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Ginkgo biloba in Alzheimer's disease: a systematic review

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Ginkgo biloba bei Alzheimer Demenz: eine systematische Übersicht

Zusammenfassung. Diese systematische Übersicht untersucht den Nutzen von Ginkgo biloba (Ginkgo) bei Alzheimer Demenz hinsichtlich patientenrelevanter Endpunkte. Dazu wurden elektronische Datenbanken und Studienregister nach randomisiert kontrollierten Studien durchsucht, die einen Vergleich von Ginkgo und Plazebo oder einer anderen Therapieoption untersuchten. Hersteller wurden um unveröffentlichte Daten gebeten. Die Ergebnisse sollten in einer Meta-Analyse zusammengefasst werden. 6 Studien waren relevant; insgesamt zeigte sich eine hohe Heterogenität in den meisten Endpunkten, mit Ausnahme der Ergebnisse zu unerwünschten Arzneimittelwirkungen. Bei Betrachtung der Studien mit einer hohen Dosierung von Ginkgo waren die Ergebnisse nach wie vor heterogen, allerdings zeigten hier alle Effekte einen Vorteil von Ginkgo. In dieser Gruppe zeigte sich für das Therapieziel „Aktivitäten des täglichen Lebens" ein Beleg; für „Kognition" und „begleitende Psychopathologie" ein Hinweis auf einen Nutzen. Ein Schaden durch Ginkgo war nicht erkennbar. Eine Abschätzung der Effektgröße für die Endpunkte war nicht möglich. Weitere Studien, insbesondere für Subgruppen der Alzheimer Demenz, sind notwendig.

Schlüsselwörter: Ginkgo biloba, EGb 761, Antidementiva, Alzheimer Demenz, systematische Übersicht

Summary. This systematic review determines the benefit of treatment with Ginkgo biloba (Ginkgo) in Alzheimer's disease (AD) concerning patient-relevant outcomes. Bibliographic databases, clinical trial and study result registries were searched for randomized controlled trials (RCTs) in patients with AD (follow-up ≥16 weeks) comparing Ginkgo to placebo or a different treatment option. Manufacturers were asked to provide unpublished data. If feasible, data were pooled by meta-analysis. Six studies were eligible; overall, high heterogeneity was shown for most outcomes, except safety aspects. Among studies administering high-dose Ginkgo (240 mg), all studies favour treatment though effects remain heterogeneous. In this subgroup, a benefit of Ginkgo exists for activities of daily living. Cognition and accompanying psychopathological symptoms show an indication of a benefit. A harm of Ginkgo is not evident. An estimation of the effect size was not possible for any outcome. Further evidence is needed which focuses especially on subgroups of AD patients.

Key words: Ginkgo biloba, EGb 761, anti-dementia drugs, Alzheimer's disease, systematic review

Introduction

With a proportion of 50–70%, Alzheimer's disease is the most common form of dementia. In Germany, the number of dementia patients is estimated to be 1 million; however, this might be an underestimation as mild cases might not be considered [1]. As this form of dementia is incurable and degenerative, the management of disease symptoms is essential. The aim of this systematic review was to evaluate the beneficial and harmful effects of a long-term treatment with Ginkgo biloba (Ginkgo) on patient-relevant outcomes in Alzheimer's disease (AD) within the German health care system. The review formed part of a health technology assessment (HTA) of Ginkgo biloba by the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG); for IQWiG's role within the German health care system as well as the general methodological approach see its method paper [2]. The full (German-language) report and protocol (Commission No. A05-19B) are available on the Institute's website [3].

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Material and methods

Eligibility criteria

We included both published and previously unpublished studies with the following characteristics:

- Randomised controlled design.
- Follow-up period $\geq$ 16 weeks, to be able to assess a long-term effect.
- Investigation of patients with mild, moderately severe and severe AD. Diagnosis had to be confirmed either by the criteria of the EMA or by commonly accepted ones such as ICD-9, ICD-10, DSM-II-R, DSM-IV or NINCDS-ADRDA.
- Comparison of Ginkgo with placebo or other medicinal or non-medicinal interventions.
- Evaluation of at least one predefined patient-relevant outcome. (In this context, the term "patient-relevant" refers to how a patient feels, functions or survives.) The following outcomes were considered: activities of daily living, cognitive functioning, psychopathology, quality of life and safety aspects.
- Language of publication: English, Dutch, French, German, Portuguese and Spanish.
- Availability of a full-text document (e.g., journal article or clinical study report). No restrictions applied for the date of publication.

