Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial

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SUMMARY

Objectives Doubt over the cost-effectiveness of the cholinesterase inhibitors in dementia has renewed interest in alternative treatments such as Ginkgo biloba. We aimed to determine the effectiveness and the safety profile of Ginkgo biloba for treating early stage dementia in a community setting.

Methods We conducted a community-based, pragmatic, randomised, double-blind, parallel-group trial where participants were given a standardised extract of Ginkgo biloba (120 mg daily) or a placebo control for 6 months. Our primary outcomes were cognitive functioning (ADAS-Cog) and participant and carer-rated quality of life (QOL-AD).

Results We recruited 176 participants, mainly through general practices. In the ANCOVA model with baseline score as a co-variate (n = 176), Ginkgo did not have a significant effect on outcome at six months on either the ADAS-Cog score (p = 0.392), the participant-rated QOL-AD score (p = 0.787) nor the carer-rated QOL-AD score (p = 0.222).

Conclusion We found no evidence that a standard dose of high purity Ginkgo biloba confers benefit in mild-moderate dementia over 6 months. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — Ginkgo biloba; Alzheimer disease; vascular dementia; randomised controlled trials

BACKGROUND

Current prescribing guidelines from the National Institute for Health and Clinical Excellence (2006) severely restrict the use of cholinesterase inhibitors (AChls). Safe, inexpensive and effective alternatives are needed for treating dementia and there is much interest in the use of the herbal medicine Ginkgo (McCarney and Warner, 2007). The benefit of Ginkgo however remains unclear. A recent Cochrane review (Birks et al., 2002), concluded that while a small effect is suggested the evidence is inconsistent. The null hypothesis was that compared to placebo, Ginkgo biloba taken for 6 months by community-dwelling individuals with mild to moderate dementia has no effect on cognitive functioning and the participant’s quality of life.

METHODS

We conducted a community-based, pragmatic, randomised, double-blind, parallel-group trial where participants were given a standardised extract of Ginkgo biloba (120 mg daily) or a placebo control for 6 months. We were interested in the effect of Ginkgo vs placebo, which is reported here, but also attempted to quantify the ‘Hawthorne effect’ (effect of trial
thought to be the active principles in the extract. To facilitate blinding, the lactose-based placebo were
identically packaged and labelled, physically indistinguishable tablets containing traces of quinine
hydrochloride to mimic the bitter taste of Ginkgo. A placebo such as this had been used before (van Dongen
et al., 2000). The trial medication was manufactured in accordance with European Union Standards and pur-
chased from Schwabe Pharma (Willmar-Schwabe-Str. 4, 76227 Karlsruhe, Germany), who certified its purity.
Both treatments were supplied in blister packs marked with the days of the week. Participants were
requested to take one 60 mg tablet twice a day for a total daily dose of 120 mg over the 6 months of
follow-up.

Follow-up
In order to assess the Hawthorne effect, participants were randomised to standard follow-up (with visits at
baseline and 2, 4 and 6 months post randomisation) or minimal follow-up (with an abbreviated assessment at
baseline and a full assessment at 6 months). We conducted the assessments in the participant’s or their
carer’s home (see Table 1).

Outcomes
The primary outcome measures were: (i) cognitive functioning, as measured by the ADAS-Cog (Rosen
et al., 1984), a 0–70 point scale with a higher score indicating worse cognition; and (ii) quality of life,
rated by the participant and their nominated carer, as measured by the QOL-AD (Logsdon et al., 1999).
Both 13-item scales, scoring between 13–52 points with a higher score indicating better quality of life.

