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This document is the Accepted Version [AM]

Citation:

SOYSAL, P., ISIK, A.T., STUBBS, B., SOLMI, M., VOLPE, M., LUCHINI, C., D'ONOFRIO, G., PILOTTO, A., MANZATO, E., SERGI, G., SCHOFIELD, Patricia and VERONESE, N. (2016). Acetylcholinesterase inhibitors are associated with weight loss in older people with dementia: A systematic review and meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry*, 87 (12), 1368-1374. [Article]

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**Acetylcholinesterase Inhibitors are associated with weight loss in older people with dementia:
A Systematic Review And Meta-Analysis**

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ABSTRACT

We conducted a systematic review and meta-analysis investigating the influence of AChEIs therapy on nutritional status and weight across observational and interventional studies. Two authors searched major electronic databases from inception until 10/14/2015 for longitudinal, open-label and randomized double blind placebo controlled (RCTs) studies of AChEIs in patients with dementia reporting nutritional status outcome data. Out of 3,551 initial hits, 25 studies (12 open-label trials, 9 RCTs and 4 longitudinal studies) including 10,792 patients with dementia were meta analyzed. In longitudinal studies (median follow-up: 6 months), a significant cumulative incidence of weight loss between baseline and follow-up evaluation was observed (studies=2; 5%; 95% CI: 1-34%, $p<0.0001$; $I^2=95\%$). These findings were confirmed in open-label trials (6%; 95% CI: 4-7%, $p<0.0001$; $I^2=78\%$). In 9 RCTs (median follow-up: 5 months), those taking AChEIs more frequently experienced weight loss than participants taking placebo (OR=2.18; 95% CI: 1.50-3.17, $p<0.0001$; $I^2=29\%$). AChEIs therapy contributes to weight loss in patients with dementia, with a twofold increased risk observed in the meta-analysis of RCTs. Clinicians should carefully consider the benefit and risk of prescribing AChEIs. Nutritional status should be routinely evaluated in patients with dementia treated with AChEIs.

Key words: Dementia; Alzheimer's Disease; nutrition; acetylcholinesterase inhibitor; weight; elderly

1. INTRODUCTION

Malnutrition and cognitive decline are two considerable geriatric syndromes associated with considerable increased risk of premature mortality. Malnutrition and cognitive decline have been recently described in close relationship several mechanism could explain it.(1, 2) One is the occurrence of repeated actions and behavioral disorders due to episodic memory and impairment in attention resulting in increased energy loss in patients with dementia.(3) Another potential explanation is alteration of the sensation of smell and taste in addition to impaired swallowing function due to cholinergic deficits.(4, 5) Cognitive deterioration affects daily functional status and instrumental activities which result in disability, dependence and decreased oral intake.(6) Chewing problems and decreased appetite significantly affect food intake in patients with dementia.(7) In light of all these possible mechanisms, the risk of malnutrition can arise even within the prodromal period of dementia.(8) Also, nearly half of elderly patients with dementia in the population are at risk of malnutrition, and malnutrition in turn accelerates cognitive impairment, increases the incidence of behavioral disorders, and decreases functionality and quality of life in this population.(9, 10,11) As a consequence, a vicious cycle maintains malnutrition and cognitive deficit.

Acetylcholinesterase inhibitors (AChEI) are the front-line pharmacotherapy in the treatment of mild to moderate dementia.(12) Although AChEI are not curative, they are able to stabilize memory and delay functional reduction.(13) However, it remains unclear how AChEI affect nutritional status (e.g. weight loss, malnutrition), a central factor that significantly influences disease progression. It has been reported that AChEIs may accelerate weight loss by increasing cholinergic activity in the gastrointestinal system and causing nausea, vomiting and diarrhea, particularly in the beginning of treatment.(14) However, others have proposed that because AChEI improve the cognitive status, with good cognitive status being essential for the prevention of malnutrition, it is possible that an improvement of nutritional status could be observed.(15) Thus, there is currently no clear understanding of the impact of AChEI on nutritional parameters in older patients with dementia and to our knowledge no meta-analysis addressing this pertinent question exists.