Search strategy and study selection

We searched for relevant primary studies and secondary publications (systematic reviews and HTA reports) in MEDLINE (1966 to September 2007), EMBASE (1980 to September 2007), the Cochrane Library (Clinical Trials, September 2007) and CHID via ADEAR (October 2005). The search strategy included terms on dementia (especially AD) and Ginkgo (including trade names). The Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments) were searched for relevant secondary publications. The full search strategy, which was developed by one information specialist and checked by another, has been described elsewhere [3]. For this publication, a search update of all databases (except CHID via ADEAR due to unavailability) was performed in January 2010. We scrutinized the reference lists of the primary and secondary publications retrieved to identify further studies. In addition, clinical trial registries and study result databases available on the Internet were screened, as were the websites of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). In order to obtain the most complete data set possible, we also asked manufacturers of the drug under assessment to supply unpublished studies and additional unpublished data from published studies. As Ginkgo has been in the market for a long time, most manufacturers produce a generic drug. The original product was developed by the company Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, who exclusively sponsored clinical trials with Ginkgo biloba and was able to supply relevant unpublished data.

Two reviewers independently screened titles and abstracts of the retrieved citations to identify potentially eligible primary and secondary publications. The full texts of these articles were obtained and independently evaluated by the same 2 reviewers by applying the full set of inclusion and exclusion criteria. All documents retrieved from non-bibliographic sources were also screened for eligibility or relevant information on studies. Disagreements were resolved by consensus.

Data extraction

The individual steps of the data extraction and risk of bias assessment procedures were always conducted by one person and checked by another; disagreements were resolved by consensus. Details of the studies were extracted using standardized tables developed and routinely used by IQWiG. Information was extracted from each included study on: (1) study characteristics, including citation, study design, length of follow-up, sample size, location, number of centres and inclusion and exclusion criteria. (2) Characteristics of the study participants, including age, gender, Mini Mental State Examination (MMSE), Syndrom-Kurztest (SKT) and Neuropsychiatric Inventory (NPI) each at baseline. (3) Outcomes and type of outcome measures: outcomes as presented above; measurement tools as used in the individual studies. (4) Risk of bias items (see below). Information and data from publications were supplemented by unpublished clinical study reports (CSRs) provided by the company Schwabe.

Assessment of risk of bias

The risk of bias in individual studies was assessed by determining the adequacy of the following quality criteria: randomisation and allocation concealment, blinding of patients and investigators, sample size calculation, handling and reporting of study discontinuations, and application of the intention-to-treat

principle. Studies were then categorized as follows: "no deficiencies" (all quality criteria met); "minor deficiencies" (deficiencies do not challenge the main conclusion); and "major deficiencies" (deficiencies challenge the main conclusion).

Data analysis

For each considered outcome, standardised mean differences were calculated as studies reported different scales within the relevant endpoints. Heterogeneity among studies was estimated by I^2 and analysed using statistical tests on heterogeneity [4]. Meta-analysis using random effect models [5] was only intended for endpoints where no substantial heterogeneity ($p > 0.2$) was observed, otherwise, forest plots were used as a visual presentation of the results only. Sensitivity analyses were planned to explore heterogeneity (e.g. caused by differing methodological quality of studies and duration of treatment or dose). Subgroup analyses of gender, age, severity of dementia and presence of different concomitant diseases were also planned. All analyses were performed with SAS.

Results

Description of studies

A total of 16 relevant publications were identified from 1392 references retrieved from bibliographic databases (Fig. 1). Of the 7 studies included, 3 were supplemented by CSRs provided by the manufacturer. Two studies [6, 7] included in the meta-analysis were unpublished at the time of inclusion in the original report, they have been published in the mean time. Schwabe 2008 [8] is still unpublished. One study [6] conducted an exploratory head to head comparison of Ginkgo *vs.* Donepezil *vs.* placebo and was not included in this publication. Details on this study can be found in the original report.

