy of publications that relied on Last-Observation-Carried-Forward as the sole form of ITT analysis while also demonstrating conditions that would promote bias (e.g. greater dropout in the treatment group), the point estimates of efficacy of such studies should be interpreted with caution.

Memantine appears to have fewer side effects relative to cholinesterase inhibitors and differential dropout is less of an issue in memantine studies. In fact, the greater dropouts in the control groups could result in Last-Observation-Carried-Forward biasing the results against this drug and underestimating its' true efficacy. It is therefore possible that, when compared to cholinesterase inhibitor research, memantine studies may be disadvantaged by the use of Last-Observation-Carried-Forward.

The concern that Last-Observation-Carried-Forward might introduce bias can be addressed by sensitivity analyses that demonstrate similar outcomes when other forms of ITT analysis are employed. Only one study[42] verified the point estimates of efficacy

calculated by Last-Observation-Carried-Forward with an alternate ITT analysis. These are only 3 positive outcomes out of the hundreds of outcomes reported in the studies reviewed. Regrettably, there is insufficient published information to assure us that Last-Observation-Carried-Forward has not introduced bias in other dementia drug studies. Rather, there is significant evidence that the risk that it has introduced bias is fairly high, particularly in cholinesterase inhibitor research where drug side effects resulting in greater treatment group dropouts are common.

The argument that results based on Last-Observation-Carried-Forward are correct because they are supported by the results of alternate analyses (e.g. observed case analysis, completer analysis, fully-evaluable population analysis, or treated per protocol analysis) is questionable if not completely invalid. These techniques do not impute missing data, but rather exclude subjects without data from analysis. Since they do not analyze all randomized patients, they are not ITT analyses. Many will be systematically biased in the same direction as Last-Observation-Carried-Forward (i.e. in favor of the group with greater, earlier and/or more severely affected dropouts), and do not represent valid confirmatory sensitivity analyses. The biases inherent in these non-ITT techniques have been highlighted by the International Conference on Harmonisation Tripartite Guideline,[80] by the European Agency for the Evaluation of Medicinal Products (EMEA)[14] as well as by a number of authors.[15,53,67,81]

Given the above, it is difficult to justify the ongoing reliance on Last-Observation-Carried-Forward as the sole form of ITT analysis in dementia studies. Other forms of ITT

analysis that do not treat dropouts artificially by freezing values at the point of dropout, but rather model for expected natural decline in dropouts, would not cost anything to perform and to publish (either as the primary analysis or as a sensitivity analysis). The modeling can be as simple as using the rate of decline noted in the control group and applying it to all dropouts. More complex modeling procedures are available in standard statistical programs. More appropriate forms of analysis have been employed in the field of dementia research. [42, 50, 52, 56-58, 68, 78, 79] Petersen's MCI study[68] may serve as a model for future research, as it employed both modelling for dropouts and sensitivity analyses of the effect of various modelling assumptions and approaches.

By demonstrating the reliance on Last-Observation-Carried-Forward as the only form of ITT analysis in a high percentage of studies that also demonstrate factors that will promote bias when Last-Observation-Carried-Forward is used (e.g. greater dropouts in the treatment group), this study provides further validation of the concerns previously raised regarding the use of Last-Observation-Carried-Forward in dementia drug trials.[2, 3, 9 – 21] The results of this study, therefore, provide a strong rationale for the reanalysis of previously published dementia studies that relied solely on Last-Observation-Carried-Forward as the only form of ITT analysis (particularly for those demonstrating greater dropout in treatment groups) and for studies that did not publish any identifiable ITT analyses.

Verifying Last-Observation-Carried-Forward based results would require individual patient data that, unfortunately, are not in the public domain. Therefore this study cannot

quantify the magnitude of the effect of the use of Last-Observation-Carried-Forward on trial results but is restricted to highlighting the prevalence and potential seriousness of the problem.

Given the fact that the concerns regarding the use of Last-Observation-Carried-Forward in dementia studies predate most of the trials reviewed and that the primary study data required for reanalysis of these studies is not in the public domain, the onus is therefore on the investigators who have published these trials to disprove the possibility that Last-Observation-Carried-Forward or non-ITT analyses have introduced bias into their trials. To do so they would need to re-analyze their studies using ITT modeling techniques that anticipate the trajectory of disease in dropouts. In order to insure the robustness of the findings based on such modeling, sensitivity analyses employing various types of modeling and varying data employed by models should be presented, as was done in Petersen's MCI study.[68] Meta-analyses that did not employ modelling for decline in individual dropouts should also be re-analysed in a similar fashion, and such an approach should be adopted by future RCTs in dementia research.