Given the aforementioned, we conducted a systematic review and meta-analysis of observational and interventional studies to determine whether patients with dementia treated with AChEIs are at increased risk of poor nutritional status including weight loss, changes in body mass index and multidimensional parameters changes.

2. METHODS

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement.(16, 17)

2.1. Search strategy

Two investigators (MS, CL) independently conducted an electronic literature search using PubMed and Scopus with no language restrictions, until 10/14/2015. In PubMed, the following controlled vocabulary terms and keywords were considered: ("donepezil"[All Fields] OR "galantamine"[All Fields] OR "rivastigmine"[All Fields] OR "cholinesterase inhibitors"[All Fields] OR "acetylcholinesterase inhibitors"[All Fields]) AND ("nutritional status"[mesh] OR "Nutrition Assessment"[mesh] OR "Nutrition Surveys"[mesh] OR "nutritional assessment"[All Fields] OR "body weight"[mesh] OR "weight"[All Fields] OR "body mass index"[All Fields] OR "BMI"[All Fields] OR "albumin"[All Fields] OR "albumins"[Mesh]). A similar search was run in Scopus. Reference lists of the articles included in the analysis and of others relevant to the topic were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered and Authors contacted for additional information if needed. Any inconsistencies were resolved by consensus with a third Author (EM).

2.2. Study selection

We only considered observational and interventional (open label and RCTs) studies that:(1) had a baseline and follow-up evaluation; (2) included patients with dementia diagnosed according standardized criteria (NINCDS-ARDRA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association or DSM: Diagnostic and Statistical Manual of Mental Disorders) (3) included at least one group taking AChEI including donepezil-DZP; galantamine-GAL; rivastigmine-RIV; (4) reported data on nutritional parameters in people taking AChEI (weight, body mass index, multidimensional tools for the

estimation of malnutrition, serum albumin levels). If the data about nutritional parameters were reported only at baseline, authors were contacted at least two times in one month for obtaining follow-up information.

Studies were excluded if: (1) did not include patients with dementia; (2) reported data on AChEI used for aims other than improving cognitive status (e.g. neostigmine, physostigmine etc.); (3) conducted in vitro and on animal models.

The studies satisfying the inclusion/exclusion criteria were included and subsequently divided according their design in: a) longitudinal: repeated observations of the nutritional variables over a follow-up period without any pre-specified intervention; b) open-label: trials with a randomization phase and with a group taking no drugs or a group taking a different dose of the same drug; c) randomized double blind placebo controlled trials (RCTs): trials with a randomization phase and a group taking placebo.

2.3.Data extraction

Two authors (PS, GS) independently recorded data extracted from the selected studies in a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS). The following information was extracted: i) characteristics of the study population (e.g. sample size, demographics, setting); ii) type of dementia (Alzheimer's disease-AD; vascular dementia; others; mixed); iii) duration of dementia (years); iv) type of drug (donepezil-DZP; galantamine-GAL; rivastigmine-RIV) with the correspondent dosage; v) mean age and mean minimal mental state examination (MMSE) (at baseline and at the follow-up where available); vi) duration of follow-up (months).

2.4.Outcomes

The primary outcomes were the changes between baseline and follow-up of the nutritional parameters (as continuous) including weight, BMI, multidimensional tools for assessing nutritional status (e.g.

mini-nutritional assessment, geriatric nutrition risk index or similar), and albumin. Since no studies included the changes of albumin between baseline and follow-up, this outcome was not included. We considered the number of those losing weight between follow-up and baseline as co-primary outcome too.

2.5. Assessment of study quality

For longitudinal and open-label trials without a comparison group, the Newcastle-Ottawa Scale (NOS) was used to assess study quality.(18) The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome. The investigators solved any discrepancies by jointly re-assessing an article (PS, MS and GS).

For RCTs, the quality of involved studies was evaluated using Jadad scale.(19) This scale includes randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study according to this scale ranges from 0-5, with higher scores indicating better quality.(20) Studies with Jadad scores ≥ 3 were considered as high-quality.