Study characteristics

All six studies compare Ginkgo biloba extract EGb761 (Ginkgo) to placebo in a double-blind, parallel, multicentre, randomised controlled trial. The comparison of 240 mg Ginkgo with placebo was performed by Kanowski 1996 [9], Napryeyenko 2007 [10], Schneider

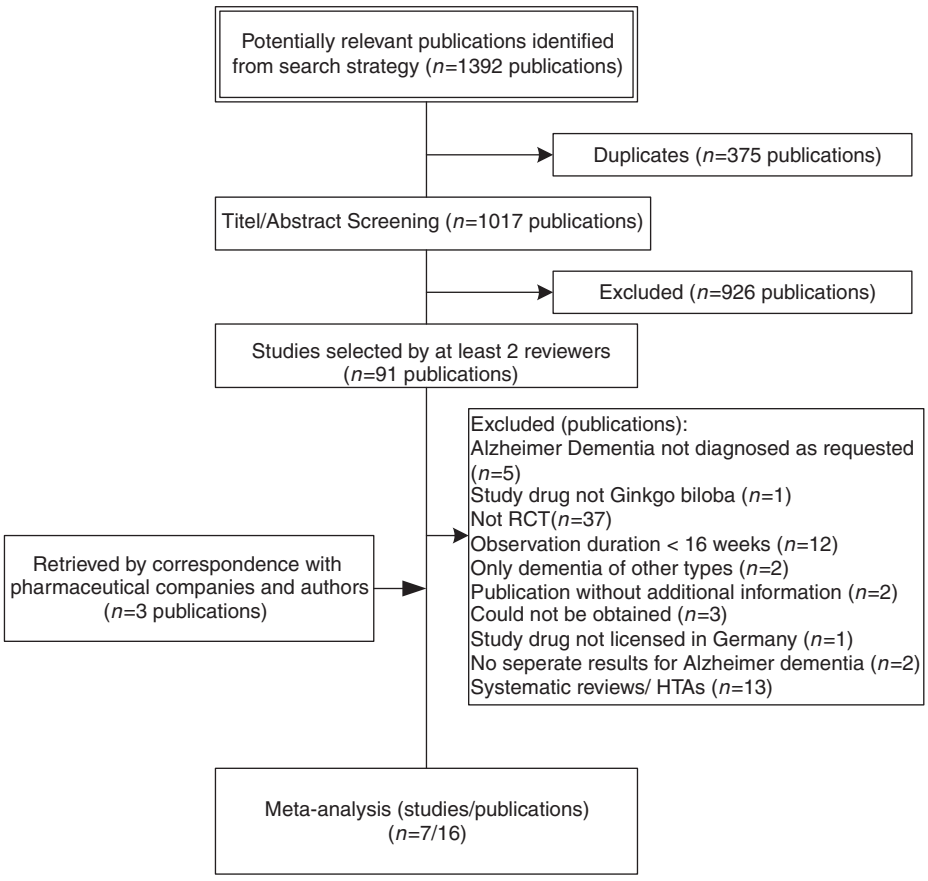

Fig. 1: Flow chart of study selection

2005 [11] and Schwabe 2008 [8]; McCarney 2007 [7] and Le Bars 1997 [12] only used the low dose of 120 mg Ginkgo. McCarney 2007 [7] used a 2 × 2 factorial design including different follow-up settings to assess the Hawthorne effect. The study duration ranged from 22 to 26 weeks, with exception of Le Bars 1997 with study duration of 52 weeks. However, an interim analysis at 26 weeks was also published and was used for reasons of comparability. All 6 studies either included AD patients only (Schneider 2005 [11]) or presented subgroup analyses for AD patients. McCarney 2007 [7] did not present a subgroup analysis; however, as the