These results are meaningful in day-to-day clinical care. Without accurate analyses, physicians cannot optimally counsel patients and families, patients and families cannot provide truly informed consent when making treatment decisions, accurate meta-analyses and pharmacoeconomic studies cannot be performed, and we cannot make reliable statements regarding whether trial results truly cross thresholds of clinical significance. Continued reliance on Last-Observation-Carried-Forward and non-ITT analyses may

result in more toxic therapies, with greater and earlier dropout, being favored over less toxic therapies. This situation may already be occurring, as the greater dropout rate in treatment groups in cholinesterase inhibitor trials vs. greater dropout in the control groups in memantine studies (Table 4) may bias results in favor of cholinesterase inhibitors relative to memantine (thereby placing memantine at a relative disadvantage).

While there is a preponderance of evidence suggesting the drugs studied have some degree of positive effect in some patients, the high prevalence of the potential source of bias uncovered in this study suggests that we cannot be confident regarding the accuracy of point estimates of efficacy of many of the studies reviewed. We may not know how effective these drugs truly are. Without confirmatory ITT analyses, the worst-case scenario of false positive trials cannot be confidently excluded.

CONCLUSIONS:

The findings of this study are of major significance. The majority of the studies reviewed (38/57 = 66%) either did not report the results of an ITT analysis (12/57 = 21%), did not verify the results of Last-Observation-Carried-Forward when conditions that could introduce bias in favor of the study drug existed (23/57 = 40%), or did not comment on the results of alternate ITT analyses performed (3/57 = 5%). Furthermore, due to lack of data on timing of dropouts and severity of disease in dropouts, these results may underestimate the true extent of the problem uncovered.

It is highly unlikely that, given the findings of this study, the point estimates of some of the hundreds of positive outcomes generated in the reviewed trials that used Last-Observation-Carried-Forward have not been altered in some way. The question is likely not '*has bias been introduced*', but rather '*how many outcomes have been biased*' and '*to what degree have they been biased*'.

Given the enormous prevalence and cost of dementia, its severe impact on patients and families, and the associated rapidly escalating drug costs that are straining the resources of public health care systems, the possibility that the use of Last-Observation-Carried-Forward may have introduced bias into research on dementia therapies is a serious concern that needs to be ruled out or, if found to be true, should be corrected.

We have come a long way in terms of improving the methodology of dementia trials by selecting more appropriate outcome measures, study designs and sample sizes. The results of this study indicate that the research community should now take the next step in the ongoing evolution of dementia RCT methodology by focusing on the analytic approaches employed in these trials.

Scientists in other areas of research involving chronic progressive disorders (e.g. Osteoporosis, Parkinson's disease, Lewy Body disease, Stroke, Multiple Sclerosis, COPD, Congestive Heart Failure, DM, Chronic Renal Insufficiency, AIDS etc.) are encouraged to perform similar reviews to examine the use of Last-Observation-Carried-Forward or non-ITT techniques in these highly prevalent and costly conditions.

Given the potentially enormous scope of this problem, the CONSORT group (www.consort-statement.org) should consider incorporating additional guidelines regarding appropriate analyses for studies of medications used to treat chronic progressive disorders. Journal editors, funding agencies, ethics review boards and drug formulary committees would then be able to request that such CONSORT recommendations be employed in future studies of dementia and other chronic progressive disorders.

Continued reliance on Last-Observation-Carried-Forward provides no benefits while creating unnecessary risk of generating biased results that will tend to favor more toxic therapies. Consequently, it is recommended that licensing agencies (e.g. US Food and Drug Administration, European Agency for the Evaluation of Medicinal Products, Health Canada etc.) review this situation in order to determine whether they should continue to accept Last-Observation-Carried-Forward analyses in research on dementias and other chronic progressive conditions.

