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[Intervention Review]

Nicergoline for dementia and other age associated forms of cognitive impairment

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ABSTRACT

Background

Nicergoline is an ergot derivative currently in use in over fifty countries for more than three decades, for the treatment of cognitive, affective, and behavioral disorders of older people. It was initially considered as a vasoactive drug and mainly prescribed for cerebrovascular disorders. Recent findings suggest other actions which has provided a rationale for the use of nicergoline for the treatment of various forms of dementia, including Alzheimer's Disease.

Objectives

To determine whether there is evidence of efficacy of nicergoline in the treatment of dementia and other age-associated forms of cognitive decline,and to assess the safety and tolerability of the drug.

Search methods

1. Electronic databases search. The Cochrane Controlled Trials Register (which contains citations from the MEDLINE, EMBASE, Psych LIT, and hand searches of geriatric, dementia, psychogeriatric journals, and conference abstracts) was searched using the following terms: 'Nicergoline', 'Sermion'.
2. Reference search. The reference lists of all obtained studies was checked.
3. Pharmaceutical company Pharmacia & Upjohn, owners of the rights to produce and market nicergoline in various different countries, was asked to provide data and reports of clinical trials. In case of unavailability of numerical data in published studies, the authors of each paper, were asked for any published or unpublished data.

Selection criteria

- All unconfounded, double-blind, randomized, placebo-controlled, published and unpublished trials were sought. Non-randomized trials were excluded. Open trials were considered for inclusion if patients were randomized to the different treatment groups.
- All patients diagnosed as having dementia or other cognitive disorder defined according to classification criteria accepted at the time of each study.
- Nicergoline given at any dose for more than one day with placebo control.

Type of outcome variables:

1. Cognitive function (as measured by psychometric tests).
2. Clinical impression (such as CIBIC or other clinical global measures of change).
3. Functional performance including dependency.

4. Behavioural disturbance.
5. Safety and acceptability as measured by the incidence of adverse effects (including side-effects) leading to withdrawal.
6. Death
7. Effect on carer
8. Use of services
9. Quality of life.

Data collection and analysis

A comprehensive search of the international literature and the producing company archives has been performed to identify all possible sources of data for this review. Only those trials fulfilling the inclusion criteria of belonging to either category A or B of allocation concealment, as defined by the Cochrane Organisation, were examined for data extraction by one reviewer. If there was doubt then the other reviewer was consulted. Data availability restricted analyses to 'completers' analyses for the outcome measures. Outcomes able to be assessed included: Behaviour, Cognition, Clinical Judgment, Tolerability, EEG.

Main results

The Sandoz Clinical Assessment Geriatric Scale (SCAG) was the outcome used in the largest number of patients (814 patients). The results from these studies were homogeneous in nature despite including patients observed for periods of time ranging from 2 months to 12 months. There was a difference in favour of the active treatment in reducing the behavioural symptoms described by this scale, -5.18 points [-8.03, -2.33]. This scale has a maximum of 133 points. The therapeutic effects of nicergoline seem to be evident by 2 months of treatment and maintained for 6 months. In general other behavioural outcome measures which include the GRS, the IADL, and the MACC and were episodically used in few studies, failed to demonstrate statistically significant results although there was a trend favouring treatment.
Cognitive assessment has been performed in a moderate number of patients with the MMSE (261 patients) and the ADAS-Cog (342 patients). No significant heterogeneity was found for these trials, despite the trials extending over periods of treatment of 3 to 12 months. There was a difference between treatment and control groups on the MMSE favouring nicergoline treatment. At 12 months the effect size was 2.86 [0.98, 4.74] The effect size for the ADAS-Cog, used exclusively with Alzheimer's disease patients, did not reveal a significant benefit. At 12 months the trend favoured treatment (-1.64 [-4.62, 1.34]). The other results from various cognitive measures tended to favour nicergoline but this was based on a small number of cases.
The clinical impression of change obtained from a total of 921 patients was homogeneous across the studies, despite reflecting changes over periods of time ranging from 2 to 12 months. The Peto odd ratio for improvement in the subjects treated with nicergoline over these varying time periods was 3.33 [2.50, 4.43].
Tolerability assessed in 1427 patients was homogeneous across all studies and demonstrated a mildly increased risk of adverse events on treatment, OR 1.51[1.10, 2.07].

Authors' conclusions

The clinical studies on nicergoline were carried out with diverse criteria and modalities of evaluation. Despite this, the 14 studies included in this review, have presented generally consistent results. Results of this meta-analysis provide some evidence of positive effects of nicergoline on cognition and behaviour and these effects are supported by an effect on clinical global impression. There was some evidence that there were increased risk of adverse effects associated with nicergoline. These results were obtained on older patients with mild to moderate cognitive and behavioural impairment of various clinical origins, including chronic cerebrovascular disorders and Alzheimer's dementia. The few studies specifically performed on patients with Alzheimer's disease were performed with too few people to give a definitive answer to the questions concerning the use of nicergoline for this form of dementia.
This drug has not been evaluated using current diagnostic categories such as MCI or in association with therapeutic agents of different nature such as cholinesterase or antioxidant drugs.

PLAIN LANGUAGE SUMMARY

Nicergoline may improve cognition and behavioural function of people with mild to moderate dementia

Nicergoline is an ergot derivative which has been registered in over 50 countries and has been used for more than three decades for the treatment of cognitive, affective, and behavioural disorders of older people. During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Since then, findings suggesting a more complex pharmacological profile of nicergoline have led to its being considered for the treatment of other forms of dementia, including Alzheimer's Disease. There is some evidence of positive effects of nicergoline on cognition and behaviour and these effects are supported by an effect on clinical global impression.There was some evidence that there was increased risk of adverse effects associated with nicergoline. This drug has not been evaluated using current diagnostic categories such as MCI or in association with therapeutic agents of different nature such as cholinesterase or antioxidant drugs.

BACKGROUND

Dementia is a clinical condition characterized by global, and usually progressive impairment of cognitive functions. These functions include memory, judgement, reasoning, perception and personality, and impairments lead to difficulties in daily life and to inappropriate behaviour. It is commonest in later life and is most often caused by Alzheimer's disease and inadequate blood supply to the brain, but is also a feature of some other diseases.

Nicergoline, 8-beta-(5-bromonicotinoylhydroxymethyl)-1,6-dimethyl-10alpha-metoxyergoline, is an ergot derivative which has been registered in over fifty countries and has been used for more than three decades for the treatment of cognitive, affective, and behavioural disorders of older people. During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Since then, findings suggesting a more complex pharmacological profile of nicergoline have led to its being considered for the treatment of other forms of dementia, including Alzheimer's Disease. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease. Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase. Nicergoline may also enhance noradrenaline and dopamine turnover in some areas of the brain. Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia. Other useful actions of nicergoline in dementia are an increase of phosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.

OBJECTIVES

To determine whether there is evidence of efficacy of nicergoline in the treatment of dementia and other age-associated forms of cognitive decline,and to assess the safety and tolerability of the drug.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded, double-blind, randomized, placebo-controlled, published and unpublished trials were reviewed. Non-randomized trials were excluded. Open trials were considered for inclusion if patients were randomized to the different treatment groups.

Types of participants

All patients diagnosed as having dementia or other cognitive disorder defined according to classification criteria accepted at the time of each study.