Tab. 1: Study characteristics

Study/ country/ duration	Patients (AD patients) *N* randomised AD patients	Age (SD)	Gender (% female)	MMSE (SD)	SKT (SD)	NPI (SD)	Drop-outs (%)
McCarney 2007/GB/ 24 weeks	176 (148)[a] Gb 120 mg = 88 P = 88	79.3 (7.8) 79.7 (7.5)	58.0 63.6	23.0 (16.9; 26.0)[b] 22.0 (13.0; 25.1)[b]	–	11.0 (0.0; 28.5)[b,c] 9.0 (0.0; 29.2)[b,c]	28.4 22.7
Kanowski 1996/GER/ 24 weeks	216 (158) Gb 240 mg = 79 P = 79	72.0 (10.0) 72.0 (10.0)	70.9 73.4	21.5 (2.3) 21.6 (2.7)	10.3 (3.1) 10.9 (3.3)	–	14.8[d]
Le Bars 1997/USA/ 52 weeks	327 (251)[e] Gb 120 mg = 120 P = 116	68.0 (10.0) 68.0 (11.0)	54.2 62.1	21.1 (5.9) 21.3 (5.6)	–	–	53.0[d] 63.4[d]
Napryeyenko 2007/UKR/ 22 weeks	400 (218) Gb 240 mg = 106 P = 112	66.0 (8.0) 64.0 (8.0)	67.3 70.9	–	16.4 (3.8) 15.8 (3.8)	19.6 (8.4) 20.1 (8.6)	1.9 3.6
Schneider 2005/USA/ 26 weeks	Gb 120 mg = 169 Gb 240 mg = 170 P = 174	78.6 (7.0) 78.1 (7.0) 77.5 (7.4)	49.7 56.5 51.7	18.2 (4.1) 17.9 (4.0) 18.2 (4.1)	–	–	20.1 17.6 22.4
Schwabe 2008/UKR/ 24 weeks	410 (333) Gb 240 mg = 163 P = 170	65.0 (10.0) 65.0 (9.0)	68.8 65.8	–	16.7 (3.9) 17.2 (3.7)	16.7 (3.9) 17.2 (3.7)	7.8 5.9

AD Alzheimer's disease, *Gb* Ginkgo, *P* placebo; [a] no separate analysis for AD patients available; [b] median (10th and 90th percentile); [c] data for patients in intensive follow-up group only; [d] information only available for total study population (including vascular dementia); [e] 15 patients dropped out after randomisation.

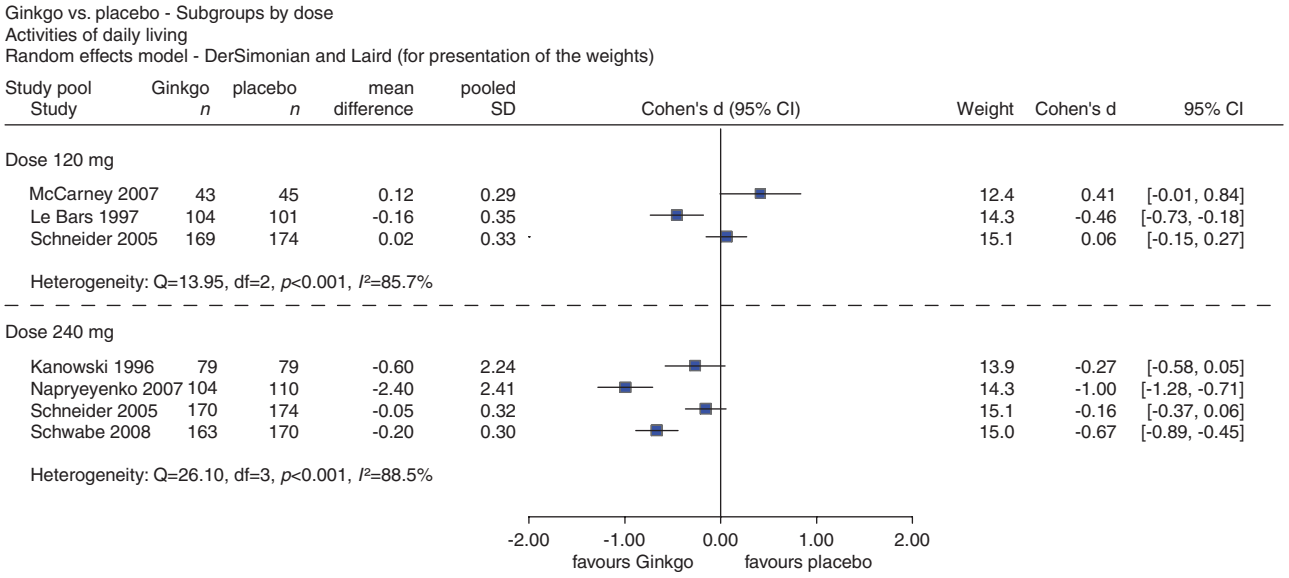

Fig. 2: Forest plot of outcome "activities of daily living". *CI* confidence interval; *SD* standard deviation

percentage of AD patients was 84%; the results were used for this review. Data are presented for AD patients where possible, if results are based on data of all patients, including vascular dementia or mixed forms, this is marked.