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Table 1: Characteristics of Included Studies (n=57)

First author & Year of study	Countries	Study funding source(s)	Interventions studied	Indication	Sample size(s)		Jadad /Schultz Quality Score
					Controls	Active Comparators	
Rogers (1996)	USA	Industry	placebo, donepezil (1, 3, 5mg)	Alzheimer's dementia	40	121	4
Rogers (Arch Intern Med 1998)	USA	Industry	placebo, donepezil (5, 10mg)	Alzheimer's dementia	153	315	4
Rogers (Neurology 1998)	USA	Industry	placebo, donepezil (5, 10mg)	Alzheimer's dementia	162	311	4
Aqid (1998)	Australia, Belgium, Czechoslovakia, Denmark, Finland, France, Germany, Ireland, Norway, Sweden, Switzerland, UK	Industry	Placebo, rivastigmine (4mg, 6mg)	Alzheimer's dementia	133	269	3
Corey-Bloom (1998)	USA	Industry	Placebo, rivastigmine (1-4mg, 6-12mg)	Alzheimer's dementia	235	464	5
Burns (1999)	Australia, Belgium, Canada, France, Germany, Ireland, New Zealand, South Africa, UK	Industry	placebo, donepezil (5, 10mg)	Alzheimer's dementia	274	544	4
Forette (1999)	Belgium, Canada, France, Norway, UK	Industry	Placebo, rivastigmine 6 – 9mg (BID, TID)	Alzheimer's dementia	24	90	4
Rösler (1999)	Australia, France, Germany, Switzerland, USA, Canada	Industry	Placebo, rivastigmine (1-4mg, 6-12mg)	Alzheimer's dementia	239	486	5
Winblad (1999)	Latvia	Not reported	placebo, memantine (10mg)	Alzheimer's dementia, Vascular dementia	84	82	3
Greenberg	USA	Public	placebo, donepezil (5mg) cross-	Alzheimer's dementia	30	30	5

			over trial				
Homma (2000)	Japan	Industry	placebo, donepezil (5mg)	Alzheimer's dementia	129	134	3
Kumar (2000)	USA	Industry (authors employed)	Placebo, rivastigmine (1-4mg, 6-12mg)	Alzheimer's dementia	103	216	3
Raskind (2000)	USA	Industry	placebo, galantomine (24, 32mg)	Alzheimer's dementia	213	423	5
Tariot (2000)	USA	Industry	placebo, galantomine (16,24mg)	Alzheimer's dementia	286	552	5
Wilcock (2000)	Canada, Finland, France, Germany, Norway, Sweden, Netherlands, UK,	Industry	placebo, galantomine, (24,32mg)	Alzheimer's dementia	215	438	5
Feldman (2001)	Canada, Australia, France	Industry	placebo, donepezil (5-10mg)	Alzheimer's dementia	146	144	5
Mohs (2001)	USA	Industry	placebo, donepezil (5-10mg)	Alzheimer's dementia	217	214	4
Tariot (2001)	USA	Industry	placebo, donepezil (5-10mg)	Alzheimer's dementia	105	103	4
Thomas (2001)	Italy	Not reported	Donepezil, vitamin E,	Alzheimer's dementia	20	20	4
Winblad (2001)	Denmark, Finland, Norway, Sweden, Netherlands	Industry	placebo, donepezil (5-10mg)	Alzheimer's dementia	144	142	5
Rockwood (2001)	USA, Canada, UK, South Africa, Australia, New Zealand	Industry	placebo, galantamine (24-32mg)	Alzheimer's dementia	125	261	5
Wilkinson (2001)	UK	Industry	placebo, galantamine (18, 24, 36mg)	Alzheimer's dementia	87	198	5
Duraiswamy (2002)	USA	Industry	placebo, rivastigmine (1-4, 6-12mg)	Alzheimer's dementia	Not reported	Not reported	3
Pratt (2002)	USA, Europe, Canada, Australia	Industry (authors employed)	placebo, donepezil (5, 10mg)	Vascular dementia	290	603	5
Erkinjuntti (2002)	Canada, Denmark, Finland, France,	Industry	placebo, 24mg galantamine	Mixed dementia, Vascular dementia	196	396	4