Secondary outcome measures were: (i) psychopathology and the resulting distress to the carer,
as measured by the Neuro-Psychiatric Inventory with caregiver Distress scale (NPI-D) (Cummings
et al., 1994), a 12-item scale scoring 12–144 for psychopathology and 0–60 for caregiver distress;
(ii) caregiver-reported daily living and social behaviour score, as measured by the Geriatric Evaluation by
Relative’s Rating Instrument (GERRI) (Schwartz, 1983), a 49-item scale scored 1–5 for each item
and averaged for the overall score, a higher score indicating greater impairment; (iii) caregiver-reported
burden of caring as measures by the 12-item Zarit Burden Interview (ZBI) (Bedard et al., 2001), scoring
0–48 with a higher score indicating greater burden; (iv) a report of caregiver health, as measured by the
visual analogue scale of the European Quality of Life Visual Analogue Scale (EQ-VAS) (The EuroQol

Participants
We recruited participants in Greater London (UK) and adjoining regions through referrals from general
practices, old age psychiatrists and other health care professionals; and from direct responses to advertising
in Alzheimer Society newsletters, London-based newspapers, and posters in Age Concern centres. As
this was a pragmatic study, we recruited people with a clinical diagnosis of dementia made by the referring
clinician rather than diagnostic criteria such as the National Institute of Neurological and Communica-
tive Diseases and Stroke/ Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA)
(McKhann et al., 1984), which are unlikely to be used widely in clinical settings. Inclusion criteria were:
aged 55 years or over; presence of a carer; informed consent or if lacking capacity, their assent and the
agreement of their nominated carer; sufficient command of English; clinical diagnosis of dementia
(subsequently sub-classified using DSM-IV criteria) (American Psychiatric Association, 2000); a Mini
Mental State Examination (MMSE) (Folstein et al., 1975) score of 12–26 inclusive; living in the com-

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Group, 1990), scoring 0–100 with higher score indicating better health; (v) a caregiver-reported global measure of benefit, by asking at the final follow-up, 'If you could continue the medication the person you care for has been receiving in this trial, would you (do you feel that it has helped him/her)?’ (Answer: yes or no); (vi) blood coagulation times as measures by Activated Clotting Time (ACT) using near-patient testing with the Coaguchek Pro DM® (Roche Diagnostics, Germany).

All outcome measures, except the global measure, are previously validated tools (and in most cases commonly) used in dementia trials. All outcomes were administered by a trained researcher during a home visit. The ADAS-Cog was scored by the researcher; all other measures were scored by the participant or their carer.

The field researchers were given full training in the use of the instruments and regular reviews were held amongst the researchers to ensure consistency in scoring the ADAS-Cog.

In keeping with the pragmatic nature of the study, other interventions were allowed during the trial, but commencement of an AChI was grounds for withdrawal. Therefore some contamination of the interventions (through factors such as education, support from local voluntary organisations and undeclared use of Ginkgo or AChIs) was possible. To evaluate the impact of this, at each follow-up visit information about non-trial Ginkgo use and visits to secondary care services was sought. All changes in conventional treatments were recorded at the 6-month assessment.

Table 1. Administration of outcome measures

<table>
<thead>
<tr>
<th>Time point in study</th>
<th>Intensive follow-up group</th>
<th>Minimal follow-up group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Questionnaire</td>
<td>Subject*</td>
</tr>
<tr>
<td>Baseline</td>
<td>ADAS-Cog, QOL-AD, NPI-D,</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>EQ-5D, ZBI</td>
<td>Carer</td>
</tr>
<tr>
<td>2 months</td>
<td>ADAS-Cog, QOL-AD, NPI-D</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>EQ-5D, ZBI</td>
<td>Carer</td>
</tr>
<tr>
<td>4 months</td>
<td>ADAS-Cog, QOL-AD, NPI-D</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>EQ-5D, ZBI</td>
<td>Carer</td>
</tr>
<tr>
<td>End of study</td>
<td>ADAS-Cog, QOL-AD, NPI-D,</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>GERRI</td>
<td>Carer</td>
</tr>
</tbody>
</table>

*Subject denotes person assessed by measure. Some assessments are completed by the carer but reporting on the participant (e.g. GERRI and NPI-D). For measures such as this the participant is the subject.

Sample size

We calculated sample size for an analysable sample of 200 participants based on 80% power and a between-group difference of four points (on a 70-point scale) on the ADAS-Cog, which is the lower limit of what we would regard as clinically significant, with a SD of 11 points (Raskind et al., 2000) using a two-tailed significance level of 5%.