Differences between study populations were observable (Tab. 1), mainly caused by varying inclusion and exclusion criteria of the studies (see Discussion). The overall methodological quality of the studies was good: 5 showed minor deficiencies and 1 [11] showed no deficiencies (details on quality assessment can be found in the original report) [3].

All six studies presented data on *activities of daily living* (ADL). The heterogeneity for all studies was high, and remains high when considering high-dose studies only ($I^2 = 88.5\%$). However, in this subgroup, Ginkgo was favoured in general (compare Fig. 2). Even though a pooled estimate could not be obtained, standardised mean differences indicated a relevant effect of Ginkgo on ADL. *Cognition* was a primary endpoint in all 6 studies. As with ADL, high heterogeneity was observable between all studies. Although heterogeneity between high dose studies was still high ($I^2 = 96.7\%$) 3 of the 4 studies of this subgroup showed a statistically

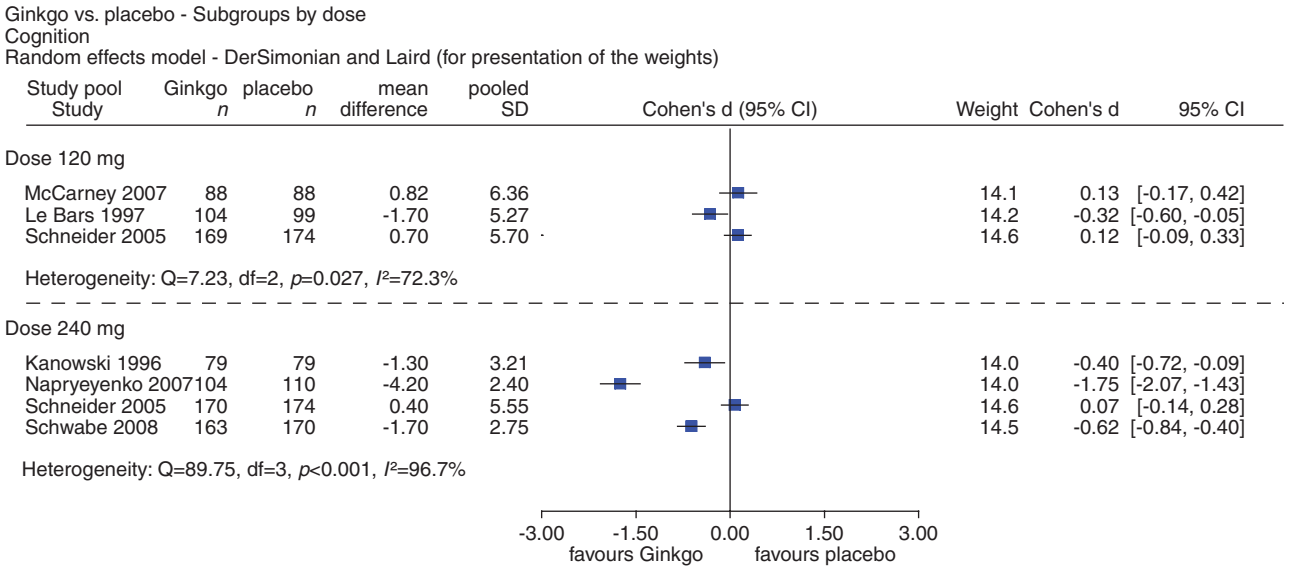

Fig. 3: Forest plot of outcome "cognition". *CI* confidence interval; *SD* standard deviation.

Tab. 2: Differences in means for secondary outcomes

Study	General symptoms (NPI[a])			Depression[a]			Quality of life		
	N	difference [Gb *vs.* P] means (95% CI)	*p*-value	*N*	difference [Gb *vs.* P] means (95% CI)	*p*-value	*N*	difference [Gb *vs.* P] means (95% CI)	*p*-value
McCarney 2007	85	4.51 (−0.15; 9.18)[b]	0.06	–	–	–	88	−0.98 (−2.55; 0.59)[c,d]	0.222
Kanowski 1996	–	–	–	156	−0.8[e,f] (n.s.)	n.s.	–	–	–
Napryeyenko 2007	124	−8.4[e] (n.s.)	<0.01	395[f,g]	−4.3 (−4.8; −3.8)[b]	<0.001	–	–	–
Schneider 2005	–	–	–	344	−0.3[e] (n.s.)	n.s.	–	–	–
Schwabe 2008	333	−3.1[e] (n.s.)	<0.001	–	–	–	333	n.s. (n.s.)	0.008[h]