	Germany, Ireland, Israel, Netherlands, Poland, UK						
Orgogozo (2002)	France, Belgium, Switzerland	Industry	placebo, memantine (20mg)	Vascular dementia	141	147	3
Wilcock (2002)	UK	Industry (authors employed)	placebo, memantine (20mg)	Vascular dementia	271	277	4
Krishnan (2003)	USA	Industry	placebo, donepezil (10mg)	Alzheimer's dementia	33	34	5
Tune (2003)	USA	Industry	placebo, donepezil (10mg)	Alzheimer's dementia	14	14	3
Reisberg (2003)	USA	Industry, Public	placebo, memantine (20mg)	Alzheimer's dementia	126	126	5
Black (2003)	USA, UK, Australia, Canada, Germany	Industry	Placebo, donepezil (5, 10mg)	Vascular dementia	199	404	5
Wilkinson (2003)	USA, Canada, Australia, Europe	Industry	Placebo, donepezil (5, 10mg)	Vascular dementia	193	423	5
AD 2000 Collaborative Group (2004)	UK	Public	Placebo, donepezil (5-10mg)	Alzheimer's dementia	244 Phase 1	242 Phase 1	4
Holmes (2004)	UK	Industry	Placebo, donepezil (10mg)	Alzheimer's dementia	55	41	5
Seltzer (2004)	USA	Industry	Placebo, donepezil (10mg)	Alzheimer's dementia	57	96	4
Tariot (2004)	USA	Industry	placebo, memantine (20mg)	Alzheimer's dementia already on donepezil	201	202	5
Bullock (2004)	Canada, Denmark, Finland, France, Germany, Israel, Netherlands, Poland, UK	Industry (authors employed)	Placebo, galantamine (24mg)	Mixed dementia	97	188	4
Salloway (2004)	USA	Industry	Placebo, donepezil (10mg)	Mild cognitive impairment	137	133	4
Karaman (2005)	Turkey	Not reported	placebo, rivastigmine (6-12mg)	Alzheimer's dementia	20	24	4
Bullock	Australia, Canada,	Industry	3-12mg of rivastigmine, 5-10mg	Alzheimer's dementia	499	495	5

(2005)	France, Germany, Italy, Spain, UK		donepezil		donepezil	rivastigmine	
Broduty (2005)	USA, Australia, Canada, South Africa, New Zealand	Industry (authors employed)	placebo, immediate release galantamine (16-24mg), prolonged release galantamine (16-24mg)	Alzheimer's dementia	324	647	5
Peterson (2005)	USA, Canada	Industry, Public	placebo, donepezil (10mg)	Mild cognitive impairment	259	253	4
Koontz (2005)	USA	Industry	placebo, galantamine (24mg)	Mild cognitive impairment	11	8	4
Dos Santos Moraes (2006)	Brazil	Public	Placebo, donepezil (10mg)	Alzheimer's dementia	18	17	4
Johannsen (2006)	Belgium, Denmark, Germany, Greece, Hungary, Iceland, Netherlands, Poland, USA	Industry	Placebo, donepezil (10mg)	Alzheimer's dementia	103	99	4
Winblad (2006)	Sweden	Industry	Placebo, donepezil (5-10mg)	Alzheimer's dementia	120	128	5
Rockwood (2006)	Canada	Industry, Public	Placebo, galantamine (16-24mg)	Alzheimer's dementia	66	64	5
Mazza (2006)	Not reported (likely Italy)	Not reported	Placebo, donepezil (5mg), Ginkgo	Alzheimer's dementia	26	25	5
Peskind (2006)	USA	Industry	Placebo, memantine (20mg)	Alzheimer's dementia	202	201	5
Auchus (2007)	21 countries (Europe, North America, Israel, Asia, Australia)	Industry (authors employed)	Placebo, galantamine (flexible dose)	Vascular dementia	391	397	4
Bakchine (2007)	Austria, Belgium, Denmark, Finland, France, Greece, Lithuania, The Netherlands, Poland, Spain,	Industry	Placebo, memantine (20mg)	Alzheimer's dementia	152	318	4

	Sweden, UK						
Black (2007)	USA, Canada, France, UK, Australia	Industry	Placebo, donepezil (10mg)	Alzheimer's dementia	167	176	5
Feldman (Lancet Neurol 2007)	14 countries	Industry	Placebo, rivastigmine (3 – 12mg)	Mild cognitive impairment	509	508	5
Feldman (J Neurol Neurosurg Psychiatry 2007)	Australia, Canada, Ireland, Italy, South Africa, UK	Industry	Placebo, rivastigmine 2 – 12 mg BID vs. TID dosing	Alzheimer's dementia	222	229 BID group 227 TID group	5
Mowla (2007)	Not reported (likely Iran)	Public	Placebo, rivastigmine 6 – 12mg, rivastigmine 6 – 12mg + fluoxetine	Alzheimer's dementia	40	41 rivastigmine alone	4
Van Dyck (2007)	USA	Industry	Placebo, memantine (20mg)	Alzheimer's dementia	172	178	5
Winblad (2007)	21 countries	Industry	Placebo, 10 cm^2 rivastigmine patch, 20 cm^2 rivastigmine patch, 12mg rivastigmine tablet	Alzheimer's dementia	302	293 (10 cm^2 patch) 303 (20 cm^2 patch) 297 (12mg tablet)	5