Types of interventions

Nicergoline given at any dose for more than one day with placebo control.

Types of outcome measures

1. Cognitive function (as measured by psychometric tests).
2. Clinical impression (such as CIBIC or other clinical global measures of change).
3. Functional performance including dependency.
4. Behavioural disturbance.
5. Safety and acceptability as measured by the incidence of adverse effects (including side-effects) leading to withdrawal.
6. Death
7. Effect on carer
8. Use of services
9. Quality of life.

Search methods for identification of studies

1. The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 4 May 2001 using the term nicergolin* and sermion. The Specialized Register at that time contained records from the following databases:

CCTR/Central: January 2001 (issue 1);
MEDLINE: 1966 to December 2000;
EMBASE: 1980 to December 2000;
PsycLit: 1887 to December 2000;
CINAHL:1982 to December 2000;
SIGLE (Grey Literature in Europe): 1980 to December 2000;
ISTP (Index to Scientific and Technical Proceedings): to May 2000;
INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
Aslib Index to Theses (UK and Ireland theses): 1970 to March 2001;
Dissertation Abstract (USA): 1861 to March 2001;
ADEAR (Alzheimer's Disease Clinical Trials Database): to March 2001;
National Research Register (including the MRC Clinical Trials Directory): January 2001 (issue 1)
Alzheimers Society Trials Database: to March 2001;
Glaxo-Wellcome Trials Database: to March 2001;
Centerwatch Trials Database: to December 2000.

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycInfo and CINAHL can be found in the Group's module.

2. Reference search. The reference lists of all obtained studies were checked.
3. Pharmaceutical company Pharmacia & Upjohn, owners of the rights to produce and market nicergoline in various different countries, was asked to provide data and reports of clinical trials. In case of unavailability of numerical data in published studies, the authors of each paper, were asked for any published or unpublished data.

Data collection and analysis

A single reviewer (MF) reviewed the list of articles and discarded irrelevant citations based on the title of the publication and its abstract. In the presence of any suggestion that the article could possibly be relevant, it was retrieved for further assessment. The two reviewers independently selected the trials for inclusion in the review from the culled citation list. Disagreements were resolved by discussion.

RESULTS

Description of studies

Eleven studies (one of which, Saletu 1995, comprised a placebo group and two separate groups of patients, with different clinical diagnoses, and thus was included twice in this review) were found compliant with the inclusion criteria and had numerical data available to be extracted for meta-analysis. Seventy-six other studies were not included predominantly because they did not include a placebo control group (and thus the studies were confounded) or had no control group at all. Other studies were outside the inclusion criteria since they included patients with diagnoses other than dementia or cognitive decline of older people.

All included studies were classified as category A in regard to allocation concealment and were performed in double-blind, parallel group fashion. Four studies were carried out in single centres, all the others were performed as multicentre.

This review is based on studies of which the clinical definitions of patients vary both according to the prevalent diagnostic mode of the time and to the different entities considered for inclusion in the individual studies. The various definitions of patients range from "Senile Cognitive Deterioration" to "Cerebral Metabolic and Nutritional Disturbances", from "Hypertension and Leukoaraiosis" to "Senile Cerebral Insufficiency", from "Chronic Cerebrovascular Disorders" to "Multi Infact Dementia (MID)", and from "Senile Dementia" to "Senile Dementia of Alzheimer's Type (SDAT)".

Most of the studies were performed using a total of 60 mg. of nicergoline per day (in some instances 20 mg three times a day, and in others 30 mg twice a day) and all used oral administration. The length of treatment ranged from a minimum of 4 weeks to a maximum of 2 years.

The studies were performed in a number of different countries including Italy, USA, Germany, and Austria.

Not all the data included in this metanalysis are from published sources; four of the included studies were obtained from the internal archives of Pharmacia & Upjohn.

Risk of bias in included studies

The two reviewers have assessed the methodological quality of each trial with particular emphasis on allocation concealment. Empirical research has shown that lack of adequate allocation concealment is associated with bias (Chalmers 1983, Schulz 1995). Indeed, concealment has been found to be more important in preventing bias than other components of allocation, such as the generation of the allocation sequence.

The trials were ranked using the Cochrane approach:

Category A (adequate) where the report describes allocation of treatment by: (i) some form of centralized randomized scheme, such as having to provide details of an enrolled participant to an office by phone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, such as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are allocated sequentially to enrolled participants; (iv) an on-site or coded computer system, given that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participant; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, opaque envelopes; (vi) other combinations of described elements of the process that provide assurance of adequate concealment.

Category B (intermediate) where the report describes allocation of treatment by: (i) use of a 'list' of 'table' to allocate assignments; (ii) use of 'envelopes' or 'sealed envelopes'; (iii) stating the study as 'randomized' without further detail.

Category C (inadequate) where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any other such approach; (iii) any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers or assignments. Trials which have taken inadequate measures to conceal allocation have been shown to yield more pronounced estimates of treatment effect than trials which have taken adequate measures. Trials with unclear allocation concealment produce estimates less pronounced than inadequately concealed trials, but more pronounced than adequately concealed trials (Chalmers 1983,).

INCLUSION CRITERIA

Trials were included if they conformed to categories A or B, while those falling into category C were excluded.

DATA EXTRACTION

Data were independently extracted by two reviewers and cross-checked. Any discrepancies were discussed. Data were not sought on every patient for each outcome measure, since single patient data were unavailable for most of the studies. To allow an intention-to-treat analysis, data were sought irrespective of compliance, whether or not the patients were subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. Unfortunately, only completers' analyses could be performed. Data for an 'on-treatment' or 'completers' analysis were abstracted from publications or internal reports and used for the analysis. In a study where a cross-over design was used, only data from the first treatment period were included. No titration periods prior to the randomized phase of the study were described in the included studies.

DATA ANALYSIS

For continuous or ordinal variables (such as psychometric test scores, clinical global impression scales, functional and quality of life scales) the main outcomes of interest are the change in score from baseline to the final assessment. If ordinal scale data appeared to be approximately normally distributed, or if the investigators' analysis suggested parametric tests to be appropriate, the outcome measures were treated as continuous data. For binary outcomes such as global impression the endpoint itself is of interest and the Peto method of the 'typical odds ratio' was used. A test for heterogeneity of the treatment effect between the trials was made using a standard chi-square statistic. If a test of heterogeneity was negative a weighted estimate of the typical treatment effect across trials, the 'typical odds ratio' (i.e. the odds of an unfavourable outcome amongst treatment-allocated patients to the corresponding odds among controls) was calculated using Peto's log-rank test adapted for ordinal data (Mulrow 1997). It was planned that if there was evidence of heterogeneity of the treatment effect within a group of trials then only data from a sub-group of studies showing homogeneity would be pooled. This procedure was not required. The null hypothesis to be tested was

that, for any of the above outcomes, nicergoline had no effect compared with placebo.

Effects of interventions

Results are described for the different outcomes comprising different methods of cognitive assessment, behavioural rating scales, global clinical impression and tolerability to the drug which were identified as the relevant measurements used in the included studies and which have varied according to the time, geographical area, type of patients, and goal of each study.

