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# Effect of treatment with *Ginkgo biloba* extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients

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**Abstract** *Objective*: Test of dose–response relationship for *Ginkgo biloba* extract EGb 761 (oral) in outpatients with acute idiopathic sudden sensorineural hearing loss (ISSHL) of at least 15 dB at one frequency within the speech range occurring less than 10 days before study inclusion. *Design*: Multicentre, randomized, double-blind phase III study comparing dosages of 120 mg twice daily and 12 mg twice daily over 8 weeks. *Main endpoint*: Recovery (in dB) of the auditory threshold from the initial measurement to the value on the last day of treatment, averaged over those frequencies from 0.25, 0.5, 1, 2, and 3 kHz for which the initial hearing loss amounted to 15 dB or more compared to the level on the opposite side. *Patients*: 106 patients with an average age of 44 ± 16 years and with hearing loss at affected frequencies 26 dB ± 9 dB included between December 1995 and July 1997. *Results*: Large majorities of both treatment groups recovered completely. In exploratory analyses of the 96 patients included according to the protocol, patients given the higher dose had less risk of not recovering well (≤10 dB residual hearing loss) (one-sided Fisher test: $P = 0.0061$), especially if they had no tinnitus ($n = 44$, $P = 0.00702$). *Conclusion*: A higher dosage of EGb 761 (oral) appears to speed up and secure the recovery of ISSHL patients, with a good chance that they will recover completely, even with little treatment. This was already observed after one week of treatment. We find it justified to treat patients who have unilateral ISSHL of less than 75 dB and neither tinnitus nor vertigo with 120 mg oral EGb 761 twice daily.

**Keywords** Sudden deafness · Sudden hearing loss · Idiopathic sudden sensorineural hearing loss · Tinnitus · *Gingko biloba* extract EGb761

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## Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) [6, 11, 24] is a symptom with no precise objective criteria for the diagnosis [33], as patients can suffer considerably even from relatively minor hearing impairments, which they find alarming and very irritating. How much the opinions of ENT specialists vary can be seen from the dependence of the incidence of the condition on public health policy. Considerable variation [37] is found even between closely neighbouring populations, e.g. between the Netherlands (8 per 100,000) and the Dutch-speaking part of Belgium (14.6 per 100,000) [42]. Opinions vary widely [42] even within the same health care system and official guidelines [19] do not specify how severe a hearing loss has to be to warrant an inpatient "shot-gun" infusion therapy that covers various advocated aetiologies [30].

Scientifically, a "valid" [32] overview of the many studies [21] into ISSHL-aetiology and the efficacy of various treatments is next to impossible [34] because of the diversity [39] not only in treatments, endpoints and outcomes but also in the study populations. For example, Byl and colleagues [6] considered a hearing loss averaging less than 34 dB to be "mild" and found that it occurred in one-sixth of all cases. In a recent survey from a major German university [46], however, this criterion applied to more than two-thirds of all cases and the least affected group (1/7 of all cases) showed an average hearing loss of only 5 dB or less. So the divergent opinions on whether the predominant pathogenesis mechanism is a viral infection [50] or a consequence of vascular risk factors [38, 44]

may result from the different patient populations studied and need not be mutually exclusive. Nevertheless, the major justification for the "gold standard" [30] of inpatient infusion schemes still has to rely on studies [31, 50] in which a rather narrow definition [49] of hearing loss is used. These studies may not be reproducible in other health care systems with different inclusion criteria [25] and in patients in whom other recovery patterns [22] dominate. Such an extension of the indication may be regarded as uncontrolled experimental treatment on a large scale [33, 34]. Clearly new research is needed on behalf of the increasing number of patients who show ISSHL at younger ages and lower frequencies [29], characteristics thatare both considered to increase the chances of recovery, so making the Hippocratic principle of *nil nocere* more important.

The practical decision on whether to treat ISSHL, and when and how, is further complicated by

1. The pressure to provide immediate and maximal treatment [28, 33] in order to maximize the chances of recovery [27] before time-consuming and noisy (i.e. potentially damaging [33]) diagnostic tests are completed to rule out specific causes [8, 41, 47], and also in order not to jeopardize the relationship with the patient [33];
2. The need to avoid further stress for ISSHL patients, who tend to lack stress-coping skills [26] and may be mostly in need of a correction of conditions such as hypertension [33], diabetes [35] and hyperlipidaemia [44];
3. The ethical need for a protocol approved by an institutional review board before experimental treatment can be administered and the legal risk that patients will tend to seek compensation [28] if their high expectations are not met.