Randomisation procedure and blinding

A 2 × 2 factorial design with two separate randomisations, resulting in participants being randomised to one of four arms, was employed. Both factors consisted of two levels: medication group (Ginkgo and placebo); and level of follow-up (minimal or standard). This produced four groups: the Ginkgo group with standard follow-up, the Ginkgo group with minimal follow-up, the placebo group with standard follow-up and the placebo group with minimal follow-up. The randomisation codes were generated using the computer algorithm RCODE v.4.8 (Schwabe, 2002).

Study medication was randomised in blocks of two and blocks were allocated to a general practice when a participant was recruited from that practice. Participants were allocated a code on entry into the trial by the researcher. Researchers undertaking the analysis and the trial statistician remained blind until completion of the analysis defined in the analysis protocol. Participants, their carers and clinicians responsible for the participant (GPs and consultants) remained
blinded to the allocation during their participation. Participants were de-blinded in the event of a serious adverse event or once all participants in that block completed or withdrew from the study. The de-blindings were administered by members of the study team not directly involved in the evaluation and were concealed from assessors and statistician. Success of blinding was tested by asking the researcher undertaking assessments and the carer to indicate whether they believed the participant had been taking Ginkgo or placebo.

Statistical methods

The analyses reported here were all planned a priori and documented in an analysis protocol. The primary analysis was intention to treat (ITT), with individuals analysed in their randomisation group, irrespective of whether they completed the trial.

In order to adjust for baseline scores, when comparing the outcomes between the treatment groups, analysis of co-variance (ANCOVA) was used. Normal distributions were assumed for the ANCOVA analyses and were checked using residuals from the regression models. If data showed substantial deviations from these assumptions, appropriate transformations were used. Adjusted differences in means (β) are presented so that a positive β value favours Ginkgo and negative value favours placebo; with 95% Confidence Intervals (CI) and p-values. Where these assumptions were not met distribution-free statistical tests were employed. Interaction between treatment group and follow-up group was assessed.

To take account of missing data in the ITT analysis, missing baseline data were imputed using hot decking, where values were selected at random from donors amongst the non-missing data set that had similar values for the filter variables. The filter variable for ADAS-Cog score was the MMSE score and for all other variables were age, sex and randomisation group. For the 6-month data, multiple imputation techniques were used with five imputations using a predictive model based approach with ordinary least-squares regression; from a distribution using baseline score, follow-up group and treatment group. Standard analysis (ANCOVA) was used for each of the resulting data sets generated by the imputation process then combined using standard explicit formulae (Rubin and Schenker, 1991). All imputed data were assumed missing at random.

Adverse events were initially evaluated by clinicians in the study team (PF and JW) and were described and recorded by treatment group in line with ICH Good Clinical Practice guidelines (ICH, 1997). Serious events were referred to the IAB. The causal relationship to the trial medication, MedDRA disease classification and category of AE were also recorded.

Two further analyses were undertaken: an analysis using all evaluable (i.e. non-imputed) data available at 6 months only and a per-protocol analysis. The per-protocol analysis investigated the effect of adherence to the treatment on the primary outcome variables. To be included in this analysis, participants needed to have: completed the study; had relevant data collected (with no imputation for missing data); been followed-up at all time points (according to his or her allocation to minimal or standard follow-up); and taken 80% or more of allocated medication.

Planned sub-group analyses were conducted on individuals who: (i) were not taking AChIs during the trial and (ii) had never taken Ginkgo before.

The analysis was conducted using SPSS v.13 (SPSS Corporation, 2004) and STATA v.8.1 (STATA Corporation, 2003). The multiple imputation analysis was conducted using SOLAS v.3.2 (Statistical Solutions Ltd, 2001).

RESULTS

Figure 1 details participant flow through the trial. Recruitment took place between February 2003 and June 2005. Baseline demographic and clinical characteristics are presented in Table 2. A total of 119 GP practices agreed to recruit participants for the trial (representing 388 individual GPs). One hundred and thirty-two participants (75%) were recruited through their GP; 29 (16%) through psychiatrists and 15 (9%) from other sources (mainly other health professionals and advertisements). All analyses are reported so that a positive value favours Ginkgo and a negative value favours placebo, irrespective of the way the scale is scored.