2.6. Statistical analysis

The meta-analysis was performed using the Comprehensive Meta-Analysis 3.0. When combining studies, the random effects model was used to account for study heterogeneity.(21) In analyses regarding longitudinal and open-label trials, means and standard deviations (SD) of weight, BMI and mini-nutritional assessment (MNA) were analyzed assessing the differences between baseline and follow-up in order to calculate within groups standardized mean differences [SMD]. Event rate was used to assess the cumulative incidence of those with weight loss between baseline and follow-up evaluation. Within-study pooled estimates were also calculated as necessary (e.g. two groups taking different doses of the same drug).

Regarding analyses including RCTs, only analyses about the number of participants losing weight were possible. The cumulative incidence of those losing weight in participants treated with AChEIs

and controls were calculated through odds ratios [OR]. All estimates were calculated together with 95% confidence intervals [CI].

Study heterogeneity was measured using the chi-squared and I-squared statistics, assuming that a $p \leq 0.05$ for the former and a value $\geq 50\%$ for the latter indicated a significant heterogeneity.(22) In pre-planned analysis, we conducted a meta-regression analysis to see whether some variables could affect results about weight loss, namely continent in which the study was conducted (North America, Europe and Asia, multicontinent), type of drug (DZP, GAL, RIV, all drugs together), type of dementia (AD, other), follow-up duration and quality. Follow-up duration was categorized according with the median of the studies included (5 months for open-label; 6 for RCTs). For open-label studies, low quality was defined as $eNOS \leq 5$ and high as $eNOS > 5$; for RCTs low quality was defined as a Jadad's score < 3 points; high as ≥ 3 points.(17, 20)

Publication bias was assessed by visually inspecting funnel plots and using the Begg-Mazumdar Kendall tau and the Egger bias test. Then, to account for publication bias, we used the trim-and-fill method, based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished (imputed) studies. (23, 24)

3. RESULTS

The search identified 3,551 non duplicated potentially eligible studies. After excluding 3,464 papers at the titles and abstract review, 87 full-text articles were examined and 25 studies (12 open-label trials, 9 RCTs and 4 longitudinal studies) were finally included in systematic-review and meta-analysis (See **Supplementary Figure 1**).

3.1. Study and patient characteristics

Study and patient characteristics are summarized in **Supplementary Tables 1-3**. Altogether the 25 studies analyzed, represented a total of 10,792 patients with dementia, the majority of whom were women (6,741; 62.5%). Most studies were conducted in North America (14 studies: 8 open-label and 6 RCTs), followed by Europe (8 studies: 3 longitudinal, 3 open-label and 1 RCT), Asia (2 studies: 1 longitudinal and 1 open-label) and across different continents (2 studies: 1 open-label and 1 RCT) (**Supplementary Tables 1-3**). Twenty-one studies were conducted among community-dwelling participants, 2 among outpatients, 2 among inpatients and 1 in nursing home setting. The majority of the studies included only patients with Alzheimer's disease (22 studies; 2 longitudinal, 11 open-label and 8 RCTs) mainly diagnosed with the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (16 studies) (**Supplementary Tables 1-3**).

3.2. Meta-analysis results

3.2.1. Longitudinal studies reporting on nutritional parameters

The four longitudinal studies included 751 subjects, mainly women (59.9%) and with a mean age of 76.4 ± 6.5 years. (15,25-27) Two studies used GAL, 1 RIV and 1 all AChEIs together. After a median follow-up period of 6 months, the mean MMSE score (baseline: 20.1 ± 4.3) did not significantly improve at follow-up ($p=0.09$, paired T-test). The quality of the studies seems to be high as shown in the **Supplementary Tables 1 and 4**.

Regarding nutritional parameters, two studies reported a significant cumulative incidence of those with weight loss between baseline and follow-up evaluation (5%; 95% CI: 1-34%, $p < 0.0001$; $I^2 = 95\%$) (**Table 1**).^(15,26) On the contrary, no significant variations in body weight, BMI, or MNA were reported in one study.⁽¹⁵⁾

It was not possible to assess publication bias due to the limited number of the studies included for each outcome.