Behavioral Rating Scales

Several types of behavioural rating scales were used in the clinical studies with nicergoline. The Sandoz Clinical Assessment Geriatric Scale (SCAG) was the one used with the largest number of patients (in total 814 patients, 405 treated with Nicergoline and 409 with placebo from 7 studies). The results from these diverse studies were homogeneous, even though they included patients with different clinical diagnoses and observed over time periods ranging from 2 months to 12 months. Using the WMD (weighted mean difference) and FE (Fixed Effect) model, the summary effect size was -5.80 [95% CI -8.18, -3.41], p=0.00001 indicating an effect in favour of the active treatment in reducing the behavioural symptoms described by SCAG. This scale has a maximum score of 133 points. The therapeutic effects of nicergoline seem to be evident by 2 months of treatment and maintained for 6 months. In general other behavioural outcome measures which include the GRS, the IADL, and the MACC and were episodically used in few studies, failed to demonstrate statistically significant results although there was a trend favouring treatment.

Cognitive Assessment

Cognitive assessment had been performed for the largest number of subjects with the MMSE and the ADAS-Cog, while only few studies used other measures. The total number of patients who underwent an examination with MMSE was 261, with 132 patients in the nicergoline group and 129 in the placebo group from 3 studies. Even though these individual studies were performed over a long period of time with different acceptable diagnostic criteria, and had a different length of observation ranging from 3 months to 12 months, no significant heterogeneity was found. The effect size of the difference between the treatment groups, favouring nicergoline treatment, was 2.32 [95% CI 1.32, 3.32] using the weighted mean difference and fixed effect model .
The ADAS-Cog was used in two studies performed for 6 and 12 months, both restricted to Alzheimer's disease patients (in total 342 patients, 176 in the nicergoline group and 166 in the placebo group). In both studies the differences tended to favour the nicergoline group (the total effect size (weighted mean difference) was -1.25 [95% CI -3.62, 1.11]) but this difference was not statistically significant.
The other results from various cognitive measures tended to favour nicergoline but were based on a small number of cases.(in total 83 patients) One of these studies, performed on a total of 61 patients, provided evidence of a significant effect of nicergoline on a measure of immediate memory when compared with placebo (effect size 3.60 [95% CI 0.50-6.70], p=0.02).

Clinical Global Impression

Clinical impression was evaluated in a total of 6 different studies with 857 patients, 420 in the nicergoline group and 437 in the placebo group. These results were obtained from periods of observation ranging from 2 months to 12 months and were homogeneous across the studies with chi-square = 7.64 (df = 6, p = 0.27). Using a fixed effects model, the Peto odds ratio for improvement in the subjects treated with nicergoline as opposed to the subjects treated with placebo was 3.33 [95% CI 2.50, 4.43] (p=0.00001).

Tolerability

Tolerability was assessed in 1362 patients, 678 treated with nicergoline and 684 treated with placebo. Safety data were also homogeneous across studies, chi-square = 14.92 (df = 9). Using a fixed effects model, the Peto Odds Ratio for frequency of adverse effects of this drug compared with placebo was 1.51 [95% CI 1.10, 2.07] indicating a modest increase of adverse effects with nicergoline .

DISCUSSION

This review examined controlled studies of nicergoline starting in 1972 and performed with diverse criteria and modalities of evaluation. Despite these potential sources of variability the data used for this meta-analysis were homogeneous in nature. The 11 included studies, out of the 124 studies considered for this review, were all double-blind, placebo controlled clinical studies with extractable numerical data and fulfilled randomization criteria adopted by the Cochrane group. Ten studies are still awaiting an assessment for inclusion, on the assumption that the authors will provide necessary data. At present, the evidence for efficacy of nicergoline is based on studies which have evaluated subjects observed over periods ranging from a minimum of two weeks to a maximum of two years and has been confirmed in different domains such as behaviour, cognition, and clinical judgement. In general, results of this meta-analysis provide some evidence that there are positive effects of nicergoline on cognition and behaviour, and these effects are confirmed by the relevant effect on clinical global impression. There was some evidence of modest problems in the tolerance for this medication.

The evidence of these results is mostly based on studies performed on older patients with mild to moderate cognitive and behavioural impairment of various clinical origins, including chronic cerebrovascular disorders and Alzheimer's dementia. The few studies specifically performed on patients with Alzheimer's disease, even though consistently indicating a trend in favour of the active treatment, were performed with too few people to give a definite answer to the questions concerning the use of nicergoline for this form of dementia.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that nicergoline may have benefits for people with dementia and chronic cognitive disorders. Nicergoline is relatively safe and easy to prescribe and use. The bulk of evidence is obtained from disorders with a cerebrovascular origin, but it is not clear whether the effect is restricted to these conditions. There is little available evidence for a useful role in the treatment of Alzheimer's dementia.

Implications for research

Since many of the studies done on nicergoline were carried out long ago, the drug has not been evaluated using currently available diagnostic categories or with or against other therapeutic agent such as cholinesterase inibitors or antioxidants.

ACKNOWLEDGEMENTS

We thank the full and useful cooperation of the Pharmacia&Upjohn personnel in Milan (Italy) who made available the unpublished data in their archives. We also gratefully acknowledge the contribution of Sara Carfagna, the consumer editor.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amaducci 1999

Methods	multinational, multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	SDAT mild to moderate; 24 patients received nicergoline, 24 placebo;

Amaducci 1999 *(Continued)*

	age > 50 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 12 months
Outcomes	ADAScog, IADL, CGIC for efficacy; adverse events for safety
Notes	CGIC data were not available. ITT (LOCF) analysis is available

Baldelli 1993

Methods	single centre, double blind, randomized, placebo controlled, parallel groups
Participants	Senile cognitive deterioration mild to moderate; 20 patients recived nicergoline, 20 placebo; age > 58 yr.
Interventions	Nicergoline or Placebo 20mg. trice a day (os) for 3 months
Outcomes	MMSE, IADL for efficacy
Notes	Patients received a concomitant psychosensory training

Battaglia 1989

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	Dementia mild to moderate; 158 patients received nicergoline, 157 placebo; age > 55 yr.
Interventions	Nicergoline or Placebo 20mg. twice a day (os) for 6 months
Outcomes	SCAG for efficacy; HR and blood pressure for safety
Notes	Only completers' analysis is available for 101nicergoline and 100 placebo cases (unpublished report from Pharmacia-Upjohn)

Bes 1999

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	Hypertension & leukoaraiosis; 36 patients received nicergoline, 36 placebo; age > 60 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 24 months
Outcomes	Rey Auditory Verbal Learning Test
Notes	ITT (LOCF) analysis is available

Crook 1996

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	SDAT mild to moderate; 74 patients received nicergoline, 75 placebo; age > 50 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 6 months
Outcomes	ADAScog, CGIC for efficacy; adverse events for safety
Notes	ITT (LOCF) analysis is available

Donoso 1979

Methods	single centre, double blind, randomized, placebo controlled, parallel groups
Participants	Senile cognitive deterioration with no signs of dementia; 11 patients received nicergoline, 11 placebo; age > 65 yr.
Interventions	Nicergoline or Placebo 10mg. trice a day (os) for 6 weeks
Outcomes	WAIS IQ
Notes	Completers' analysis

GCISN 1985

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	Senile cerebral insufficiency mild to moderate; 82 patients received nicergoline, 80 placebo; age > 55 yr.
Interventions	Nicergoline or Placebo 20mg. twice a day (os) for 6 months
Outcomes	SCAG for efficacy; adverse events for safety
Notes	It describes also a crossover study but with no data available for inclusion in this review