Table 2: Types of ITT and non-ITT analyses employed and number of contraindications to Last Observation Carried Forward

(LOCF)

Study (Author, Journal)	Number of contraindications to the use of LOCF				Type of ITT analysis performed	Non-ITT analyses indicated	Only performed non-ITT analysis OR Type of ITT analysis not specified	LOCF is only form of ITT analysis + Explicitly demonstrates factors that can introduce bias in favor of the study drug in LOCF analysis
	Greater	Earlier	More rapid	TOTAL number				

	dropout rate in treatment group? (if yes, dropout rates provided)	dropouts in treatment group?	progressors in treatment dropout group?	of contraindication to the use of LOCF				
Donepezil in Alzheimer's Dementia								
Rogers 1996	No	Not ruled out	Not ruled out	0 - 2	LOCF described although the term 'LOCF' not explicitly used	None		
Rogers Arch Intern Med 1998	**Yes** Placebo 7% 5mg 10% 10mg 18%	Not ruled out	Not ruled out	1 - 3	LOCF	FEP		+
Rogers Neurology 1998	**Yes** Placebo 20% 5mg 15% 10mg 32%	Not ruled out	Not ruled out	1 - 3	LOCF	FEP		+
Burns 1999	**Yes** Placebo 20% 5mg 22% 10mg 26%	Not ruled out	Not ruled out	1 - 3	LOCF	FEP, OCA, Retrieved Dropout		+
Greenberg 2000	**Yes** Placebo 5% 5mg 10%	Not ruled out	Not ruled out	1 - 3	Type of ITT analysis not specified	Type of analysis not specified	+	
Homma 2000	No	Not ruled out	Not ruled out	0 - 2	Type of ITT analysis not specified	TPP	+	
Feldman 2001	No	No	Not ruled out	0 - 1	LOCF	OCA		
Mohs 2001	No	Not ruled out	Not ruled out	0 - 2	LOCF	OCA		
Tariot 2001	No	Not ruled out	Not ruled out	0 - 2	LOCF	OCA		
Thomas 2001	No	No	No	0	No ITT analysis performed	CA	+	
Winblad 2001	No	No	Not ruled out	0 - 1	LOCF	OCA		
Krishnan 2003	No	Not ruled out	Not ruled out	0 - 2	LOCF	OCA		
Tune 2003	No	Not ruled out	Not ruled out	0 - 2	Type of ITT analysis not specified	Type of analysis not specified		

							+	
AD2000 Collaborative Group, 2004; *(Alzheimer's and Mixed dementia)*	No	Not ruled out	**Yes**	1 - 2	Most recent previous score was used (similar to LOCF), if one existed; if not, then the next subsequent valid score was substituted	None		+
Holmes 2004	No	Not ruled out	**Yes**	1 - 2	LOCF	OCA		+
dos Santos Moraes 2006	No	No	No	0	Type of ITT analysis not specified	Type of analysis not specified	+	
Seltzer 2004	**Yes** Placebo 19% 10mg 27%	Not ruled out	Not ruled out	1 - 3	LOCF	FEP		+
Johannsen 2006	No	Not ruled out	Not ruled out	0 - 2	LOCF	OCA		
Winblad 2006	**Yes** Placebo 18% 5/10mg 26%	Not ruled out	Not ruled out	1 - 3	**LOCF, Modelling - replaced missing data with the mean of the observed values for the change from baseline to month 6 in the placebo group (LOCF and Modelling provided similar point estimates in SIB, ADCS-ADL-severe, CGI-I, MMSE, NPI)**	CA		
Mazza 2006	No	Not ruled out	Not ruled out	0 - 2	Type of ITT analysis not specified		+	
Black 2007	**Yes** Placebo 24% 10mg 34%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		+
Rivastigmine in Alzheimer's dementia								
Agid 1998	**Yes** Placebo 6% 4mg 12% 6mg 15%	Not ruled out	Not ruled out	1 - 3	No ITT analysis performed	OCA	+	
Corey-Bloom 1998	**Yes** Placebo 7% 1-4mg 15%	**Yes**	Not ruled out	2 - 3	LOCF	OCA		