3.2.2. Open-label trials reporting on nutritional parameters

The 12 open-label trials followed 5,730 patients with dementia, with a mean age of 76.0 ± 7.0 years and mainly women for a median of 6 months (**Supplementary Table 2**).⁽²⁸⁻³⁹⁾ The mean duration of the disease was 4.2 ± 3.1 years. Seven studies used RIV, 5 DZP and 1 all the AChEI together. The mean baseline MMSE was of 16.4 ± 3.7 , while the comparison with the follow-up values was not possible due to limited data available for this outcome (8 studies did not report the MMSE value at the follow-up, 4 as a change and one as absolute value). The quality of the studies included suggested a high risk of bias as shown by the median eNOS score (5; range: 4-8) (**Supplementary Table 2 and 4**).

Regarding nutritional parameters, twelve studies reported a higher proportions of subjects with weight loss during follow-up period in those taking AChEI (6%; 95% CI: 4-7%, $p < 0.0001$; $I^2 = 78\%$) (**Table 1**).^(28-30, 32-39) There was no evidence of publication bias as shown by Kendall's tau (-0.17; $p = 0.45$) or Egger's test (slope = -0.33 ± 1.56 ; $p = 0.84$).

Only one study assessed weight and BMI change between baseline and follow-up reporting no significant variations in these 2 parameters (**Table 1**).⁽³¹⁾

3.2.3. Randomized controlled trials reporting data on weight loss

Nine RCTs were included in our meta-analysis reporting, among nutritional parameters, only data about subjects with weight loss in the treated and placebo group during follow-up.⁽⁴⁰⁻⁴⁸⁾ The median follow-up time was 6 months (range: 2-24).

As reported in **Supplementary Table 3**, 4,311 patients with dementia treated with AChEI (5 studies: GAL; 2: DZP; 2: RIV) were compared to 2,699 taking placebo. The mean age was 75.1 ± 3.9 and 75.7 ± 4.2 in the treated and placebo groups, respectively, and in both groups women were more present than men. Baseline MMSE score was 17.1 ± 2.6 and 17.0 ± 2.6 in the treated and placebo group, respectively. Data about MMSE scores at follow-up were insufficient for verifying the efficacy of these drugs on cognitive status assessed with this tool.

The quality of the studies, assessed through the Jadad's scale, was rated as good for 7 and low for other 2 (**Supplementary Tables 3 and 5**). For these studies the most common source of possible bias was the lack of the data about dropouts and withdrawals, as shown in **Supplementary Table 5**.

As reported in **Figure 1**, 6% (268/4,311) in those taking AChEI and 3% (81/2,699) in those taking placebo reported a weight loss/decrease leading to two fold increased risk of weight loss (OR=2.18; 95%CI: 1.50-3.17, $p < 0.0001$; $I^2 = 29\%$). There was no evidence of publication bias as shown by Kendall's tau (0.14; $p = 0.60$) or Egger's test (slope= 1.35 ± 1.01 ; $p = 0.22$).

3.3. Meta-regression analysis

In the meta-regression analysis, we investigated if the continent in which the study was performed, the type of AChEI used or dementia, follow-up duration and quality of the studies could influence the results regarding weight loss in open-label and randomized controlled trials.

As shown in **Table 2**, no moderator emerged as significant for the analyses about weight loss in open-label trials. On the contrary, we observed an increased risk of weight loss in RCTs made in North America, using DZP or GAL, including only AD, and with a long follow-up period and high quality (**Table 2**).

4. DISCUSSION

In this meta-analysis including 26 studies and 10,792 patients with dementia, we found that participants taking AChEIs experienced an increased risk of weight loss (compared to baseline in longitudinal and open-label trials, and vs. placebo in RCTs). We observed no other significant differences in nutritional parameters were evident, but there was a paucity of studies considering other outcomes. Our meta-analysis from 9 RCTs demonstrates that the weight loss experienced by patients with dementia treated with AChEIs is double that reported in placebo.