Herrmann 1997

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	MID; 70 patients received nicergoline, 69 placebo; age 55-85 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 6 months
Outcomes	SCAG, MMSE, CGI for efficacy; adverse events for safety
Notes	

Nappi 1997

Methods	multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	SDAT or MID mild to moderate; 51patients received nicergoline, 50 placebo; age 60-80 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 12 months
Outcomes	SCAG, MMSE, CGI for efficacy; adverse events for safety
Notes	

Roelandts 1994

Methods	multinational, multicentre, double blind, randomized, placebo controlled, parallel groups
Participants	Senile dementia mild to moderate; 82 patients received nicergoline, 80 placebo; age > 55.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 6 months
Outcomes	SCAG, GRS, MACC for efficacy; adverse events for safety
Notes	

Saletu 1995

Methods	single centre, double blind, randomized, placebo controlled, parallel groups
Participants	MID mild to moderate; 24 patients received nicergoline, 26 placebo; age > 60 yr.
Interventions	Nicergoline or Placebo 30mg. twice a day (os) for 8 weeks
Outcomes	SCAG, MMSE, CGI, EEG/ERP for efficacy; side effects for safety
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ardia 1985	cross-over study with no data divided for each arm
Battaglia 1990	controlled study vs another active drug
Battaglia 1995b	preliminary data of another included study
Bente 1979	controlled study vs dihydroergotoxin-mesylate
Bernini 1977	not a controlled study
Blaha 1979	clinical study with geriatric patients with transitory cognitive and behavioural deficits

Study	Reason for exclusion
Brambilla 1978	controlled study between three different dosage of nicergoline
Cascone 1978	data not available in numerical form
Crook 1997a	not clinical study
Crook 1997b	preliminary results of another included study
Dauverchain 1979	not controlled study. Chronic cerebrovascular insufficiency
Efimov 1991	not controlled clinical study, Diabetic patients
Fabbrini 1995	not controlled study
Gara 1993	controlled study vs pentoxifylline in cerebral atherosclerosis patients
Guardamagna 1972	not controlled study
Iliff 1979	not controlled study. Blood flow in patients with cerebrovascular disease
Kaemmerer 1980	not controlled study
Kobayashi 1992	not controlled study
Kugler 1984	not controlled study
Kugler 1985	controlled study vs dihydroergotamine mesilate in patients with cerebral insufficiency
Kugler 1990	clinical study on normal subjects taking barbiturates
Ladurner 1991	controlled clinical study vs co-dergocrine mesilate in patients with multinfarct dementia
Maiolo 1972	not controlled study
Man'kovskii 1989a	controlled study vs prostacyclin in brain hypoxia
Man'kovskii 1989b	not controlled study
Marolda 1978	controlled study vs eburnamonine
Michelangeli 1975	clinical study performed with chronic cerebrovascular patients included without a formal assessment of cognitive deficits but on the basis only of clinical signs of vascular pathology
Miletto 1976	not controlled study
Moglia no year	a review of different studies
Montanini 1973	not controlled study
NCSG 1990	controlled study vs ergoloid mesylates
Nico 1981	controlled study vs papaveroline on cerebral ischaemic vasculopathy
no author 1989	data presented in another included study

Study	Reason for exclusion
Ohtomo 1986a	controlled study vs Ca-hopantenate
Ohtomo 1986b	controlled study vs Hydergine
Ohtomo 1986c	not controlled study
Prencipe 1974	not controlled study
Saletu 1979a	multiple treatments controlled study run in a cross-over fashion with each patient taking all different treatments at different periods of the observation
Saletu 1980	review with no data in numerical format
Saletu 1987	controlled study vs a different dosage of nicergoline
Saletu 1996a	same data of another included study
Saletu 1996b	same data of another included study
Saletu 1997	same data of another included study
Samso 1979	not controlled neurophysiological study on patients with chronic cerebrovascular disorders
Schneider 1994	controlled study vs antagonic-stress
Shtok 1985	controlled study vs dihydroergotoxin on cerebral haemodynamics of patients with acute and chronic cerebrovascular diseases
Toni 1973	not controlled study
Vesel'skii 1991	not placebo controlled clinical study
Vesel'skii 1992	not placebo controlled clinical study
Winblad 2000	not a clinical study, a review

DATA AND ANALYSES

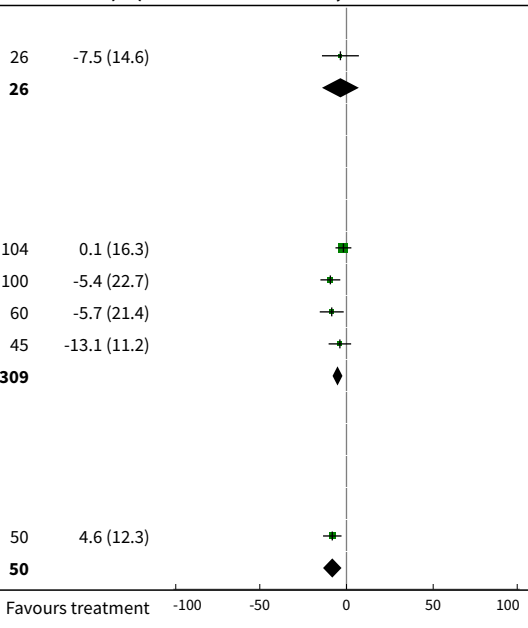
Comparison 1. Behavioral Rating Scales

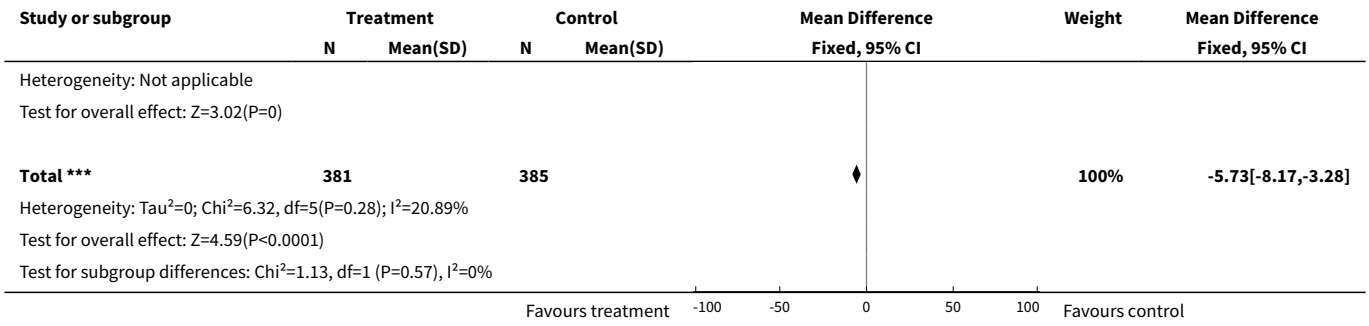
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SCAG total scores	6	766	Mean Difference (IV, Fixed, 95% CI)	-5.73 [-8.17, -3.28]
1.1 Scag total score after 2 months	1	50	Mean Difference (IV, Fixed, 95% CI)	-3.5 [-14.14, 7.14]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 SCAG total score after 6 months	4	615	Mean Difference (IV, Fixed, 95% CI)	-5.18 [-8.03, -2.33]
1.3 SCAG total score after 12 months	1	101	Mean Difference (IV, Fixed, 95% CI)	-8.19 [-13.51, -2.87]
2 GRS total scores	1	200	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-3.50, 1.10]
2.1 GRS total score after 6 months	1	200	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-3.50, 1.10]
3 MACC total scores	1	200	Mean Difference (IV, Fixed, 95% CI)	1.4 [-2.31, 5.11]
3.1 MACC total scores after 6 months	1	200	Mean Difference (IV, Fixed, 95% CI)	1.4 [-2.31, 5.11]
4 IADL total score	2	234	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.70, 0.36]
4.1 IADL total score after 3 months	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.80, 2.20]
4.2 IADL total score after 12 months	1	194	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.87, 0.39]