	6-12mg 35%							+
Forette 1999	**Yes** Placebo 21% 6 – 9mg via bid dosing 50% 6 – 9mg via tid dosing 38%	Not ruled out	Not ruled out	1 - 3	No ITT analysis performed	FEP	+	
Rösler 1999	**Yes** Placebo 13% 1-4 mg 14% 6–12mg 32%	**Yes**	Not ruled out	2 - 3	LOCF	OCA		+
Kumar 2000	**Yes** Placebo 16% 1–4 mg 14% 6–12mg 33%	Not ruled out	Not ruled out	1 - 3	No ITT analysis performed	OCA	+	
Doraiswamy 2002	Not ruled out	Not ruled out	Not ruled out	0 - 3	LOCF	OCA		
Karaman 2005	**Yes** Placebo 0% 6–12mg 13%	No	No	1	No ITT analysis performed	OCA	+	
Bullock 2005 *(Rivastigmine vs. Donepezil)*	**Yes** Donepezil 5–10mg 36% Rivastigmine 3–12mg 47%	**Yes**	Not ruled out	2 - 3	LOCF	OCA, FEP		+
Feldman 2007 J Neurol Neurosurg Psychiatry	**Yes** Placebo 15% Riv bid 24% Riv tid 17%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA. Retrieved dropout + LOCF		+
Mowla 2007	No	Not ruled out	Not ruled out	0 - 2	Type of analysis not specified	Type of analysis not specified	+	
Winblad 2007	**Yes** Placebo 12% 10cm^2 22% 20cm^2 21% 12mg 22%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA Retrieved dropout		+
Galantamine in Alzheimer's Dementia								

Study								
Raskind 2000	**Yes** Placebo 9% 24 mg 32% 32 mg 42%	Not ruled out	Not ruled out	1 - 3	LOCF, **The time response relationship for change in ADAScog/11 was analysed using generalized linear interactive modelling (results of modelling not provided)**	OCA		
Tariot 2000	**Yes** Placebo 16% 8 mg 23% 16mg 22% 24 mg 22%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		**+**
Wilcock 2000	**Yes** Placebo 13% 24mg 20% 32mg 25%	Not ruled out	Not ruled out	1 - 3	Term LOCF not employed but technique described in paper, **The time response relationship for change in ADAScog/11 was analysed using generalized linear mixed modelling (results of modelling not provided)**	OCA		
Rockwood 2001	**Yes** Placebo 11% 24 or 32mg 33%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		**+**
Wilkinson 2001	**Yes** Placebo 16% 18 mg 28% 24 mg 28% 36 mg 48%	Not ruled out	Not ruled out	1 - 3	LOCF	TPP		**+**
Brodaty 2005	**Yes** Placebo 23% Galantamine immediate release 31% Galantamine Prolonged Release 25%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		**+**
Rockwood 2006	No	Not ruled out	Not ruled out	0 - 2	LOCF , **Mixed effects modelling (point estimates of outcomes based on modelling not provided)**	OCA		
Memantine In Alzheimer's Dementia								
Winblad 1999 (both Alzheimer's	No	Not ruled out	Not ruled out	0 - 2	**Missing endpoint data replaced by worst ranks**	TPP		

Study								
and Vascular dementia studied)								
Reisberg 2003	No	Not ruled out	Not ruled out	0 - 2	LOCF, **Replaced missing values with mean observed value for decline in placebo group (point estimates of outcomes based on modelling not provided)**	OCA		
Tariot 2004	No	Not ruled out	Not ruled out	0 - 2	LOCF	OCA		
Peskind 2006	No	Not ruled out	Not ruled out	0 - 2	LOCF, Mixed models repeated measures (MMRM) **(point estimates of outcomes based on modelling not provided)**	OCA		
Bakchine 2007	Yes Placebo 11% 20mg 16%	Not ruled out	Not ruled out	1 - 3	LOCF mentioned but results not provided	CA, OCA	+	
Van Dyck 2007	No	Not ruled out	Not ruled out	0 - 2	LOCF, Mixed models repeated measures (MMRM) **(point estimates of outcomes based on modelling not provided)**	OCA		
Donepezil in <u>Vascular Dementia</u> and <u>Mixed Dementia</u>								
Pratt 2002	**Yes** Placebo 15% 5 mg 18% 10 mg 29%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		+
Black 2003	**Yes** Placebo 15% 5 mg 19% 10 mg 28%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		+
Wilkinson 2003	**Yes** Placebo 17% 5 mg 19% 10 mg 25%	**Yes**	Not ruled out	2 - 3	LOCF	OCA		+
Galantamine in <u>Vascular Dementia</u> and <u>Mixed Dementia</u>								
Erkinjuntti 2002	**Yes** Placebo 15% 24 mg 26%	**Yes**	Not ruled out	2 - 3	LOCF, Mixed Effects model **(results of modelling not provided)**	OCA		+
Bullock 2004	**Yes** Placebo 14%	Not ruled out	Not ruled out	1 - 3	Used term 'Observed Case analysis' but describe LOCF	None		