Clearly, our results demonstrating that AChEIs are associated with increased weight loss are a concern, particularly given that the medication groups are routinely prescribed around the world for this patient group. To our knowledge, our meta-analysis is the first to demonstrate this relationship. The largest demographic group at high risk of inadequate diet and malnutrition is elderly population. Ageing is associated with a decline in a number of physiological functions that can impact nutritional status, including reduced lean body mass and a resultant decrease in basal metabolic rate, decreased gastric secretion and changes in the oral cavity, sensory function deficits, changes in fluid and electrolyte regulation.(49) Chronic comorbidities such as dementia, and medications can also contribute to malnutrition in these patients. The percentage of malnutrition and the risk of malnutrition in elderly patients, who have been newly diagnosed with dementia, were found as 11.2% and 42.2% in one study.(15) There are numerous studies that demonstrate a close relation between cognitive and functional deficits with malnutrition in patients with dementia.(1,8-10) This association could be attributed to the repetitive tasks and restlessness frequently occurring in these patients due to episodic memory, apraxia, executive planning difficulties and impaired attention and to the use of a large amount of energy in trying to complete the activities of daily living.(3) In addition, cognitive deterioration contributes to decrease oral intake by affecting daily functional status and instrumental activities, and chewing problems, eating difficulties due to the olfactory and taste dysfunction and decreased appetite might also affect food intake.(7) For these reasons, malnutrition is one of the most common problems in demented subjects, and this problem seems to be relevant since it is strongly

related with cognitive decline, progress of the disease, institutionalization, mortality, decline in functional status, poorer quality of life, and increase in caregiver burden.(50)

Conversely, it has been reported that AChEIs, might improve nutritional aspects through anti-inflammatory effects over cholinergic pathways and their improving sensation of smell and taste .(5,51) Moreover, improvement in swallowing function due to increased acetylcholine concentration by AChEIs may have an additional role in improving nutritional aspects.(52) On the contrary, these medications frequently cause weight loss by increasing cholinergic activity in the gastrointestinal system and nausea, vomiting and diarrhea.(53) Therefore, our meta-analysis sheds light on an important topic, within which the data was previously equivocal.

In our meta-analysis, we found that a small proportion of people taking AChEIs experienced weight loss in longitudinal or open-label studies. Although these findings were significant when compared to baseline, they should be interpreted cautiously. First, no significant variations in mean body weight, BMI, or MNA values were reported. Second, the short follow-up of the studies included (median=5 months) is far from the common clinical experience in which patients with dementia take these medications for years. It thus remains unclear how the long-term usage of AChEIs affects nutritional status, which is one of the factors that significantly influence disease progression.

In the RCTs, we found that the percentage of those weighting loss was double in those treated with AChEIs compared to those treated with placebo. However, the incidences in both groups were relatively small (6 and 3%), particularly thinking that malnutrition and unintentional weight loss affect about half of the patients with dementia.(54) Furthermore, the increased risk of weight loss was more evident in RCTs using DZP or GAL, with a longer follow-up period, while this was not observed in RCTs related to RIV. This information might be of particular interest to the prescribing clinician. However, it is noteworthy that the reason why RIV, but not DZP and GAL, is associated with less apparent weight loss, could also be related to the improvement in appetite and swallowing over above-mentioned mechanisms by inhibiting butyrylcholinesterase as well as acetylcholinesterase as previously reported (15). Another reason might be that transdermal

rivastigmine has better tolerability and lower gastrointestinal side effects compared with oral formula.(55) An additional reason could be the lack of power for the studies exploring the effects of RIV, since only two studies investigated nutritional parameters in those taking this drug. Nonetheless, future comparative studies with adequate follow up should seek to address the comparative efficacy and side effects of these differing medication classes with a particular emphasis on monitoring weight. Clinically, considering our results, it is important that prescribing clinicians carefully consider the risk and benefit ratio of each different medication. Routine monitoring of nutritional status, in particular weight, should form part of good clinical practice in patients with dementia treated with these medication.