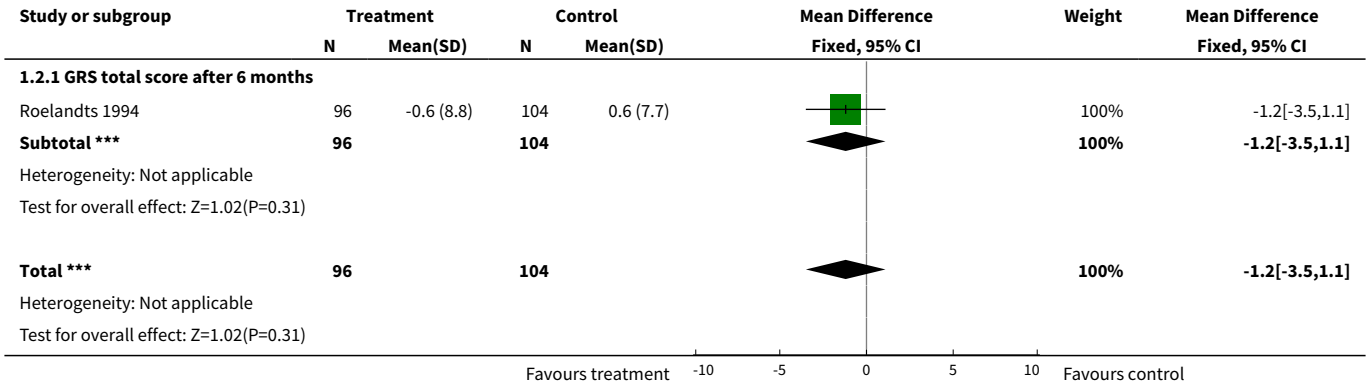
Analysis 1.1. Comparison 1 Behavioral Rating Scales, Outcome 1 SCAG total scores.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 Scag total score after 2 months							
Saletu 1995	24	-11 (22.6)	26	-7.5 (14.6)		5.28%	-3.5[-14.14,7.14]
Subtotal ***	**24**		**26**			**5.28%**	**-3.5[-14.14,7.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.64(P=0.52)							
1.1.2 SCAG total score after 6 months							
Roelandts 1994	96	-1.7 (16.7)	104	0.1 (16.3)		28.58%	-1.77[-6.35,2.81]
Battaglia 1989	101	-14.7 (18.5)	100	-5.4 (22.7)		18.26%	-9.3[-15.02,-3.58]
Herrmann 1997	61	-14.2 (17.1)	60	-5.7 (21.4)		12.56%	-8.51[-15.41,-1.61]
GCISN 1985	48	-16.9 (19.8)	45	-13.1 (11.2)		14.19%	-3.81[-10.3,2.68]
Subtotal ***	**306**		**309**			**73.59%**	**-5.18[-8.03,-2.33]**
Heterogeneity: Tau^2=0; Chi^2=5.19, df=3(P=0.16); I^2=42.18%							
Test for overall effect: Z=3.56(P=0)							
1.1.3 SCAG total score after 12 months							
Nappi 1997	51	-3.6 (14.9)	50	4.6 (12.3)		21.13%	-8.19[-13.51,-2.87]
Subtotal ***	**51**		**50**			**21.13%**	**-8.19[-13.51,-2.87]**

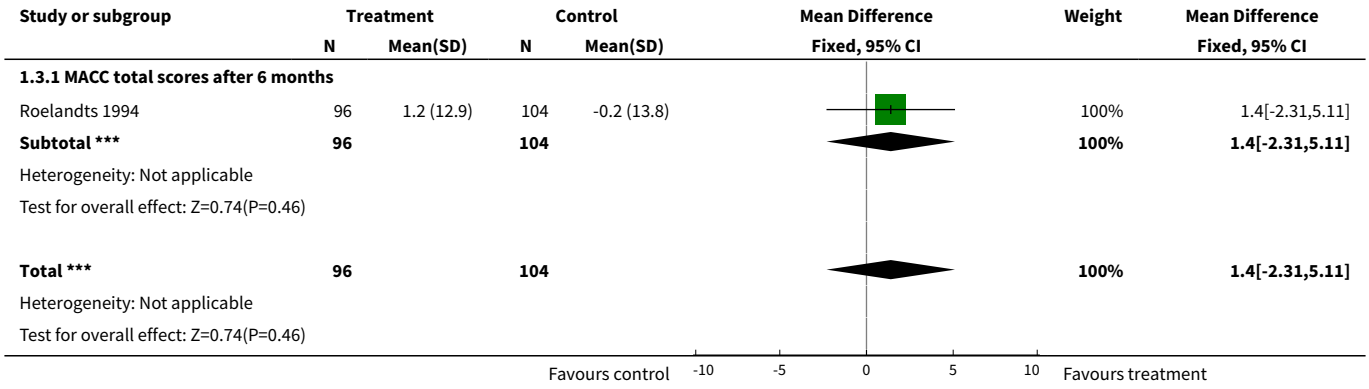




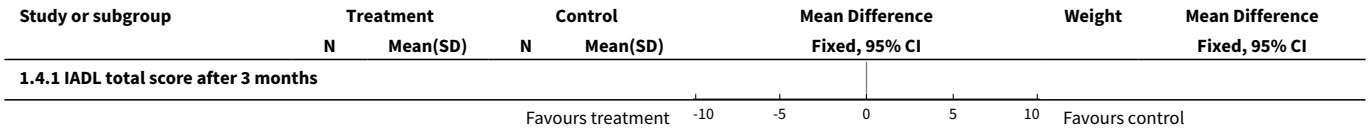
Analysis 1.2. Comparison 1 Behavioral Rating Scales, Outcome 2 GRS total scores.