	24 mg 22%							**+**
Auchus 2007	**Yes** Placebo 15% 8-24mg 24%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA		**+**
Memantine in <u>Vascular Dementia</u> and <u>Mixed Dementia</u>								
Orgogozo 2002	**Yes** Placebo 16% 20 mg 21%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA, TPP		**+**
Wilcock 2002	No	Not ruled out	Not ruled out	0 - 2	LOCF	TPP		
Donepezil in <u>Mild Cognitive Impairment (MCI)</u>								
Salloway 2004	**Yes** Placebo 17% 10 mg 32%	Not ruled out	Not ruled out	1 - 3	LOCF	OCA, FEP		**+**
Petersen 2005	**Yes** Placebo 25% 10 mg 36%	**Yes**	**Yes**	3	**Employed a sensitivity analysis consisting of a number of simulations (modelling)**	**For secondary outcomes "missing values were imputed with the use of a projection method appropriate for assessing responses among subjects with neurodegenerative diseases."**		
Galantamine in <u>Mild Cognitive Impairment (MCI)</u>								
Koontz 2005	**Yes** Placebo 36% 24 mg 50%	Not ruled out	Not ruled out	1 - 3	Type of analysis not specified	Description suggests OCA	**+**	
Rivastigmine in <u>Mild Cognitive Impairment (MCI)</u>								
Feldman 2007 Lancet Neurology	No	Not ruled out	Not ruled out	0 - 3	LOCF described although the term 'LOCF' not explicitly used	OCA		

Abbreviations: LOCF = Last Observation Carried Forward; FEP = Fully Evaluable Population analysis; CA = Completer Analysis; TPP = Treatment Per Protocol analysis; ATA = As Treated Analysis; OCA = Observed Case Analysis; SIB = Severe Impairment Battery; ADCS-ADL-severe = the Modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease; CGI-I = Clinical Global Impression of Improvement; MMSE = Mini-mental State Examination; NPI = Neuropsychiatric Inventory.

Table 3: Type of Efficacy Analysis Used/Described

Characteristic	Frequency (% of total) Some studies employed > one technique in each category
Use of ITT principle	
# that indicated use of an ITT analysis	45/57 (79 %)
Last Observation Carried Forward (LOCF)	42/57 (74 %)
Modeling (results provided)	**9/57 (16 %)**
Use of non-ITT techniques**	44/57 (77 %)
Observed Case Analysis (OCA)	35/57 (61 %)
Fully Evaluable Population analysis (FEP)	5/57 (9 %)
Treatment Per Protocol analysis (TPP)	5/57 (9 %)
Completer Analysis (CA)	3/57 (5 %)
Discussion of data analysis issues	
# mentioning importance of missing data	10/57 (18 %)
# discussing limits of LOCF or non-ITT analysis	7/57 (12 %)

*note that studies may have used more than one approach

Table 4: Account of Dropouts by Drug Class

	Cholinesterase Inhibitors (n=49 studies)		Memantine (n=8 studies)	
Description of drop-outs				
# that described total study drop-outs	46/49 (94 %)		8/8 (100 %)	
# studies with larger dropout in experimental group	**36/49 (73 %)**		**2/8 (25 %)**	
# studies with larger dropout in control group	**8/49 (16 %)**		**2/8 (25 %)**	
Similar dropout rates between groups	**2/49 (4 %)**		**4/8 (50 %)**	
Timing of dropouts				
# of articles describing drop-out timing	7/49 (14 %)		0/8 (0 %)	
	Control Group N = 7275	**Experimental Groups N = 11969**	**Control Group N = 1349**	**Experimental Groups N = 1539**
# completing study	6050	9198	1099	1315
DROPOUT RATE	**16.8 %**	**23.2 %**	**18.5 %**	**14.6 %**