Unfortunately, more critical expert opinions [20, 43, 48] on the necessity for extensive therapy are largely ignored by the media, so a large number of ISSHL-patients who would have recovered spontaneously undergo extensive infusion therapy with dextrose and hydroxyethyl starch (HES), i.e. substances which can have considerable side effects [2, 33]. In view of the high spontaneous recovery rate and the side effects of infusion therapy it appears acceptable to offer patients a closely monitored outpatient test treatment without infusion, with the possibility of an informed choice at any time of starting infusion therapy or other more invasive treatments [12, 18, 44, 45] which may prove more effective for selected patients. This may also be expected to benefit patients with less severe hearing loss who now get less treatment and do not recover as well as more severe cases [17].

A particularly promising herbal extract for such treatment is EGb 761 (oral) [9], a standardized extract of dried leaves of *Ginkgo biloba* with multiple neuron-protective components [1], which has been proved to be effective for ISSHL-related impairments. It has proven topically morphometric [13] as well as cognitive [40] efficacy and side effects comparable to those of a placebo. For treatment of ISSHL, EGb 761 has been shown to compare well with piracetam [3], naftidrofuryl [23], hyperbaric oxygen therapy [36], and nicergoline [14].

The purpose of the present study on outpatients seeking treatment for ISSHL from ENT specialists in Germany was to document the efficacy of EGb 761 (oral) by establishing a dose–response relationship. Efficacy was measured as the mean recovery of the hearing threshold from the initial findings to the last day of treatment over those frequencies between 250 and 3000 Hz where the initial loss of hearing was more than 15 dB compared to the level in the other ear. The assumption was that patients taking 240 mg/day over 8 weeks would show better recovery than those taking only 24 mg/day.

## Methods

### Investigational plan

The trial was planned as a multicentre randomized double-blind phase III study with two groups of outpatients with acute unilateral ISSHL of at least 15 dB at one frequency (250, 500, 1000, 2000 or 3000 Hz) which had appeared less than 10 days previously. The patients were treated by 19 ENT specialists in two parallel groups over eight weeks between December 1995 and July 1997.

Patients were only included if the affected ear showed no conductive deafness, signs of inflammation, suspected retrocochlear dysacousis, injury, or Menière's disease, and if the hearing loss (HL) was less than 75 dB. Patients with known severe renal or hepatic insufficiency or cardiovascular diseases, non-controllable diabetes, severe gastrointestinal disturbances or malabsorption syndrome w ere excluded, as were breast-feeding women, women of childbearing age taking no contraception, and suspected alcoholics. Patients taking the following concomitant medication were also excluded: aminoglycoside antibiotics, diuretics, vasoactive medication, CNS-stimulating drugs, tranquillizers, antihistamines, nitrates, calcium antagonists, β-blockers, platelet aggregation inhibitors, and anticoagulants.

ENT status examinations and routine blood tests were performed on inclusion (day 0) in the study and at the end of the study treatment. Medication consisted of coated tablets which were to be taken twice a day, starting on the day of the initial visit (day 0). Tablets were supplied in packages labelled with the individual treatment numbers assigned to each patient. Tablets for group L (lower dose group) contained 12 mg and for group H (higher dose group) 120 mg of EGb 761 (oral). On days $3 \pm 1$, $7 \pm 1$, $14 \pm 2$, $28 \pm 2$, $42 \pm 2$, and $56 \pm 2$ the patients were re-examined and the remaining medication was counted. Patients who failed to take medication for five consecutive days or 20% of the total 8 weeks were regarded as drop-outs.

The HL average overall frequencies relative to hearing in the other ear at the time of study inclusionare not a good parameter for measuring recovery if the median HL at any one frequency is only about 15 dB. Audiogram results were mostly rounded to the nearest 5 dB and at an HL of 10 dB patients started to withdraw from treatment, considering themselves fully recovered. A modified average was therefore used in this study, extending only over those frequencies out of 250, 500, 1000, 2000, and 3000 Hz for which the initial hearing loss amounted to 15 dB or more compared to hearing on the opposite side. The main endpoint for the prospective analysis was the recovery (in dB) of the auditory threshold from the initial measurement to the value on the last day of treatment, averaged over the individual affected frequencies. For the safety analysis and the confirmatory analysis of the main criterion of efficacy, an intention-to-treat basis with a last-value carry-forward procedure for missing audiometric data was determined, with Wilcoxon's rank sum test to be performed with a one-sided error level of $\alpha = 0.05$.

**Table 1** Group averages of initial tone audiometry thresholds in both ears and at all measured frequencies. *H* high dose group, *L* low dose group

| | Treatment group | 250 Hz (dB) | 500 Hz (dB) | 1000 Hz (dB) | 2000 Hz (dB) | 3000 Hz (dB) |
|---|---|---|---|---|---|---|
| Affected ear | H | 30 ± 14 | 28 ± 13 | 24 ± 14 | 28 ± 16 | 34 ± 21 |
| | L | 27 ± 16 | 23 ± 15 | 27 ± 18 | 27 ± 18 | 36 ± 18 |
| Other ear | H | 13 ± 8 | 12 ± 7 | 12 ± 7 | 16 ± 12 | 18 ± 15 |
| | L | 13 ± 9 | 13 ± 9 | 13 ± 9 | 16 ± 12 | 20 ± 15 |

An estimated case number of up to 300 had been computed on the basis of data obtained from inpatients who had taken EGb761 in similar dosages in addition to infusion therapy. The exact case number was to be determined by an interim analysis [4] of the data collected from the first 60 patients completing the study. The one-sided hypothesis ($H_0$) to be tested was that efficacy in the H group was less than or equal to efficacy in the L group. The study was to be terminated if the *P* value determined did not fall within the interval $0.0233 < P_1 < 0.5$, i.e. if there was sufficient evidence to confirm efficacy or if the difference between the efficacies of the two test treatments was expected to be clinically irrelevant.

The investigational plan was approved by an institutional ethical review board and monitored according to the guidelines for good clinical practice. A steering committee was to decide about continuation of the study after the intermediary analysis.

### Assignment of patients and blinding

Randomization was done in blocks of four in order to achieve balanced randomization for each centre taking part and in the interim analysis. According to the randomization list, the sponsor of this study, Intersan GmbH (Einsteinstrasse, 76275 Ettlingen, Germany ), produced labelled medication and emergency unblinding envelopes with patient numbers on the outside. On inclusion in the study patients were assigned a number in sequence within the block open at the centre they attended. Following common double-blind design, neither patients nor investigators knew which treatment group they were assigned to. Each sealed envelope contained information about the treatment group to which the patient was assigned. Each investigator obtained the envelopes for the patients he or she treated, and identical envelopes were kept by the director of the clinical study. The investigator was only allowed to open an envelope in case of an emergency, in order to take appropriate action. No envelopes, however, needed to be opened. On completion of the study all envelopes were returned to the sponsor.

## Results

### Inclusion

The 106 patients who could be evaluated included 53 males and 53 females. The average age in the two groups was 42 ± 16 years (L) and 46 ± 15 years (H). The initial average hearing thresholds assessed by pure tone audiometry were similar in both groups (Table 1).

The numbers of patients in whom the various frequencies were affected are given in Table 2. Tinnitus in the affected ear was found in 26 out of 50 patients in the L group and in 30 out of 56 in the H group. Vertigo was reported in one patient in the L group and five patients in the H group.

### Withdrawals

The numbers of withdrawals classified according to reason for withdrawal are given in Table 3.

**Table 2** Numbers of patients in whom hearing at the various frequencies was initially affected (≥ 15dB hearing loss relative to the other ear). *H* high dose group, *L* low dose group

| | 250 Hz | 500 Hz | 1000 Hz | 2000 Hz | 3000 Hz |
|---|---|---|---|---|---|
| L | 25 | 26 | 19 | 18 | 23 |
| H | 30 | 33 | 20 | 21 | 29 |

**Table 3** Withdrawals for various reasons in both treatment groups for the original analysis set, with numbers for the retrospective set done according to the protocol in parentheses. *H* high dose group, *L* low dose group

| Group | *n* | Restitution of hearing[a] | Inefficacy | Lack of compliance | Other |
|---|---|---|---|---|---|
| H | 56 (49) | 3 (3) | 3 (2) | 1 (0) | 4 (4) |
| L | 50 (44) | 0 (0) | 3 (3) | 7 (5) | 7 (6) |
| | | | | One-sided Fisher *P* 0.0203 (0.0209) | |

[a] According to the judgement of the physician

### Adverse events

Nine adverse events were documented in eight patients (H: $n = 3$; L: $n = 5$). Nausea and gastrointestinal discomfort were reported in three patients (H: $n = 2$; L: $n = 1$). One case of headache appeared in the H group and two cases of tinnitus were documented in the L group. Two serious adverse events were reported under the L dosage. One patient suffered myocardial inflammation and one patient was admitted to hospital with severe vertigo. Neither event was judged to be related to the study drug. In general, the dose of the study drug had no apparent effect on the frequency or severity of side effects.

