REVIEW

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 acetylcholinesterase inhibitors (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 randomised double-blind placebo controlled (randomised controlled trials (RCTs)) studies of AChEIs in patients with dementia reporting nutritional status outcome data. Out of 3551 initial hits, 25 studies (12 open-label trials, 9 RCTs and 4 longitudinal studies) including 10 792 patients with dementia were meta-analysed. 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% to 34%, p<0.0001; I^2=95%). These findings were confirmed in open-label trials (6%; 95% CI 4% to 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 to 3.17, p<0.0001; I^2=29%). AChEIs therapy contributes to weight loss in patients with dementia, with a 2-fold 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.

INTRODUCTION

Malnutrition and cognitive decline are two considerable geriatric syndromes associated with a considerably increased risk of premature mortality. Malnutrition and cognitive decline have been recently described in close relationship with several mechanisms that could explain this association.[1 2] One is the occurrence of repeated actions and behavioural 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 the light of all these possible mechanisms, the risk of malnutrition can arise even within the prodromal period of dementia.[8] Also, nearly half of the elderly patients with dementia in the population are at risk of malnutrition, which in turn accelerates cognitive impairment, increases the incidence of behavioural disorders, and decreases functionality and quality of life in this population.[9–11] As a consequence, a vicious cycle maintains malnutrition and cognitive deficit.

Acetylcholinesterase inhibitors (AChEIs) are the front-line pharmacotherapy in the treatment of mild-to-moderate dementia.[12] Although AChEIs are not curative, they are able to stabilise memory and delay functional reduction.[13] However, it remains unclear how AChEIs affect nutritional status (eg, 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 diarrhoea, particularly at the beginning of treatment.[14] However, others have proposed that since AChEIs improve the cognitive status, with good cognitive status being essential for the prevention of malnutrition, it is possible that an improvement in 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 the best of our knowledge, no meta-analysis addressing this pertinent question exists.

Given the aforementioned limitations, 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 (BMI) and multidimensional parameter changes.

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]

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Search strategy

Two independent investigators (MS, CL) checked the literature as of 10/14/2015, using PubMed and Scopus with no language restrictions. 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).

Study selection

We only considered observational and interventional (open-label and randomised controlled trials (RCTs)) studies that: (1) had a baseline and follow-up evaluation; (2) included patients with dementia diagnosed according to standardised 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, BMI, 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 1 month for obtaining follow-up information.

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

The studies satisfying the inclusion/exclusion criteria were included and subsequently divided according to their design in: (1) longitudinal: repeated observations of the nutritional variables over a follow-up period without any prespecified intervention; (2) open-label: trials with a randomisation phase and with a group taking no drugs or a group taking a different dose of the same drug; (3) randomised double-blind placebo controlled trials (RCTs): trials with a randomisation phase and a group taking placebo.

Data extraction

Two authors (PS, GS) independently recorded data extracted from the selected studies in a standardised Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (BS). The following information was extracted: (1) characteristics of the study population (eg, sample size, demographics, setting); (2) type of dementia (Alzheimer's disease (AD), vascular dementia, others, mixed); (3) duration of dementia (years); (4) type of drug (DZP, GAL, RIV) with the correspondent dosage; (5) mean age and mean Mini-Mental State Examination (MMSE; at baseline and at the follow-up where available); (6) duration of follow-up (months).

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 (eg, mini-nutritional assessment (MNA), 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 a coprimary outcome too.

Assessment of study quality

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

For RCTs, the quality of involved studies was evaluated using the Jadad scale.[19] This scale includes randomisation (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 to 5, with higher scores indicating better quality.[20] Studies with Jadad scores ≥3 were considered as high quality.

Statistical analysis

The meta-analysis was performed using the Comprehensive Meta-Analysis V.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 SDs of weight, BMI and MNA were analysed assessing the differences between baseline and follow-up in order to calculate within-groups standardised mean differences (SMDs). 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 (eg, 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 ORs. All estimates were calculated together with 95% CIs.

Study heterogeneity was measured using the χ^2 and I^2 statistics, assuming that a $p \leq 0.05$ for the former and a value ≥50% for the latter indicated a significant heterogeneity.[22] In preplanned analysis, we conducted a metaregression 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 categorised according to the median of the studies included (5 months for open-label; 6 for RCTs). For open-label studies, low quality was defined as eNOS≤5 and high as eNOS>5; for RCTs, low quality was defined as a Jadad score<3 points; high as ≥3 points.[17 20]

Publication bias was assessed by visually inspecting funnel plots and using the Begg-Mazumdar Kendall τ 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

centre of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished (imputed) studies.[23 24]

RESULTS

The search identified 3551 non-duplicated potentially eligible studies. After excluding 3464 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 the systematic review and meta-analysis (see online supplementary figure S1).

Study and patient characteristics

Study and patient characteristics are summarised in online supplementary tables S1–3. Altogether, the 25 studies analysed represented a total of 10 792 patients with dementia, the majority of whom were women (6741; 62.5%). Most studies were conducted in North America (14 studies: 8 open-label and 6 RCTs), followed by Europe (7 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; see online supplementary tables S1–3). Twenty-one studies were conducted among community-dwelling participants, two among outpatients, one among inpatients and one in a nursing home setting. The majority of the studies included only patients with AD (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; see online supplementary tables S1–3).

Meta-analysis results

Longitudinal studies reporting on nutritional parameters

The four longitudinal studies included 751 participants, mainly women (59.9%) and with a mean age of 76.4±6.5 years.[15 25–27] Two studies used GAL, one RIV and one 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 online 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% to 34%, p<0.0001; I^2=95%; table 1).[15 26] In contrast, 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 studies included for each outcome.

Open-label trials reporting on nutritional parameters

The 12 open-label trials correspondent to 13 cohorts followed 5730 patients with dementia, with a mean age of 76.0 ±7.0 years and mainly women for a median of 6 months (see online supplementary table S2).[28–39] The mean duration of the disease was 4.2±3.1 years. Seven studies used RIV, five DZP and one all the AChEIs together. The mean baseline MMSE was 16.4±3.7, while the comparison with the follow-up values was not possible due to limited data availability for this outcome (eight studies did not report the MMSE value at the follow-up, four as a change and one as an 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; see online supplementary tables S2 and S4).

Regarding nutritional parameters, 12 cohorts reported a higher proportion of participants with weight loss during the follow-up period in those taking AChEIs (6%; 95% CI 4% to 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 τ (−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 two parameters (table 1).[31]

RCTs reporting data on weight loss

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

As reported in online supplementary table S3, 4311 patients with dementia treated with AChEIs (five studies: GAL; two: DZP; two: RIV) were compared with 2699 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 more women were present than men. The baseline MMSE score was 17.1

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

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

Bold values represent significant results (p<0.05).
*Event rate.
†Standardised mean difference.
BMI, body mass index; MNA, mini-nutritional assessment.

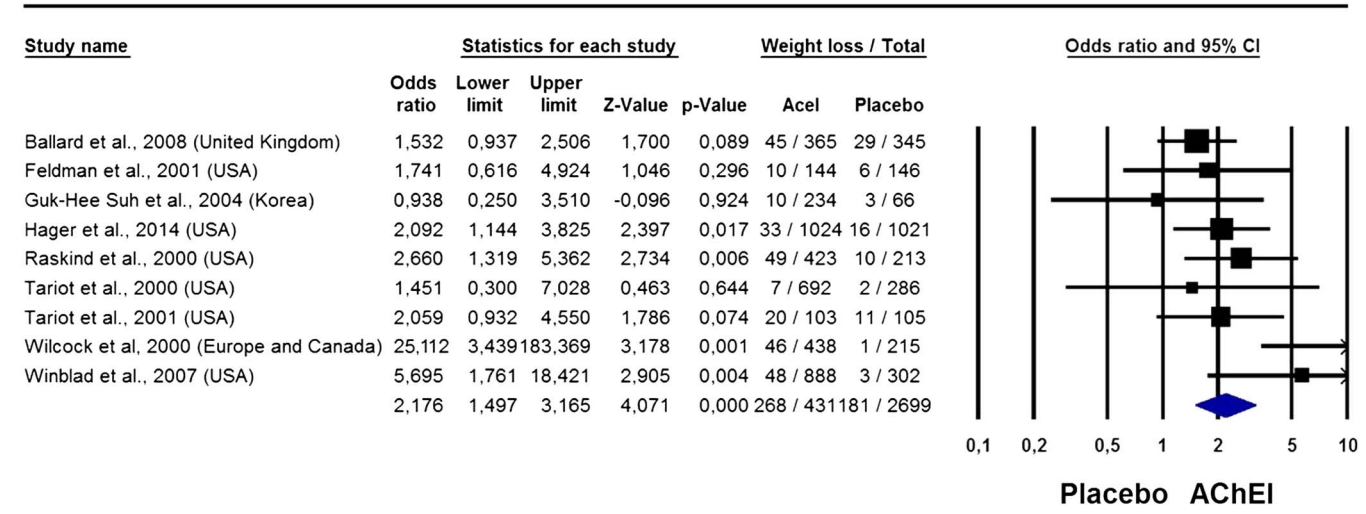

Figure 1 OR for weight loss in the acetylcholinesterasic inhibitors (AChEI) group versus placebo in randomised controlled trials.

±2.6 and 17.0±2.6 in the treated and placebo groups, 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 scale, was rated as good for seven and low for the other two (see online supplementary tables S3 and S5). For these studies, the most common source of possible bias was the lack of data about dropouts and withdrawals, as shown in online supplementary table S5.

As reported in figure 1, 6% (268/4311) in those taking AChEI and 3% (81/2699) in those taking placebo reported a weight loss/decrease leading to a twofold increased risk of weight loss (OR=2.18; 95% CI 1.50 to 3.17, p<0.0001; I^2=29%). There was no evidence of publication bias as shown by Kendall's τ (0.14; p=0.60) or Egger's test (slope=1.35 ±1.01; p=0.22).

Metaregression analysis

In the metaregression 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 RCTs.

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).

DISCUSSION

In this meta-analysis including 25 studies and 10 792 patients with dementia, we found that participants taking AChEIs experienced an increased risk of weight loss (compared with baseline in longitudinal and open-label trials, and vs placebo in RCTs). We observed that no other significant differences in nutritional parameters were evident, but there was a paucity of studies considering other outcomes. Our meta-analysis from nine 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 the best of 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 the 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 a decreased 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 participants, and this problem seems to be relevant since it is strongly related to cognitive decline, progress of the disease, institutionalisation, 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

Table 2 Strata for ORs for weight loss in RCTs and open-label trials

Moderator	Strata	Analysis details	Open label (event rate)	RCTs (ORs)
Continent	North America	*Pooled estimate*, estimate (95% CI)	**0.05 (0.04 to 0.07)**	**2.40 (1.67 to 3.46)**
		p Value for estimate	<0.0001	<0.0001
		Heterogeneity, I^2 (p value)	78% (<0.0001)	0% (0.56)
		Number of studies	8	5
	Europe and Asia	*Pooled estimate*, estimate (95% CI)	**0.07 (0.05 to 0.11)**	1.44 (0.91 **to** 2.29)
		p Value for estimate	<0.0001	0.12
		Heterogeneity, I^2 (p value)	61% (0.08)	0% (0.49)
		Number of studies	3	2
	Multicontinent	*Pooled estimate*, estimate (95% CI)	**0.05 (0.03 to 0.07)**	5.75 (0.43 to 77.5)
		p Value for estimate	<0.0001	0.19
		Heterogeneity, I^2 (p value)	–	82% (0.02)
		Number of studies	1	2
		p Value*	0.33	0.17
Type of drug	DZP	*Pooled estimate*, estimate (95% CI)	**0.05 (0.03 to 0.08)**	**1.94 (1.03 to 3.36)**
		p Value for estimate	<0.0001	<0.0001
		Heterogeneity, I^2 (p value)	88% (<0.0001)	0% (0.80)
		Number of studies	5	2
	GAL	*Pooled estimate*, estimate (95% CI)	No studies available	**2.35 (1.21 to 4.56)**
		p Value for estimate		0.01
		Heterogeneity, I^2 (p value)		49% (0.10)
		Number of studies		5
	RIV	*Pooled estimate*, estimate (95% CI)	**0.06 (0.05 to 0.08)**	2.64 (0.74 **to** 9.38)
		p Value for estimate	<0.0001	0.13
		Heterogeneity, I^2 (p value)	45% (0.09)	75% (0.04)
		Number of studies	7	2
	All drugs	*Pooled estimate*, estimate (95% CI)	**0.01 (0.00 to 0.07)**	No studies available
		p Value for estimate	<0.0001	
		Heterogeneity, I^2 (p value)	–	
		Number of studies	1	
		p Value*	0.10	0.87
Type of dementia	AD	*Pooled estimate*, estimate (95% CI)	**0.05 (0.04 to 0.07)**	**2.40 (1.56 to 3.70)**
		p Value for estimate	<0.0001	<0.0001
		Heterogeneity, I^2 (p value)	80% (<0.0001)	33% (0.16)
		Number of studies	11	8
	Others	*Pooled estimated*, estimate (95% CI)	**0.08 (0.04 to 0.14)**	1.53 (0.94 **to** 2.51)
		p Value for estimate	<0.0001	0.09
		Heterogeneity, I^2 (p value)	–	–
		Number of studies	1	1
		p Value*	0.33	0.18
Follow-up duration†	Short	*Pooled estimate*, estimate (95% CI)	**0.06 (0.04 to 0.08)**	1.84 (0.93 **to** 3.63)
		p Value for estimate	<0.0001	0.08
		Heterogeneity, I^2 (p value)	80% (<0.0001)	41% (0.17)
		Number of studies	7	4
	Long	*Pooled estimate*, estimate (95% CI)	**0.06 (0.04 to 0.08)**	**2.55 (1.52 to 3.70)**
		p Value for estimate	<0.0001	<0.0001
		Heterogeneity, I^2 (p value)	81% (<0.0001)	35% (0.19)
		Number of studies	5	5
		p Value*	1.00	0.50
Quality‡	Low	*Pooled estimate*, estimate (95% CI)	**0.05 (0.04 to 0.07)**	2.37 (0.41 **to** 13.89)
		p Value for estimate	<0.0001	0.34
		Heterogeneity, I^2 (p value)	78% (<0.0001)	75% (0.05)
		Number of studies	8	2
	High	*Pooled estimate*, estimate (95% CI)	**0.07 (0.05 to 0.10)**	**2.09 (1.45 to 3.00)**
		p Value for estimate	<0.0001	<0.0001
		Heterogeneity, I^2 (p value)	50% (0.11)	27% (0.22)
		Number of studies	4	7
		p Value*	0.23	0.89

Bold values represent significant results (p<0.05).
*p Value for the interaction across strata.
†Follow-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.
‡Quality: for open-label studies, low quality was defined as eNOS≤5 and high >5; for RCTs, low quality was defined as a Jadad score<3 points; high as ≥3 points.
AD, Alzheimer's disease; CI, confidence interval; DZP, donepezil; GAL, galantamine; NOS, Newcastle-Ottawa Scale; RCT, randomised controlled trial; RIV, rivastigmine.

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] However, these medications frequently cause weight loss by increasing cholinergic activity in the gastrointestinal system and nausea, vomiting and diarrhoea.[53] Therefore, our meta-analysis sheds light on an important topic within which the data were 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 with 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 losing weight was double in those treated with AChEIs compared with those treated with placebo. However, the incidence in both groups was 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 the aforementioned mechanisms by inhibiting butyrylcholinesterase as well as acetylcholinesterase as previously reported.[15] Another reason might be that transdermal RIV 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 medications.

Although our meta-analysis is the first to explore 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 little information exists in nutritional parameters, other than weight loss. 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 the 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 versus patch formulations of AChEIs, but it could be important 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.

CONCLUSION

The treatment with AChEIs is associated with a significant risk of weight loss in patients with dementia in the elderly. Data from nine RCTs found that people taking AChEIs are two times more likely to experience weight loss than in those in the placebo group. In the light of our findings, when prescribing AChEIs, people in clinical practice should routinely monitor nutritional status in patients with dementia. Further studies are required to compare the relative risk and benefit of different AChEIs medications taking in consideration other nutritional parameters.

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REFERENCES

1 Orsitto G. Different components of nutritional status in older inpatients with cognitive impairment. *J Nutr Health Aging* 2012;16:468–71.
2 Naseer M, Forssell H, Fagerström C. Malnutrition, functional ability and mortality among older people aged ⩾60 years: a 7-year longitudinal study. *Eur J Clin Nutr* 2016;70:399–404.
3 Sergi G, De Rui M, Coin A, *et al*. Weight loss and Alzheimer's disease: temporal and aetiologic connections. *Proc Nutr Soc* 2013;72:160–5.
4 Uwano C, Suzuki M, Aikawa T, *et al*. Rivastigmine dermal patch solves eating problems in an individual with advanced Alzheimer's disease. *J Am Geriatr Soc* 2012;60:1979–80.
5 Schofield PW, Finnie S, Yong YM. The role of olfactory challenge tests in incipient dementia and clinical trial design. *Curr Neurol Neurosci Rep* 2014;14:479.
6 Volkert D, Chourdakis M, Faxen-Irving G, *et al*. ESPEN guidelines on nutrition in dementia. *Clin Nutr* 2015;34:1052–73.
7 Claggett MS. Nutritional factors relevant to Alzheimer's disease. *J Am Diet Assoc* 1989; 89:392–6.
8 Khater MS, Abouelezz NF. Nutritional status in older adults with mild cognitive impairment living in elderly homes in Cairo, Egypt. *J Nutr Health Aging* 2011;15:104–8.
9 Roqué M, Salvà A, Vellas B. Malnutrition in community-dwelling adults with dementia (NutriAlz Trial). *J Nutr Health Aging* 2013;17:295–9.
10 Vellas B, Lauque S, Gillette-Guyonnet S, *et al*. Impact of nutritional status on the evolution of Alzheimer's disease and on response to acetylcholinesterase inhibitor treatment. *J Nutr Health Aging* 2005;9:75–80.
11 Guerin O, Soto ME, Brocker P, *et al*. Nutritional status assessment during Alzheimer's disease: results after one year (the REAL French Study Group). *J Nutr Health Aging* 2005;9:81–4.
12 Lam B, Hollingdrake E, Kennedy JL, *et al*. Cholinesterase inhibitors in Alzheimer's disease and Lewy body spectrum disorders: the emerging pharmacogenetic story. *Hum Genomics* 2009; 4:91–106.
13 Samochocki M, Höffle A, Fehrenbacher A, *et al*. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. *J Pharmacol Exp Ther* 2003;305:1024–36.
14 Droogsma E, van Asselt DZB, van Steijn JHM, *et al*. Effect of long-term treatment with galantamine on weight of patients with Alzheimer's dementia. *J Nutr Health Aging* 2013;17:461–5.
15 Soysal P, Isik AT. Effects of acetylcholinesterase inhibitors on nutritional status in elderly patients with dementia: a 6-month follow-up study. *J Nutr Health Aging* 2016;20:398–403.

16 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61:344–9.
17 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
18 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2012.
19 Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
20 Jadad AR. The merits of measuring the quality of clinical trials: is it becoming a Byzantine discussion? *Transpl Int* 2009;22:1028.
21 Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
22 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
23 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
24 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
25 Schmidt R, Lechner A, Petrovic K. Rivastigmine in outpatient services: experience of 114 neurologists in Austria. *Int Clin Psychopharmacol* 2002;17:81–5.
26 Thavichachart N, Phanthumchinda K, Chankrachang S, *et al*. Efficacy study of galantamine in possible Alzheimer's disease with or without cerebrovascular disease and vascular dementia in Thai patients: a slow-titration regimen. *Int J Clin Pract* 2006;60:533–40.
27 Wattmo C, Jedenius E, Blennow K, *et al*. Dose and plasma concentration of galantamine in Alzheimer's disease—clinical application. *Alzheimers Res Ther* 2013;5:2.
28 Bullock R, Touchon J, Bergman H, *et al*. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin* 2005;21:1317–27.
29 Cumbo E, Ligori LD. Differential effects of current specific treatments on behavioral and psychological symptoms in patients with Alzheimer's disease: a 12-month, randomized, open-label trial. *J Alzheimers Dis* 2014;39:477–85.
30 Cummings J, Froelich L, Black SE, *et al*. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm^2) in Alzheimer's disease. Dement Geriatr Cogn Disord 2012;33:341–53.
31 D'Onofrio G, Sancarlo D, Addante F, *et al*. A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2015;30:965–75.
32 Doody RS, Corey-Bloom J, Zhang R, *et al*. Safety and tolerability of donepezil at doses up to 20 mg/day: results from a pilot study in patients with Alzheimer's disease. *Drugs Aging* 2008;25:163–74.
33 Farlow MR, Salloway S, Tariot PN, *et al*. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. *Clin Ther* 2010;32:1234–51.
34 Farlow MR, Grossberg GT, Sadowsky CH, *et al*. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. *CNS Neurosci Ther* 2013;19:745–52.
35 Farlow MR, Sadowsky CH, Velting DM, *et al*. Evaluating response to high-dose 13.3 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease. *CNS Neurosci Ther* 2015;21:513–19.
36 Figiel GS, Koumaras B, Meng X, *et al*. Long-term safety and tolerability of rivastigmine in patients with Alzheimer's disease switched from donepezil: an open-label extension study. *Prim Care Companion J Clin Psychiatry* 2008;10:363–7.
37 Potkin SG, Alva G, Gunay I, *et al*. A pilot study evaluating the efficacy and safety of rivastigmine in patients with mixed dementia. *Drugs Aging* 2006;23:241–9.
38 Relkin NR, Reichman WE, Orazem J, *et al*. A large, community-based, open-label trial of donepezil in the treatment of Alzheimer's disease. *Dement Geriatr Cogn Disord* 2003;16:15–24.
39 Rockwood K, Black S, Bedard MA, *et al*. Specific symptomatic changes following donepezil treatment of Alzheimer's disease: a multi-centre, primary care, open-label study. *Int J Geriatr Psychiatry* 2007;22:312–19.
40 Ballard C, Sauter M, Scheltens P, *et al*. Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantagE study. *Curr Med Res Opin* 2008;24:2561–74.
41 Winblad B, Cummings J, Andreasen N, *et al*. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule. *Int J Geriatr Psychiatry* 2007;22:456–67.
42 Feldman H, Gauthier S, Hecker J, *et al*. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001;57:613–20.
43 Suh GH, Yeon Jung H, Uk Lee C, *et al*. A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. *Clin Ther* 2004;26:1608–18.
44 Hager K, Baseman AS, Nye JS, *et al*. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. *Neuropsychiatr Dis Treat* 2014;10:391–401.
45 Raskind MA, Peskind ER, Wessel T, *et al*. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000;54:2261–8.
46 Tariot PN, Pierre N. Tariot M, *et al*. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* 2001;49:1590–9.
47 Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *BMJ* 2000;321:1445–9.
48 Tariot PN, Solomon PR, Morris JC, *et al*. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;54:2269–76.
49 Brownie S. Why are elderly individuals at risk of nutritional deficiency? *Int J Nurs Pract* 2006;12:110–18.
50 Brooke J, Ojo O. Enteral nutrition in dementia: a systematic review. *Nutrients* 2015;7:2456–68.
51 Dando R, Roper SD. Acetylcholine is released from taste cells, enhancing taste signalling. *J Physiol (Lond)* 2012;590 13):3009–17.
52 Jia YX, Li JQ, Matsui T, *et al*. Neurochemical regulation of swallowing reflex in guinea pigs. *Geriatr Gerontol Int* 2001;1:56–61.
53 Stewart JT, Gorelik AR. Involuntary weight loss associated with cholinesterase inhibitors in dementia. *J Am Geriatr Soc* 2006;54:1013–14.
54 Droogsma E, van Asselt D, De Deyn PP. Weight loss and undernutrition in community-dwelling patients with Alzheimer's dementia: From population based studies to clinical management. *Zeitschrift Gerontol Geriatr* 2015;48:318–24.
55 Sadowsky CH, Micca JL, Grossberg GT, *et al*. Rivastigmine from capsules to patch: therapeutic advances in the management of Alzheimer's disease and Parkinson's disease dementia. *Prim Care Companion CNS Disord* 2014;16(5).