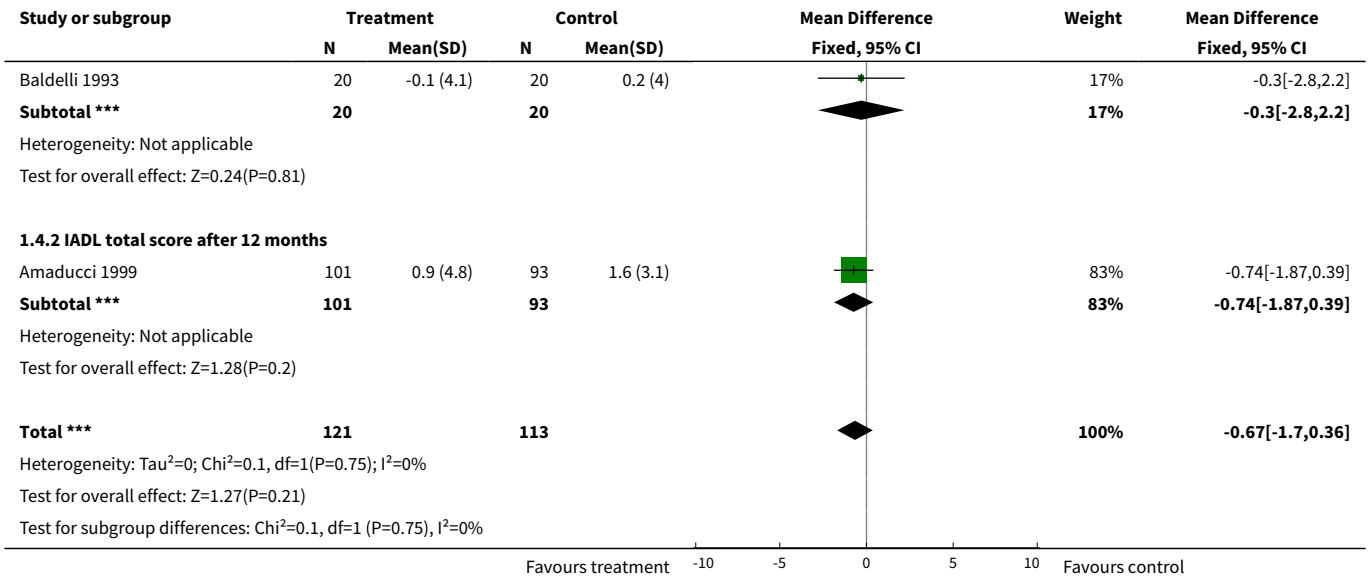


Analysis 1.3. Comparison 1 Behavioral Rating Scales, Outcome 3 MACC total scores.



Analysis 1.4. Comparison 1 Behavioral Rating Scales, Outcome 4 IADL total score.