### Prospective analysis

The planned intermediate analysis performed after 60 patients had been included showed that at an optimistic estimate the number of patients needed to reach a one-sided $P = 0.025$ was more than 600. After this result became available the study was discontinued, as set out in the protocol.

Details on the main endpoint are given in Table 4. The HL had recovered almost completely in the large majority of cases at the end of the treatment period, irrespective of the dosage. The small difference in the endpoint estimates for the two groups is medically irrelevant and the statisti-

**Table 4** Recovery in hearing thresholds averaged over the affected (≥ 15 dB) frequencies. *H* high dose group, *L* low dose group

| Group | Minimum (dB) | Median (dB) | Maximum (dB) | Average (dB) |
|---|---|---|---|---|
| L | –10 | 25 | 43 | 22.24 ± 13.99 |
| H | – 5 | 25 | 45 | 24.55 ± 9.11 |

cal analysis as planned found no overall statistically significant differences between the two study groups.

## Retrospective analysis

After completion of the prospective analysis, a subsequent re-analysis of the database showed that 13 patients had been included in deviation from the protocol. Among these 13, the inclusion criterion of at least 15 dB HL relative to the other ear could not be established in 11 cases (L: $n = 6$; H: $n = 5$); also, in the H group, one patient had been included irrespective of anticoagulant therapy and one initial tone audiogram was incomplete so no last-value carry-forward procedure was possible. A revised analysis set was identified which consisted of all patients who had been included according to the protocol (IAP). For the exploratory efficacy re-analysis of this set, all missing tone audiogram data were completed by a last-value carry-forward procedure.

The subsequent retrospective analysis of the patients who had been included according to the protocol (the IAP set) showed the following evidence for an advantage of the high dosage (H) group:

1. The risk of failing to improve measurably (≥ 5 dB) was diminished at the high dosage: of the 49 patients in group H, one patient did not improve vs seven patients of the 44 in group L (one-sided Fisher test: $P = 0.0202$);
2. At high dosage the patients had a better chance of being "healed", if "healed" is defined as the residual HL being too minor for inclusion in the study at the initial visit, i.e. ≥ 15 dB at any one frequency (Table 5). The advantage does not depend on the definition of "healed" as long as it is not chosen too narrowly. This can be seen from the cumulative distribution functions in Figs. 1 and 2. Detailed figures are given in Table 5 for the cut-off value from the inclusion criteria and for a slightly different one defined by the patients themselves, namely the maximal HL at which a patient withdrew due to subjective complete recovery (10 dB);
3. The majority of the patients already experienced the high dosage advantage after one week of treatment; only 20 out of 49 (40%) in group H still had an HL average over the affected frequencies of > 5 dB vs 28 out of 44 (64%) for the L group (one-sided Fisher test: $P = 0.02294$);
4. The recovery in the low-tone area occurred faster in group H. A measure for the speed of the recovery is the HL integrated over the time of the study. The area under the curve of the linear interpolation of hearing loss

**Table 5** Number of patients who had not been "healed" after 8 weeks according to two different criteria for the residual maximal hearing loss at any one measured frequency (see text). *H* high dose group, *L* low dose group

| Group | *n* | ≥ 15 dB | > 10 dB |
|---|---|---|---|
| H | 49 | 6 | 6 |
| L | 44 | 14 | 16 |
| One-sided Fisher *P* | | 0.0202 | 0.0061 |

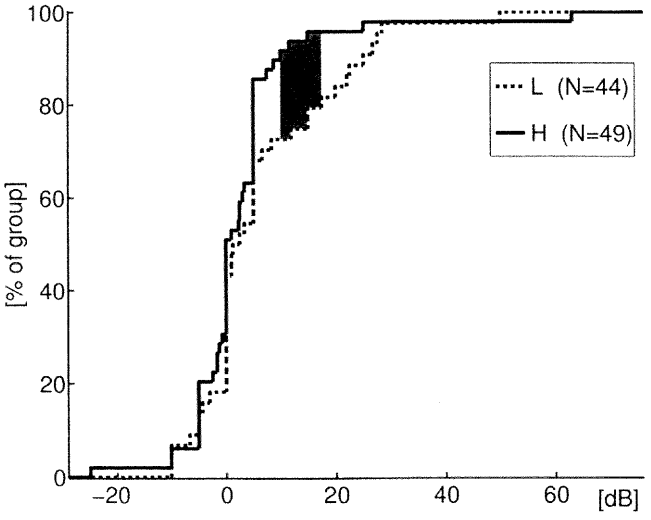


**Fig. 1** Cumulative distribution of residual hearing loss (HL) after 8 weeks of treatment relative to the other ear when inclusion was averaged over the affected frequencies. The *shaded area* between the two staircase curves denotes the range of cut-off criteria values, which result in a one-sided Fisher $P < 0.025$