Although our meta-analysis is the first exploring the effects of AChEIs on nutritional parameters and included a large number of studies and participants, there are some limitations that should be mentioned. The main limitation is that very few information exists in nutritional parameters other than weight loss were available. More research using multidimensional parameters and parameters exploring protein malnutrition is needed. Second, the effects of AChEIs on different types of dementia were not evaluated because of limited number of patients with non-Alzheimer dementia. However, in several countries, the use of AChEIs is not licensed for AD. Third, the definition of weight loss differed across studies and there was limited information on the magnitude of weight loss. Fourth, we were not able to distinguish the effect of oral vs. patch formulations of AChEIs, but it could be of importance since patches could have less nutritional side effects. Fifth, we were not able to verify if the use of these medications was followed by a real improvement in cognitive function probably necessary to improve nutritional status. A last limitation is the short follow-up of the studies included.

5. CONCLUSION

The treatment with AChEIs is associated with a significant risk of weight loss in patients with dementia in the elderly. Data from 9 RCTs found people taking AChEIs are two times more likely to experience weight loss than in the placebo. In light of our findings, when prescribing AChEIs, people

in clinical practice should routinely monitor nutritional status in patients with dementia. Further studies with adequate follow up are required, comparing the relative risk and benefit ration of different medications and should seek to consider other nutritional parameters.

ACKNOWLEDGMENTS

We would thank for their contribution to our work: Carina Wattmo, Skåne University Hospital, Malmö, Sweden; Iskandar Tamimi, Traumatology and Orthopedic Surgery Department, Hospital Regional Universitario Carlos Haya, Malaga, Spain.

Funding: no.

Conflict of interest: none.

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Table 1. Meta-analysis of longitudinal studies and open-label trials findings about nutritional parameters.

Type of study	Number of studies	Number of participants	Effect size (95% CI)	Heterogeneity
<u>Weight loss (compared to baseline)</u>				
Longitudinal	2	604	0.05 (0.01-0.34)^a	Tau ² = 2.53; Chi ² = 24.0, df = 1 (P<0.0001); I ² = 95 %
Open-label	12	5640	0.06 (0.04-0.07)^a	Tau ² = 0.18; Chi ² = 51.9, df = 11 (P<0.0001); I ² = 78 %
<u>Weight change (compared to baseline)</u>				
Longitudinal	3	676	0.01 (-0.13; 0.15) ^b	Tau ² = 0.00; Chi ² = 2.49, df = 2 (P=0.29); I ² = 20 %
Open-label	1	90	0.06 (-0.24; 0.35) ^b	-
<u>BMI change (compared to baseline)</u>				
Longitudinal	2	147	0.15 (-0.33; 0.63) ^b	Tau ² = 0.08; Chi ² = 2.97, df = 1 (P=0.09); I ² = 66%
Open-label	1	90	0.21 (-0.08; 0.50) ^b	-
<u>MNA change (compared to baseline)</u>				
Longitudinal	1	116	0.08 (-0.17; 0.34) ^b	-
Open-label			No studies available	

Notes: ^aEvent rate; ^b: standardized mean difference. Abbreviations: **BMI:** Body mass index., **MNA:** Mini Nutritional Assessment

Figure 1. Odds ratio for weight loss in acetylcholinesterasic inhibitors (AChEI) group vs. placebo in randomized controlled trials.