ITT analysis

There was no significant interaction between the two factors of treatment group and level of follow-up. In the ANCOVA model with baseline score as a co-variate (n = 176), compared to placebo, Ginkgo did not have a significant effect on outcome at 6 months on either the ADAS-Cog score (adjusted mean difference β = −0.823; 95% CI −2.701, 1.055; p = 0.392), the participant-rated QOL-AD score (β = −0.187; 95% CI −1.542, 1.168; p = 0.787) nor the carer-rated QOL-AD score (β = −0.981; 95% CI −2.551, 0.589; p = 0.222).
Analysis with evaluable data

Treatment group did not have a significant effect on outcome at 6 months on either the ADAS-Cog score \((n = 140; \beta = -0.608; 95\% CI -2.609, 1.393; p = 0.549)\), the participant-rated QOL-AD score \((n = 142; \beta = -0.431; 95\% CI -1.717, 0.856; p = 0.509)\) nor the carer-rated QOL-AD score \((n = 131; \beta = -0.963; 95\% CI -2.597, 0.670; p = 0.245)\).

Per protocol analysis

Treatment group did not have a significant effect on outcome at 6 months on either the ADAS-Cog score \((n = 104; \beta = -1.583; 95\% CI -3.972, 0.807; p = 0.192)\), the carer-rated QOL-AD score \((n = 97; \beta = 0.077; 95\% CI -1.667, 1.820; p = 0.931)\) nor the participant QOL-AD score \((n = 103; \beta = -0.652; 95\% CI -2.219, 0.916; p = 0.411)\).

Sub-group analyses

Sub-group analyses were conducted using participants who were not on an AChI at baseline \((n = 118)\); and on those who had never taken Ginkgo before \((n = 135)\). No significant differences emerged (data not shown). The ITT analyses are only reported here.

Analysis of ADAS-Cog score amongst those not on an AChI showed there was no significant effect of treatment group using imputed data \((\beta = -0.095; 95\% CI -2.481, 2.291; p = 0.938)\). Neither was there a significant effect of treatment group on carer-rated QOL-AD \((\beta = -0.7656; 95\% CI -2.854, 1.323; p = 0.474)\); or on participant-rated QOL-AD \((\beta = -0.363; 95\% CI -1.981, 1.255; p = 0.661)\).

Amongst participants who had never taken Ginkgo before \((n = 135)\), there was no significant effect of treatment group on ADAS-Cog score \((\beta = -1.306; 95\% CI -3.785, 1.736; p = 0.304)\); carer-rated QOL-AD score \((\beta = -0.5708; 95\% CI -2.547, 1.405; p = 0.572)\); or participant-rated QOL-AD \((\beta = -0.983; 95\% CI -2.483, 0.518; p = 0.202)\).

Secondary outcomes

Global outcome, as judged by the carer in response to the question on whether they would continue with the treatment, was not found to be significantly related to treatment group (number who said ‘yes’ in

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Excluded (n=470)
- Age (n=5)
- Bleeding abnormalities (n=2)
- Blood coagulation times (n=3)
- Concomitant illness (n=22)
- Cough didn’t arrange assessment during recruitment (n=16)
- Current Warfarin therapy (n=12)
- English language ability (n=3)
- Continued Ginkgo use (n=13)
- MMSE score <12 (n=20)
- MMSE score >26 (n=79)
- No carer (n=15)
- Non-consent of carer (n=112)
- Non-consent of GP (n=1)
- Non-consent of potential participant (n=151)
- Outside catchment area (n=1)
- Potential participant died before interview (n=11)
- Uncontactable (n=11)
the placebo group was 36 (51%) and 29 (43%) in the Ginkgo group; \( \chi^2 = 0.911; \) df = 1; \( p = 0.340 \). Further secondary outcomes are detailed in Table 3.

**Blinding**

Of those carers followed up at 6 months who responded to the question on blinding, approximately half declined to guess whether their care-recipient received Ginkgo or placebo during the trial (\( n = 66; 49\% \)). For the remainder (\( n = 69; 51\% \), blinding was effective \( \kappa = 0.18; \) \( p = 0.115 \). The researchers were also effectively blinded: of the 129 evaluable cases the researcher did not hazard a guess in approximately half (\( n = 62 \)) and the level of agreement in the remaining 67 was poor \( \kappa = 0.081; \) \( p = 0.462 \).

**Safety (adverse events and coagulation times)**

A total of 63 adverse events were recorded by 57 of the participants (the greatest number reported by any one individual was three). Of these, 29 were in the placebo...
There was one fatal cerebral haemorrhage in the Ginkgo group, this was the subject of an emergency code break and was referred to the IAB, who considered that it did not justify terminating the trial. Table 4 details the MedDRA classifications of the adverse events by treatment group.

There was no significant difference in clotting time at six months for participants who adhered to the treatment regime and had evaluable data ($n = 93; \beta = 1.843; 95\% \text{ CI } -0.488, 4.133; \text{ } p = 0.113$).

### DISCUSSION

We found no evidence that a standard dose (120 mg daily) of high purity Ginkgo biloba conferred benefit in mild-moderate dementia over 6 months. The only significant findings (analysis with evaluable data and per protocol analysis of carer-rated function, as measured by the GERRI) favoured the placebo group. The mean difference found between the groups on the GERRI was 0.12 points, which is unlikely to be clinically significant (Erkinjuntti et al., 2002).

This study was conducted independently of the pharmaceutical industry and funded by a National charity. Studies funded by the pharmaceutical industry generally show larger effect sizes compared with independent studies (Lexchin et al., 2003; Perlis et al., 2005). Strengths of this study include the use of a placebo laced with quinine, to reduce the risk of de-blinding; and standardised outcome measures to allow a direct comparison with other dementia trials.

Our results suggest that Ginkgo is ineffective in this context. There are alternative explanations for our findings, although we consider them to be improbable. Because of the recruitment shortfall, type II error is a possibility but unlikely. There was no apparent trend in our results (the non-significant differences mostly favoured placebo) and we consider this study to have had sufficient power to reliably detect any clinically significant differences.

### Table 3. Adjusted difference in means for primary and secondary outcomes

<table>
<thead>
<tr>
<th>Measure</th>
<th>N</th>
<th>Adjusted difference in means (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog$^2$</td>
<td>176</td>
<td>$-0.823 (-2.701, 1.055)$</td>
<td>0.392</td>
</tr>
<tr>
<td>Participant-rated QOL-AD$^2$</td>
<td>176</td>
<td>$-0.187 (-1.542, 1.168)$</td>
<td>0.787</td>
</tr>
<tr>
<td>Carer-rated QOL-AD$^2$</td>
<td>176</td>
<td>$-0.981 (-2.551, 0.589)$</td>
<td>0.222</td>
</tr>
<tr>
<td>NPI$^3$</td>
<td>88$^3$</td>
<td>$-4.512 (-9.176, 0.152)$</td>
<td>0.061</td>
</tr>
<tr>
<td>NPI-D$^3$</td>
<td>88$^3$</td>
<td>$-2.364 (-5.325, 0.597)$</td>
<td>0.121</td>
</tr>
<tr>
<td>GERRI$^4$</td>
<td>88$^4$</td>
<td>$-0.119 (-0.241, 0.003)$</td>
<td>0.060</td>
</tr>
<tr>
<td>ZBI$^5$</td>
<td>176</td>
<td>$-0.017 (-2.463, 2.429)$</td>
<td>0.989</td>
</tr>
<tr>
<td>EQ-VAS$^2$</td>
<td>176</td>
<td>$-1.6715 (-5.922, 2.579)$</td>
<td>0.442</td>
</tr>
</tbody>
</table>

$^1$Positive values favour Ginkgo.
$^2$No significant differences were found in the analyses with evaluable data or in the per-protocol analyses.
$^3$Outcome measure administered at baseline in standard follow-up group only.
$^4$Significant difference found in the analysis with evaluable data ($n = 75; \beta = 0.142; 95\% \text{ CI } 0.027, 0.257; \text{ } p = 0.016$) and in the per protocol analysis ($n = 51; \beta = 0.156; 95\% \text{ CI } 0.033, 0.279; \text{ } p = 0.014$); in both cases, it indicates a more favourable outcome in the placebo group.

Group and 28 were in the Ginkgo group. There was one fatal cerebral haemorrhage in the Ginkgo group, this was the subject of an emergency code break and was referred to the IAB, who considered that it did not justify terminating the trial. Table 4 details the MedDRA classifications of the adverse events by treatment group.

There was no significant difference in clotting time at six months for participants who adhered to the treatment regime and had evaluable data ($n = 93; \beta = 1.843; 95\% \text{ CI } -0.488, 4.133; \text{ } p = 0.113$).

### Table 4. MedDRA classification of the adverse events by treatment group

<table>
<thead>
<tr>
<th>MedDRA category</th>
<th>Placebo group</th>
<th></th>
<th></th>
<th>Ginkgo group</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Serious</td>
<td>Total</td>
<td></td>
<td>Serious</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>006 Infections and infestations</td>
<td>1</td>
<td>2</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>008 Blood and lymphatic system</td>
<td>0</td>
<td>2</td>
<td></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>011 Metabolism and nutrition</td>
<td>1</td>
<td>1</td>
<td></td>
<td>0</td>
<td>2</td>
<td></td>
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<tr>
<td>012 Psychiatric</td>
<td>1</td>
<td>5</td>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>013 Nervous system</td>
<td>0</td>
<td>5</td>
<td></td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>015 Ear and labyrinth</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>016 Cardiac</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
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<tr>
<td>017 Vascular</td>
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<td>0</td>
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<td>018 Respiratory, thoracic and mediastinal</td>
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<td>4</td>
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<td></td>
</tr>
<tr>
<td>019 Gastrointestinal</td>
<td>1</td>
<td>5</td>
<td></td>
<td>0</td>
<td>7</td>
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<tr>
<td>020 Hepatobiliary</td>
<td>1</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>021 Skin and subcutaneous tissue</td>
<td>1</td>
<td>3</td>
<td></td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>022 Musculoskeletal and connective tissue</td>
<td>0</td>
<td>2</td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
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<tr>
<td>023 Renal and urinary</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>025 Reproductive system and breast</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Grand total</td>
<td>8</td>
<td>33</td>
<td></td>
<td>8</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

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differences: the sample size we achieved would have detected a difference of 6 points on the ADAS-cog with over 90% power. The differences in baseline ADAS-Cog scores between the treatment groups were due to chance as the trial was randomised and fully concealed. All analyses took account of these differences in baseline score between groups. While it would have been of interest to conduct sub-group analyses looking at for example diagnosis, the study was not powered to do so.

In this study, we only recruited participants who were able to read and write English and this may have introduced sampling bias and undermined the representativeness of the study. It was difficult to control for this however as there were no validated versions of the questionnaires used available in the languages needed. Another possible source of sampling bias is the geographical limitations of our catchment area. In general however our sample’s baseline demographics do seem similar to data presented from other dementia trials and our catchment area included a population of around 15,000,000 (ONS, 2005). The heterogeneity of the sample is a hallmark of pragmatic clinical trial design (Gartlehner et al., 2006).

The importance of early intervention in the management of dementia is clear and there is a need for a safe, effective treatment that could slow down the progression of dementia and that can be used at an early stage of the disease, in a community setting. This, combined with a desire among the public to embrace complementary and alternative therapies explains the enduring interest in Ginkgo. However we are not sure whether this interest is warranted. Although Ginkgo appears safe in use we found no evidence that it provides a clinically significant benefit and we do not recommend its use in routine dementia care.

CONFLICT OF INTEREST

Robbert van Haselen provided some consultancy services to Schwabe Pharma in 2005, unrelated to this research. All the other authors have no conflicts of interest.

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