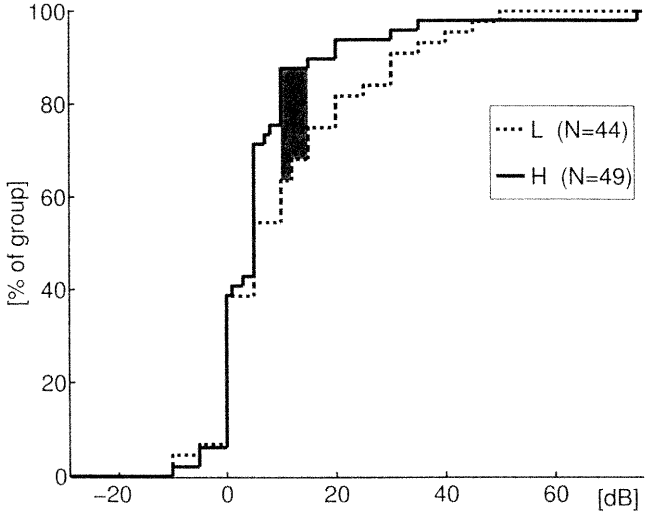


**Fig. 2** Cumulative distributions of the maximal residual HL after 8 weeks of treatment relative to the other ear upon inclusion (at any frequency). The *shaded area* between the two staircase curves denotes the range of cut-off criteria values, which result in a one-sided Fisher $P < 0.025$

**Table 6** Number of patients who had not been "healed" after 8 weeks according to two different criteria for the residual maximal hearing loss at any one measured frequency (see text) evaluated separately according to the occurrence of tinnitus before the initial visit. *H* high dose group, *L* low dose group

| | | *n* | ≥ 15dB | > 10dB |
|---|---|---|---|---|
| No tinnitus | H | 23 | 1 | 1 |
| | L | 21 | 7 | 8 |
| | One-sided Fisher *P* | | 0.0162 | 0.007 |
| Tinnitus | H | 26 | 5 | 5 |
| | L | 23 | 7 | 8 |
| | One-sided Fisher *P* | | 0.282 | 0.182 |

over time (measured in dB*d) does not depend on the fluctuating advantage at any one visit or cut-off value. Recovery of the HL at 500 Hz, i.e. the frequency which was affected in most patients (see Table 2), was faster in group H (one-sided Mann-Whitney rank sum test $P = 0.02381$);

5. The advantage of the high dosage treatment occurred almost exclusively in the 44 patients in the IAP set who had not experienced tinnitus before the initial outpatient visit;
   – Among the patients without tinnitus, high dosage almost guaranteed complete recovery, while low dosage resulted in a two out of three chance of recovery. Among patients with tinnitus, there was only a slight advantage for group H (see Table 6);
   – The faster recovery at high dosage was also most pronounced among the patients without tinnitus [one-sided Mann-Whitney rank sum test for the area under the curve for HL averaged over the affected (≥ 15 dB initially) frequencies: $P = 0.01677$] and the difference between the two groups was correlated with the speed of recovery: The 30% of patients in both groups who recovered fastest showed the least difference.

It appears that after one week there were already patients without tinnitus in both groups who had recovered fully and that in these patients the dosage does not make much difference in this parameter. However, patients who recover fast in fact also benefit from high dose treatment. Seven of the 44 patients without tinnitus recovered completely (HL < 5 dB at all frequencies) within one week of treatment and all seven were in the high dosage group (one-sided Fisher $P = 0.0064$).

## Discussion

The main aim of the study was not achieved, because the vast majority of patients recovered almost completely (see Table 5). For these patients, the degree of recovery was determined by the initial HL [33] and not by the dosage. Even for the remaining HL at the end of the treatment (rather than the baseline-corrected parameter: HL improvement), the differences between the groups concerned only one-third of the patients, namely those with the greatest remaining HL in their group. The other two-thirds appear to have reached a state of residual minor HL at which no dosage-dependent recovery could be observed. The high dosage treatment may therefore serve as a precautionary measure against the one in three risk of not recovering completely, but for the majority of patients recovery after 8 weeks is independent of the dosage.

Which patients would actually benefit from the high dosage individually – rather than in the form of better group statistics – could not be deduced from the level of the initial HL. The patients who recovered most slowly at low dosage did not show any particularly severe HL initially.

Which patients do not recover at all with the high dosage medication cannot be learned from this study. The single patient who did not recover among the 49 in the high dosage group was exceptional in that his HL ranged between 50 and 75 dB, he had experienced an episode of vertigo, and he continued to suffer from a headache and worsening tinnitus. He left the study on day 4 due to lack of efficacy, and the subsequent values were carried forward from then.

The relatively high benefit of the high dosage treatment for patients without tinnitus may be specific to the population in the present study – just like the high percentage of such patients. Other studies with more stringent inclusion criteria found no effect on the chance of spontaneous recovery for patients suffering from more severe HL [48]; also the long-term prognosis does not depend on the presence of tinnitus [15] or any particular treatment at all. For the short-term prognostic significance of tinnitus with other therapies, however, previously published results appear contradictory. Danino and colleagues [10] reported that ISSHL patients experiencing tinnitus have a better chance of recovering under a 5-day infusion regime with prednisone, dextran, histamine, vitamin C, papaverine and diazepam [5]. The patients involved in their study, however, had much more severe HL than those considered in the present one. On the other hand, Hoffmann and colleagues [23] reported slower recovery for patients with tinnitus who received infusion therapy with HES and either EGb 761 or naftidrofuryl. Consequently, future efficacy studies for EGb 761 in ISSHL patients should probably consider patients with and without tinnitus separately. Studies on the effect of EGb 761 on tinnitus itself have been reviewed by Ernst and Stevinson [16]; results on its efficacy in equilibrium disorders have also been reviewed [7].

The improvement in hearing thresholds with the high dosage treatment was not limited strictly by the initial HL among the patients in this study. There was even evidence of "overshooting recovery" with the high dosage: in the high dosage group 50% of the patients achieved better hearing thresholds than in the contralateral ear for frequencies up to 2000 Hz, compared to 10% of the patients receiving a low dosage. The improvement with the high dosage even extended to the other ear: at 250 and 500 Hz,

hearing improved measurably (≥ 5 dB) (H: 14 out of 49; L: 3 out of 44) (one-sided Fisher test: $P = 0.0061$). The unilateral ISSHL may be accompanied by a measurable bilateral deterioration of the hearing thresholds at the low frequencies which can recover under high dosage therapy in about 50% of all cases. In order to confirm this speculation, however, a comparison with a matched healthy control group would be necessary.

The number of patients included with HL milder than specified in the protocol may be representative and emphasizes the importance of the *nil nocere* principle for the treatment mentioned in the introduction. The large number of withdrawals with incomplete recovery appears peculiar to outpatient ISSHL treatment. The remarkable frequency of withdrawals due to lack of compliance in the low dosage group is a reason for concern. If the high dosage had helped to avoid compliance problems, e.g. by improvement of memory [40], the H patients would have had a better chance of being observed until recovery, while the dosage-independent improvement in the many dropouts in the low dosage group would have been lost to analysis due to the last-value carry-forward procedure. Closer evaluation of the data shows, however, that the difference in recovery of HL between treatment groups was not related to a difference in dropouts in this study. The enhanced dropout frequency in the low-dosage group occurred mainly among the patients with tinnitus, who as a group showed little benefit from the high dosage, and there was no apparent correlation with a particularly slow recovery of hearing thresholds. Among the patients without tinnitus, the number of withdrawals was evenly distributed among the treatment groups.

## Conclusion

EGb 761 (oral) appears to speed up and improve the recovery of those patients with uncomplicated ISSHL who have a good chance of recovering completely. Among the 23 patients with average HL and no signs of tinnitus who were treated with 120 mg EGb 761 twice daily, all got better and all but one recovered to an HL of better than 10 dB at all measured frequencies. High dosage improves the chance of cure compared to low dosage, and the advantage can already be seen after one week of treatment. Side effects irrespective of dosage appear to be comparable to those with a placebo. As this treatment is well tolerated, it may be preferable to infusion therapy in uncomplicated cases of moderately severe ISSHL. The results of this study are exploratory rather than conclusive, however, largely because the recovery rate under the low dosage treatment had been underestimated in planning the study.

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