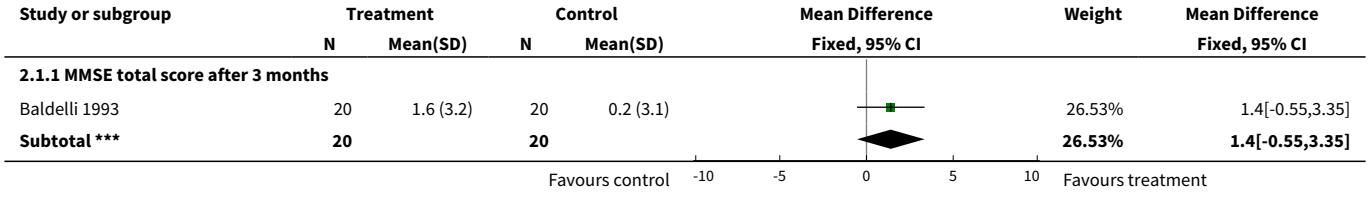


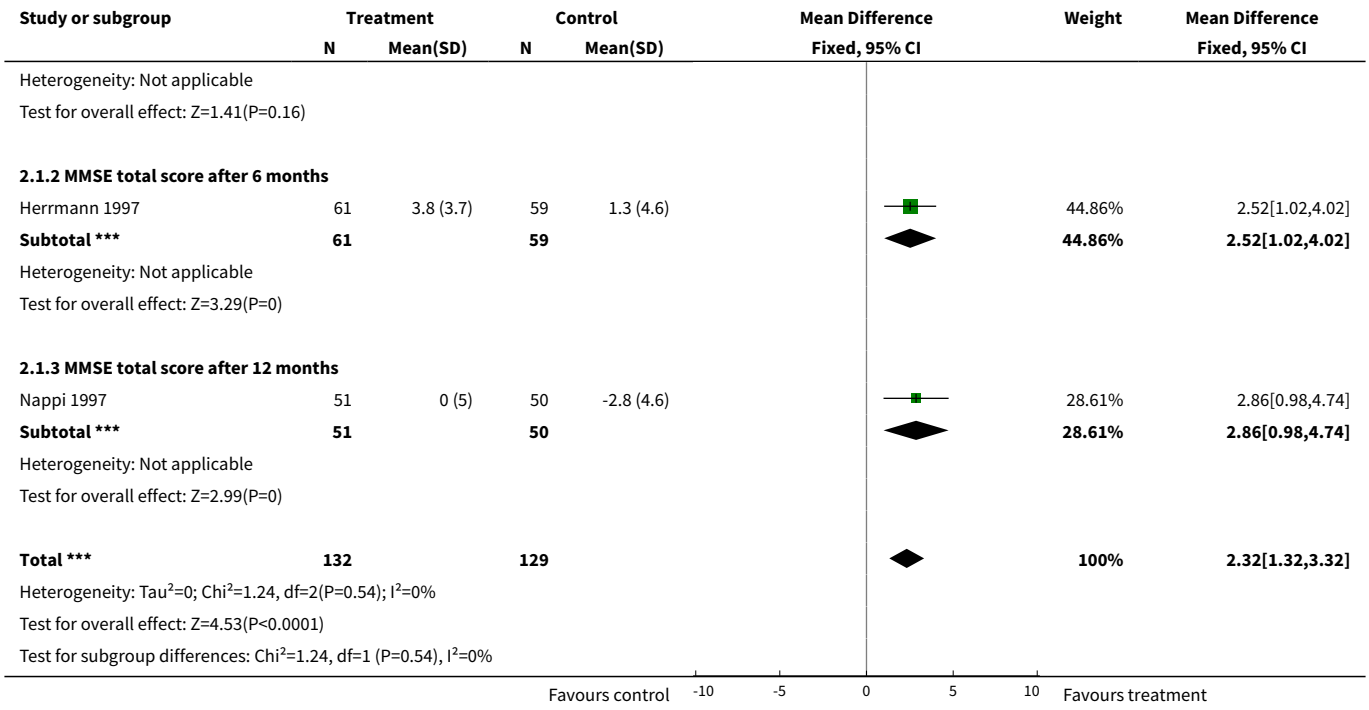


Comparison 2. Cognitive Assessment

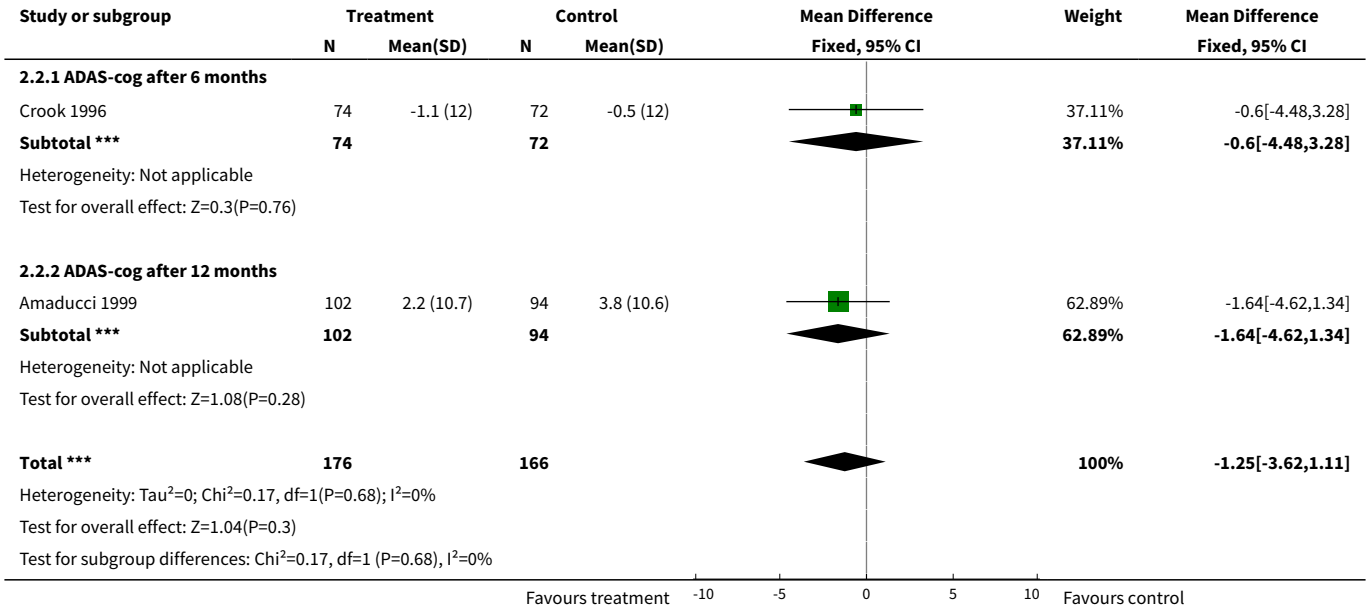
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 MMSE total score	3	261	Mean Difference (IV, Fixed, 95% CI)	2.32 [1.32, 3.32]
1.1 MMSE total score after 3 months	1	40	Mean Difference (IV, Fixed, 95% CI)	1.40 [-0.55, 3.35]
1.2 MMSE total score after 6 months	1	120	Mean Difference (IV, Fixed, 95% CI)	2.52 [1.02, 4.02]
1.3 MMSE total score after 12 months	1	101	Mean Difference (IV, Fixed, 95% CI)	2.86 [0.98, 4.74]
2 ADAS-cog	2	342	Mean Difference (IV, Fixed, 95% CI)	-1.25 [-3.62, 1.11]
2.1 ADAS-cog after 6 months	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-4.48, 3.28]
2.2 ADAS-cog after 12 months	1	196	Mean Difference (IV, Fixed, 95% CI)	-1.64 [-4.62, 1.34]
3 AVLT, immediate memory	1	61	Mean Difference (IV, Fixed, 95% CI)	3.6 [0.50, 6.70]
4 WAIS IQ	1	22	Mean Difference (IV, Fixed, 95% CI)	1.0 [-6.27, 8.27]

Analysis 2.1. Comparison 2 Cognitive Assessment, Outcome 1 MMSE total score.

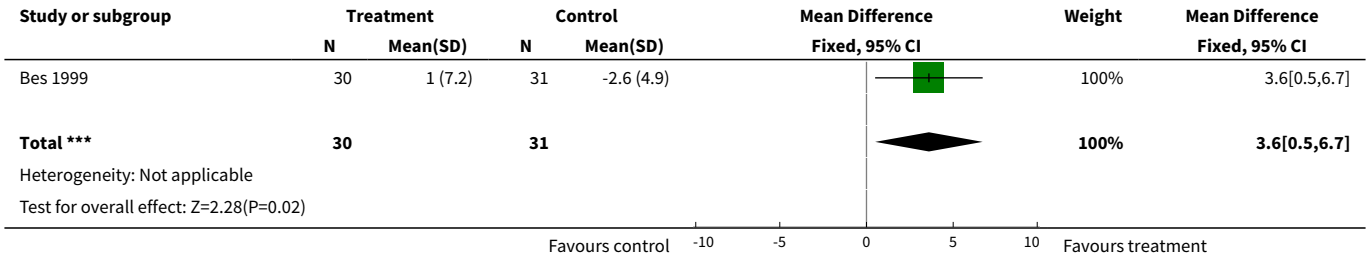




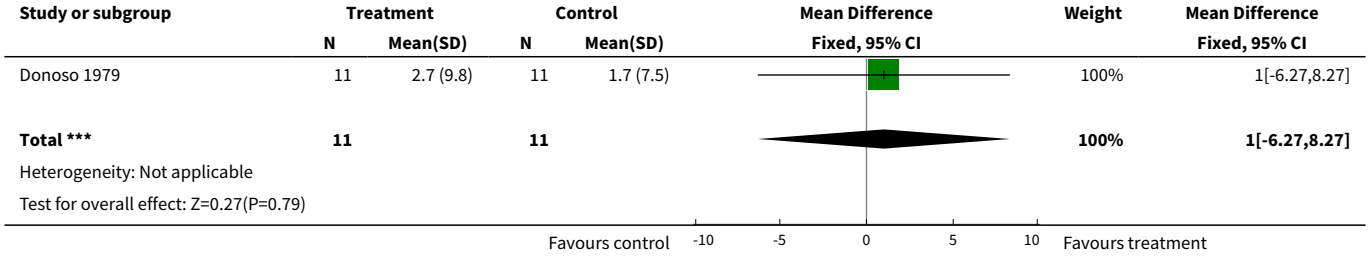
Analysis 2.2. Comparison 2 Cognitive Assessment, Outcome 2 ADAS-cog.



Analysis 2.3. Comparison 2 Cognitive Assessment, Outcome 3 AVLT, immediate memory.



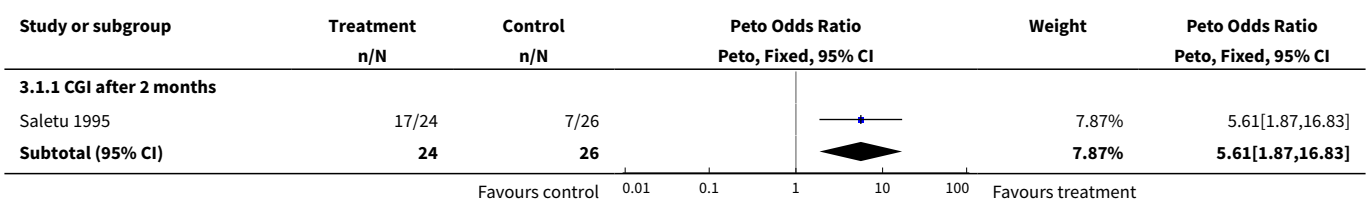
Analysis 2.4. Comparison 2 Cognitive Assessment, Outcome 4 WAIS IQ.