AD Alzheimer's disease, *Gb* Ginkgo, *P* placebo, *n.s.* not stated; [a] negative values favour Ginkgo; [b] prefix changed, due to consistency; [c] carer-rated quality of life; [d] Quality of Life in Alzheimer's disease (QOL-AD) used by Digger, Quality of Life Questionnaire for people with dementia (DEMQOL-PROXY) used by Schwabe; [e] calculated by review authors; [f] Montgomery-Asberg Depression Rate Scale (MADRS) used by Kanowski; Hamilton Rating Scale for Depression (HAMD) used by Napryeyenko and Schneider; [g] results for total study population, not only Alzheimer's disease; [h] results in favour of Ginkgo.

significant result favouring Ginkgo. However, the effect size could not be determined, as pooling was not possible (Fig. 3). The results of the remaining outcomes are presented in Tab. 2. *Accompanying psychopathological symptoms* were captured as measurements of general symptoms and depression. *General symptoms* were assessed by 3 studies [7, 8, 10], but McCarney 2007 [7] assessed the NPI in the intensive follow-up group only and used a low dose of Ginkgo. The result, a numerical effect in favour of placebo, is therefore not comparable with the findings of the other two studies. The significant effects in the studies Napryeyenko 2007 [10] and Schwabe 2008 [8] indicated a positive effect of high-dose Ginkgo on general symptoms. Due to high heterogeneity, the results were not pooled in a meta-analysis. *Depressive symptoms* were evaluated by 3 studies [7–9]. Limitations occur as Kanowski 1996 [9] and Napryeyenko 2007 [10] did not give a separate analysis for AD patients and Kanowski 1996 [9] only reported the per-protocol analysis. Although all studies show at least a numerical benefit of Ginkgo, the data have to be interpreted with caution. McCarney 2007 [7] showed no statistical significant effect of Ginkgo on *quality of life*, Schwabe 2008 [8] however showed a significant effect in favour of Ginkgo. For none of the considered *safety aspects* any evidence for a harmful effect of Ginkgo was observed. Yet the number of patients withdrawing due to adverse events was statistically significantly larger among Ginkgo patients than those taking placebo.

Subgroups

Although the factors "age" and "accompanying psychopathological symptoms" had a modifying effect especially on the outcomes "activities of daily living" and "cognition", an interpretation was difficult due to insufficient information. The modifying effects of the factors "sex", "severity of dementia" and "presence of concomitant diseases" could not be quantified.

Discussion

There is evidence of a benefit of high-dose (240 mg) Ginkgo for the outcome "activities of daily living". For patients taking this dose there are also indications of a benefit for the outcomes "cognitive function" and "general psychopathological symptoms". However, the conclusion that Ginkgo has a beneficial effect is based on very heterogeneous results; therefore no potential effect size can be estimated. In addition, due to inclusion criteria of the according studies, there is an indication that this benefit is only present in patients with accompanying psychopathological symptoms. The results on adverse drug effects are inconsistent. Regarding serious adverse events and overall adverse events, there was no indication of harm caused by Ginkgo. However, evidence was available that with Ginkgo, more patients discontinued the study due to adverse events.

While this assessment was focused on the benefit of Ginkgo for patients with AD, many other systematic reviews and HTA reports have used a wider indication, namely dementia of any kind. The Cochrane review by Birks et al. [13] stated in 2002 that there are promising findings for the benefit of Ginkgo, yet, larger and methodologically better trials are needed due to inconsistencies among the most recently published trials. Since then, most published systematic reviews led to similar conclusions [14–16]. Merely Gabryelewicz et al. [17] stated in 2005 that they did not see any evidence for a beneficial effect of Ginkgo. The most recent update of the Cochrane review by Birks et al. [18] dated from 2009 and included the studies by McCarney et al. [7], Napryeyenko et al. [10] and Schneider et al. [11]. The authors conclude that there is only inconsistent and unreliable evidence, for a predictable and clinical significant benefit of Ginkgo for people with dementia or cognitive impairment. The Cochrane Review had different inclusion and exclusion criteria compared to our review, hence the comparability is restricted. Birks et al. [18] included e.g. short-term studies (<16 weeks) and patients with any type of dementia. Furthermore, the results of yet another unpublished study (Schwabe 2008 [8]) with favourable findings for Ginkgo were not included in the Cochrane update. The most recent systematic review by Weinmann et al. [19] again assessed dementia of any type and included studies with duration of at least 12 weeks, yet the authors presented subgroup analyses for AD patients. The review described statistically significant effects in favour of Ginkgo for the outcomes ADL and cognition, with a high heterogeneity. The authors conclude that a high dose (240 mg) of Ginkgo might be necessary to yield clinical relevant effects. Likewise, they promote the desirability of head to head trials to compare the effectiveness of Ginkgo to other anti-dementia medications. The current German guideline provided by 2 scientific associations concludes that there is not sufficient evidence to recommend treatment with Ginkgo biloba [1].

Although this assessment found beneficial effects of Ginkgo for AD patients, a clear recommendation for the use of Ginkgo cannot be given. One problem is the substantial heterogeneity between the effects of

included studies which cannot be credited to a specific factor. As the findings were dominated by 2 studies, conducted in an Eastern European health-care setting with an explicit patient group, the interpretation of the results is further complicated. Furthermore, all studies differed enormously considering in- and exclusion criteria. While e.g. the presence of accompanying psychopathological symptoms was required by Napryeyenko 2007 [10] and Schwabe 2008 [8], Schneider 2005 [11] explicitly excluded patients with such symptoms. The other 3 studies did not mention any limitations. Another reason for heterogeneity might have been the time point of study execution. After publication of the 2 oldest studies [9, 12], standard treatment for AD changed as anticholinesterases were approved in the late 90s. Prescription of Ginkgo decreased in Germany, as anticholinesterases began to dominate the treatment regimes [20]. The studies Napryeyenko 2007 [10], Schwabe 2008 [8] and Yancheva 2006 [6] were executed in Eastern Europe (Ukraine and Bulgaria) mainly to make the recruitment of patients for a placebo-controlled trial possible, which was becoming complicated in the western industrialised countries (Schneider 2005 [11]). The findings of Napryeyenko 2007 [10] are astonishingly large, neither the other included Ginkgo studies nor the studies assessing the effect of anticholinesterases show comparable effect sizes [21]. The statements regarding the benefit of Ginkgo seem to be only applicable to a specific study population in a specific setting.

A statement regarding the benefit of Ginkgo for specific subgroups is not possible, as data for these subgroups are sparse. However, the findings of this review indicate that future studies should use a high dose (240 mg) of Ginkgo as there were hints of effect modification. Long-term data are mostly lacking and would be desirable in particular for safety aspects. A prevention trial with a follow-up of 42 months observed hints for increased risk of strokes and transient ischemic attacks among older people taking Ginkgo [22]. Data to analyse the risk of these side effects among patients with AD are lacking. At present, the effects of anti-dementia medication of any kind are discussed, as the clinical significance of the effects is yet not accurately defined [23]. Ginkgo, anticholinesterases and memantine are the medications listed in the group of anti-dementia drugs by the current ATC-classification. Head to head comparisons of Ginkgo with the other drugs are mostly lacking, only 1 exploratory study [6] was identified and could not be included in the benefit assessment. The appraisal of Ginkgo compared to other anti-dementia medications is therefore not possible.

Conclusion

For the outcome ADL, there is evidence of a benefit of high-dose (240 mg) Ginkgo. In patients taking this dose, there are also indications of a benefit for the outcomes cognition and accompanying psychopathological symptoms. However, the conclusion that Ginkgo has a beneficial effect is based on very heterogeneous results; therefore no summarizing conclusion can be made on the potential effect size. The benefit of Ginkgo compared with other drugs approved for AD is unclear, as only one explorative study investigated a direct comparison. Despite the consideration of the Ginkgo dose in the interpretation of the results, the considerable heterogeneity could not be adequately explained. Additional studies designed specifically to investigate individual subgroups of patients with AD are needed to enable subgroup-specific conclusions to be drawn. As the results of this benefit assessment were dominated by 2 studies that were not conducted in the health-care setting of a Western country, future studies should be carried out in a Western setting. Appropriate comparator studies with other anti-dementia drugs are an alternative option. Data from long-term studies would also be desirable to assess potential beneficial and adverse effects of long-term therapy with Ginkgo.

Conflict of interest

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