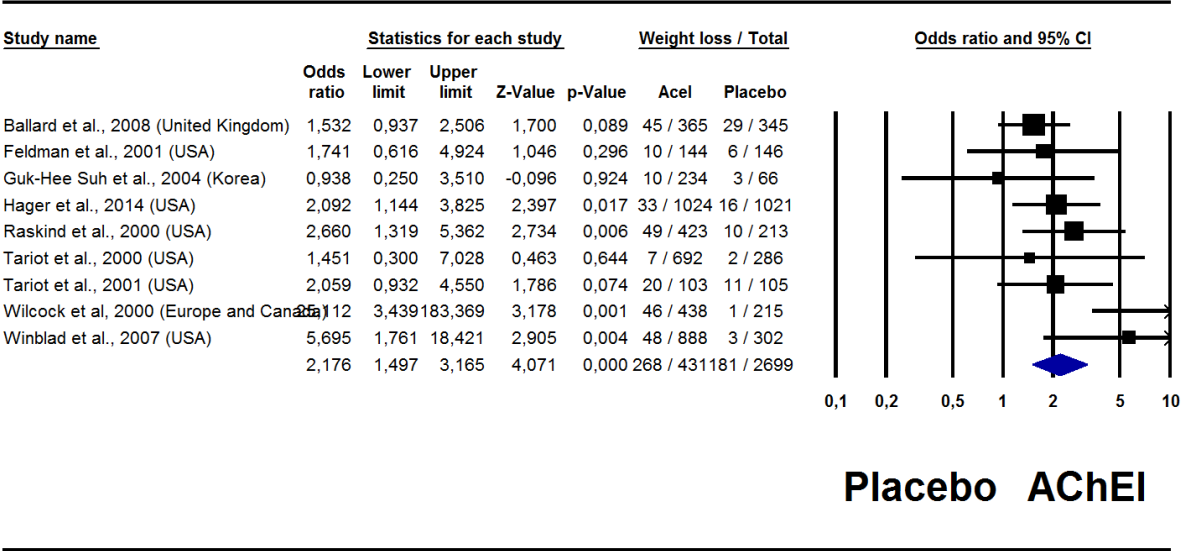


Table 2. Strata for odds ratios for weight loss in randomized controlled (RCTs) and open-label trials.

Moderator	Strata	Analysis details	Open-label (event rate)	RCTs (ORs)
Continent	North America	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.05 (0.04-0.07) <0.0001 78% (<0.0001) 8	2.40 (1.67-3.46) <0.0001 0% (0.56) 5
	Europe and Asia	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.07 (0.05-0.11) <0.0001 61% (0.08) 3	1.44 (0.91-2.29) 0.12 0% (0.49) 2
	Multicontinent	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.05 (0.03-0.07) <0.0001 - 1	5.75 (0.43-77.5) 0.19 82% (0.02) 2
		P-value ^a	0.33	0.17
Type of drug	DZP	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.05 (0.03-0.08) <0.0001 88% (<0.0001) 5	1.94 (1.03-3.36) <0.0001 0% (0.80) 2
	GAL	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	No studies available	2.35 (1.21-4.56) 0.01 49% (0.10) 5
	RIV	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.06 (0.05-0.08) <0.0001 45% (0.09) 7	2.64 (0.74-9.38) 0.13 75% (0.04) 2
	All drugs	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i> P-value ^a	0.01 (0.00-0.07) <0.0001 - 1 0.10	No studies available 0.87

Type of dementia	AD	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.05 (0.04-0.07) <0.0001 80% (<0.0001) 11	2.40 (1.56-3.70) <0.0001 33% (0.16) 8
	Others	<i>Pooled estimated</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i> P-value^a	0.08 (0.04-0.14) <0.0001 - 1 0.33	1.53 (0.94-2.51) 0.09 - 1 0.18
Follow-up duration^b	Short	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.06 (0.04-0.08) <0.0001 80% (<0.0001) 7	1.84 (0.93-3.63) 0.08 41% (0.17) 4
	Long	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i> P-value^a	0.06 (0.04-0.08) <0.0001 81% (<0.0001) 5 1.00	2.55 (1.52-3.70) <0.0001 35% (0.19) 5 0.50
Quality^c	Low	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i>	0.05 (0.04-0.07) <0.0001 78% (<0.0001) 8	2.37 (0.41-13.89) 0.34 75% (0.05) 2
	High	<i>Pooled estimate</i> , estimate (95%CI) P-value for estimate <i>Heterogeneity, I²</i> (P-value) <i>Number of studies</i> P-value^a	0.07 (0.05-0.10) <0.0001 50% (0.11) 4 0.23	2.09 (1.45-3.00) <0.0001 27% (0.22) 7 0.89

Abbreviations: **AD:** Alzheimer Disease, **DZP:** donepezil, **GAL:** galantamine, **OR:** odds ratio, **RIV:** rivastigmine.

Notes:

^a P-value for the interaction across strata.

^bFollow-up: for RCTs short follow-up was defined as studies with a mean follow-up period ≤ 5 months; long as RCTs with a follow-up period > 5 months.

^cQuality: for open-label studies, low quality was defined as eNOS ≤ 5 and high > 5 ; for RCTs low quality was defined as a Jadad's score < 3 points; high as ≥ 3 points.