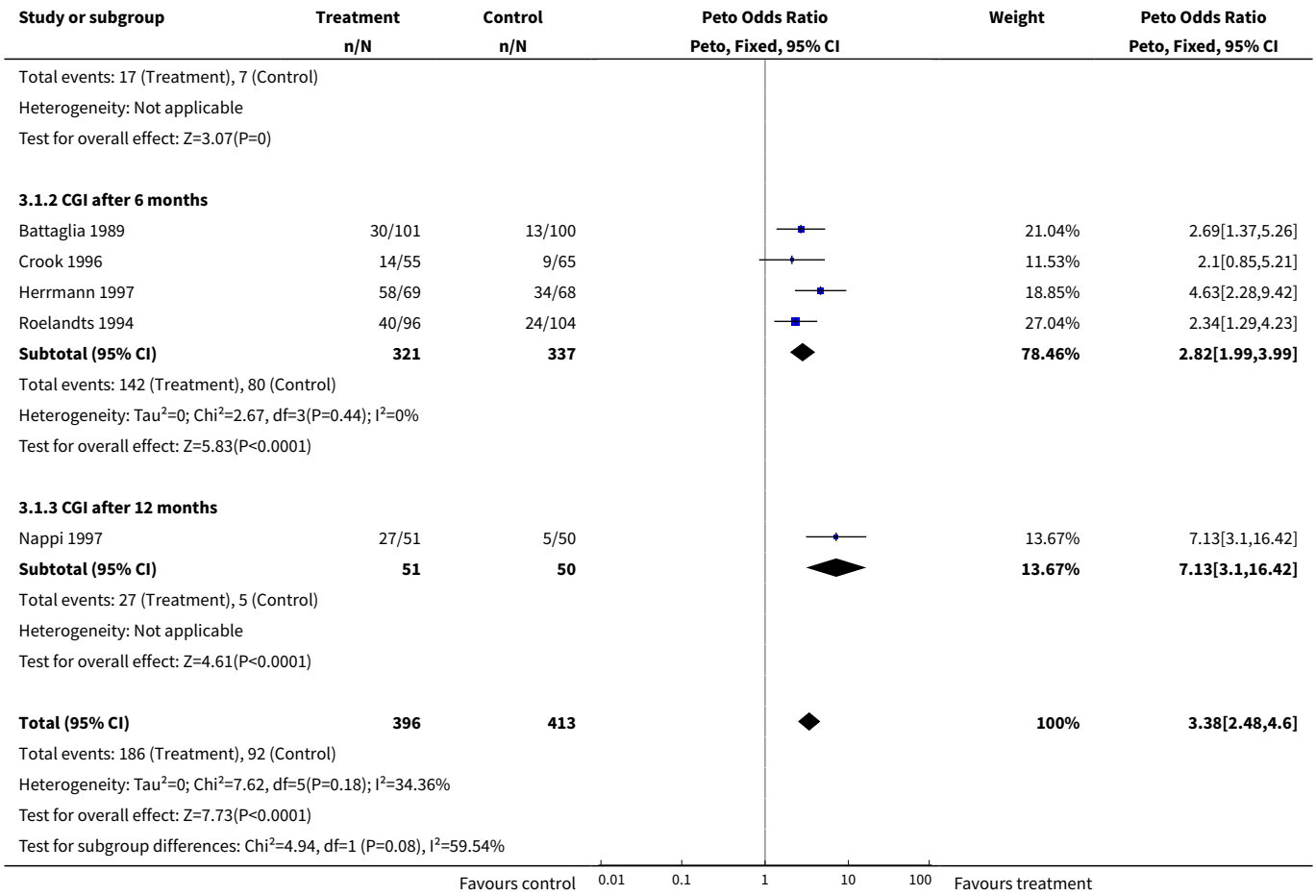


Comparison 3. Clinical Evaluation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global Impression (number showing improvement)	6	809	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [2.48, 4.60]
1.1 CGI after 2 months	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.61 [1.87, 16.83]
1.2 CGI after 6 months	4	658	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.82 [1.99, 3.99]
1.3 CGI after 12 months	1	101	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.13 [3.10, 16.42]

Analysis 3.1. Comparison 3 Clinical Evaluation, Outcome 1 Clinical Global Impression (number showing improvement).

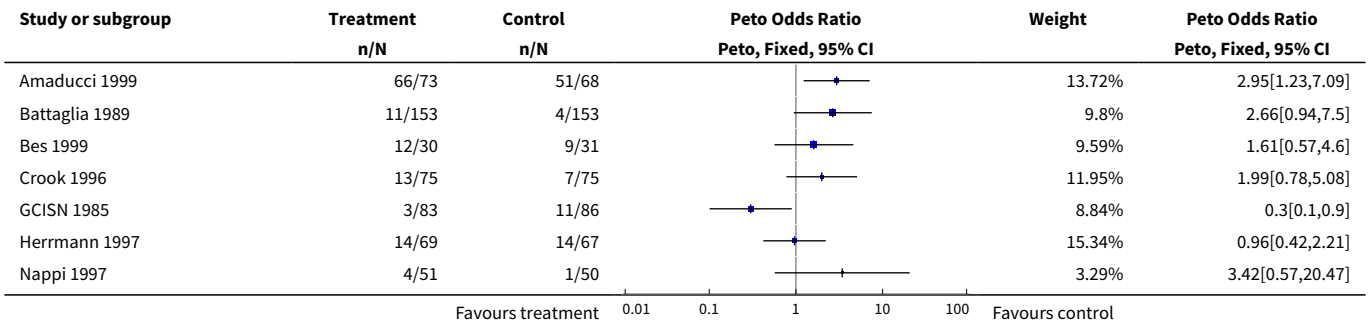


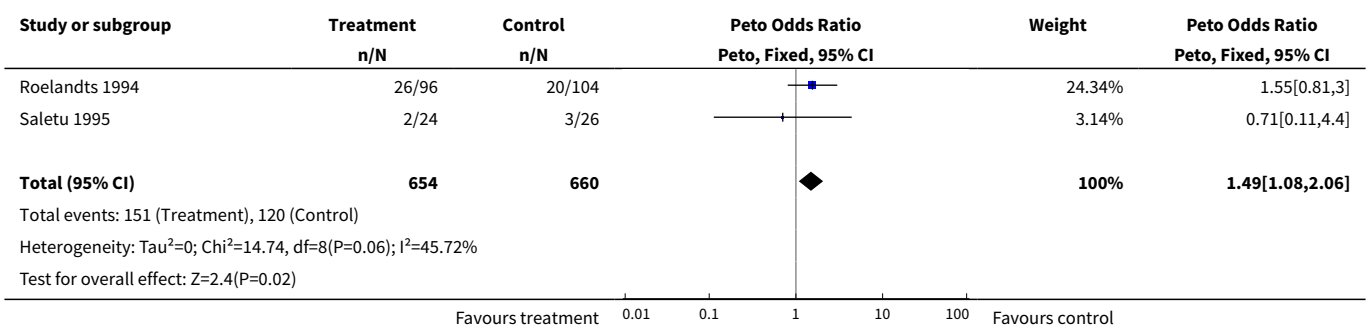


Comparison 4. Tolerability

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 total number suffering at least one adverse events	9	1314	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [1.08, 2.06]

Analysis 4.1. Comparison 4 Tolerability, Outcome 1 total number suffering at least one adverse events.





WHAT'S NEW

Date	Event	Description
5 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 4, 2001

Date	Event	Description
24 August 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-MF produced a culled reference list for approval of LF. MF obtained the unpublished references and extracted the data from all references. MF wrote the first draft of the review.
-LF: checked the analyses and revised the protocol and review.
-MF: all correspondence

-CDCIG contact editor: Peter Whitehouse

DECLARATIONS OF INTEREST

In past years one of the authors (MF) has worked as consultant for Farmitalia (later incorporated into Pharmacia) in the development of some clinical studies with nicergoline. None of those studies was of interest for this review owing to the type of patients considered or the research protocol used.

INDEX TERMS

Medical Subject Headings (MeSH)

Cognition Disorders [*drug therapy]; Dementia [*drug therapy]; Nicergoline [*therapeutic use]; Nootropic Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans