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[Intervention Review]

Vinpocetine for cognitive impairment and dementia

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ABSTRACT

Background

Vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (Vinca minor) and discovered in the late 1960s. Although used in human treatment for over twenty years, it has not been approved by any regulatory body for the treatment of cognitive impairment. Basic sciences studies have been used to claim a variety of potentially important effects in the brain. However, despite these many proposed mechanisms and targets, the relevance of this basic science to clinical studies is unclear.

Objectives

To assess the efficacy and safety of vinpocetine in the treatment of patients with cognitive impairment due to vascular disease, Alzheimer's disease, mixed (vascular and Alzheimer's disease) and other dementias.

Search methods

The Cochrane Dementia and Cognitive Improvement Group's Specialized Register was searched on 23 March 2009 using the terms vinpocetin*, cavinton, kavinton, Rgh-4405, Tcv-3B, "ethyl apovincaminate", vinRx, periwinkle, "myrtle vincapervinc" and cezayirmeneksesi. This register contains up to date references from major health care databases like MEDLINE and EMBASE as well as records from trials databases in the field of dementia.The manufacturers of vinpocetine were asked for information on trials of vinpocetine for dementia. In addition we tried to collect articles not listed in MEDLINE or other sources on the Internet (e.g. articles in Hungarian and Romanian).

Selection criteria

All human, unconfounded, double-blind, randomized trials in which treatment with vinpocetine was administered for more than a day and compared to control in patients with vascular dementia, Alzheimer's dementia or mixed Alzheimer's and vascular dementia and other dementias. Non-randomized trials were excluded.

Data collection and analysis

Data were independently extracted by the two reviewers (SzSz and PW) and cross-checked. Data from "washout" periods were not used for the analysis. For continuous or ordinal variables, such as cognitive test results, the main outcomes of interest were the change in score from baseline. The categorical outcome of global impression was transformed to binary data (improved or not improved) as was the occurrence of adverse effects; here the endpoint itself was of interest and the Peto method of the "typical odds ratio" was used. A test for heterogeneity of treatment effects between the trials was made if appropriate. Data synthesis and analysis were performed using the Cochrane Review Manager software (RevMan version 4.1).

Main results

All identified studies were performed before and in the early 1990s and used various terms and criteria for cognitive decline and dementia. The three studies included in the review involved a total of 583 people with dementia treated with vinpocetine or placebo. The reports of these studies did not make possible any differentiation of effects for degenerative or vascular dementia. The results show benefit associated with treatment with vinpocetine 30 mg/day and 60 mg/day compared with placebo, but the number of patients treated for six months or more was small. Only one study extended treatment to one year. Adverse effects were inconsistently reported and without regard for relationship to dose. The available data do not demonstrate many problems of adverse effects but intention-to-treat data were not available for any of the trials.

Authors' conclusions

Although the basic science is interesting, the evidence for beneficial effect of vinpocetine on patients with dementia is inconclusive and does not support clinical use. The drug seems to have few adverse effects at the doses used in the studies. Large studies evaluating the use of vinpocetine for people suffering from well defined types of cognitive impairment are needed to explore possible efficacy of this treatment.

PLAIN LANGUAGE SUMMARY

Insufficient evidence of benefits of vinpocetine for people with dementia

Preclinical data of uneven quality suggest a potential beneficial effect of vinpocetine in chronic cerebrovascular diseases and on cognitive performance in a variety of animal models. Clinical trials to test these hypotheses were performed before currently used criteria for dementia had become generally accepted. The results show improvement after the treatment with vinpocetine versus placebo, but the number of demented patients treated for at least six months was small. The available data does not demonstrate many side effect problems. Although the basic science is interesting, the evidence for beneficial effect of vinpocetine on patients with dementia is inconclusive and does not support clinical use.

BACKGROUND

Vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (Vinca minor), and was discovered in the late 1960s. Although used in human treatment for over twenty years, it has not been approved by any regulatory body for the treatment of cognitive impairment. Basic sciences studies have been invoked to claim a variety of potentially important effects in the brain. However, the relevance of these findings in basic science to clinical studies is unclear. Vinpocetine has been claimed to improve cerebral metabolism, increase glucose and oxygen consumption by the brain, and improve its resistance to hypoxia (Erdo 1990), and to elevate cerebral ATP and cAMP levels. It has been shown to improve cerebral microcirculation and increase cerebral blood flow by inhibiting platelet aggregation (Kuzuya 1982), improving red blood cell deformability (Hayakawa 1992) and reducing cerebral vascular resistance. A neuroprotective effect has been claimed through blocking voltage-gated sodium channels (Bönöczk 2000; Molnár 1995; Rataud 1994) and potentiating the effect of adenosine in cytotoxic hypoxia (Krieglstein 1991).

Vinpocetine has been claimed to enhance neurotransmitter production release or concentration in the brain. Some animal experiments have demonstrated a beneficial effect of vinpocetine on memory and learning deficits induced by scopolamine and hypoxia (DeNoble 1986; DeNoble 1987).

A PET study (Szakall 1998) of the administration of vinpocetine to chronic stroke patients demonstrated an increase in glucose uptake and release in non-affected territories of brain. A review performed by Nagy 1998 suggests that vinpocetine might be effective in the treatment of chronic psycho syndromes caused by cerebral changes of vascular or degenerative origin. Vinpocetine has also been claimed to enhance memory function in young healthy volunteers (Coleston 1988).

Vinpocetine is recommended by the manufacturer for the treatment of cerebrovascular disorders, cognitive decline, and dementia. It has also been recommended for acute stroke, and is still used for this indication in several countries. The evidence in justification of this usage does not meet modern regulatory standards, and bias exists in some of the sources of information. A Cochrane review (Bereczki 1997) concluded that there is insufficient evidence to justify the use of vinpocetine for the acute phase of cerebrovascular disease.

OBJECTIVES

To assess the efficacy and safety of vinpocetine in the treatment of patients with cognitive impairment due to vascular disease, Alzheimer's disease, mixed (vascular and Alzheimer's disease) and other dementias.

METHODS

Criteria for considering studies for this review

Types of studies

All human, unconfounded, double-blind, randomized trials in which treatment with vinpocetine was administered for more than a day and compared with control in patients with vascular dementia, Alzheimer's dementia or mixed Alzheimer's and vascular dementia and other dementias. Non-randomized trials were excluded.

Types of participants

We planned to evaluate all trials involving people with dementia, who fulfilled accepted criteria for the classification of dementia. Modern diagnostic criteria include DSM (APA 1987, APA 1994), ICD-10 (WHO 1992), NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association) (McKhann 1984), NINDS-AIREN (National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences) (Román 1993) or accepted equivalents. Unfortunately, all of the studies were performed before these criteria had become generally accepted and used less precise classifications such as Lauter's criteria for organic psycho syndrome.

Lauter's (Lauter 1980) criteria:
1. Mild organic psycho-syndrome: signs of brain performance deficiency and personality change beginning with patient complaints about deficiencies in attention and concentration, poor adaptation to new situations and loss of motivation and emotional stability. These impairments to be of a degree described as causing a slight impairment in social competence.
2. Moderate organic psycho-syndrome: evidence of cognitive deficit or personality changes, impairing the patients' life activities and needing psychiatric intervention. Patients at this level require assistance, but not constant supervision and care.

Types of interventions

We planned to include placebo-controlled trials of any duration with any route of administration.

Types of outcome measures

The primary outcomes of interest were:
Cognitive function (as measured by psychometric tests)
Global impression
Quality of life
Functional performance
Effect on carer
Death
Safety and adverse effects

Outcome measurements in the included studies were:
1. Syndrom-Kurztest - SKT (Erzigkeit 1986). This is a brief battery used mainly in German-speaking countries. It includes nine performance subtests, each limited to one minute, including naming objects and numerals, reversal naming, immediate and delayed recall, recognition memory, arranging and replacing blocks, and counting symbols. The test cluster into two factors - memory and attention deficit. Time-based scoring requires subjects to perform rapidly; higher scores represent worse performances. In the included studies, only patients with at least a score of nine points (representing a well-accepted cut-off value for cognitive deficit) were admitted.
2. Clinical Global Impression Scale - CGI Scale (Guy 1976). This is used to assess both severity of illness and clinical improvement, by comparing the condition of the person at the beginning and at the end of treatment. A seven-point scoring system is usually

used with low scores showing decreased severity and/or overall improvement.

Search methods for identification of studies

The trials were identified from a series of searches of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group of which the last one was done on 23 March 2009 using the terms vinpocetin*, cavinton, kavinton, Rgh-4405, Tcv-3B, "ethyl apovincaminate" , vinRx, periwinkle, "myrtle vincapervinc" and cezayirmeneksesi.

This register contains records from the following major healthcare databases *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. For more detailed information on what the Group's Specialized Register contains see the Cochrane Dementia and Cognitive Improvement Group methods used in reviews.

The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS and a number of trial registers and grey literature sources were also searched separately on 23 March 2009 for records added to these databases after the original search was performed for this review in January 2007 . The search strategies used to identify relevant controlled trials for this review can be found in Appendix 1.

In addition to this we requested that manufacturers (Gedeon Richter Ltd., Budapest, Hungary; COVEX SA, Madrid, Spain; Takeda Chemical Industries Ltd., Osaka, Japan and Thiemann Arzneimittel, Waltrop, Germany) of vinpocetine give us information about all randomized and controlled trials on vinpocetine in dementia and cognitive impairment. Gedeon Richter Ltd. and COVEX SA replied but no additional trials were found.

Data collection and analysis

Identification of studies

The screening of the references retrieved by the search was performed independently by the two reviewers (SzSz and PW) who independently selected trials. Disagreements were resolved by discussion and persisting differences were to be adjudicated by an editor from the Cochrane Dementia and Cognitive Improvement Group (JGE).

Quality assessment

The same two reviewers (SzSz and PW) assessed the methodological quality of each trial. The quality of the methodology of each selected trial was rated using the criteria of the Cochrane Collaboration Handbook (Mulrow 1997):

Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Inadequate concealment
Trials were included if they conform to categories A or B, and those falling into category C were excluded.

Data extraction

Data were independently extracted by the same two reviewers (SzSz and PW) and cross-checked. Any discrepancies were discussed. Individual patient data were unavailable for selected studies and only completers' analysis was possible. Data from "washout" periods were not used for the analysis.

Data analysis

For continuous or ordinal variables such as cognitive test result the main outcomes of interest were the change in score from baseline. The categorical outcome of global impression measured by CGI was transformed in binary data (improved or not improved) as was the incidence of adverse effects; here the endpoint itself was of interest and the Peto method of the "typical odds ratio" was used. A chi-square test for heterogeneity of treatment effects between the trials was made if appropriate.

RESULTS

Description of studies

All identified studies were performed before and in the early 1990s and used various terms and criteria for cognitive decline and dementia. Studies described as double-blind and placebo-controlled but without mentioning randomization were excluded. There were three Italian trials (Balestreri 1987; Manconi 1986; Peruzza 1986) falling into this category but these studies had also other deficiencies such as unclear inclusion criteria based only on Mini-Mental State Examination (MMSE: Folstein 1975) results.

The three included studies (Blaha 1989; Fenzl 1986; Hindmarch 1991) from Germany enrolled patients who fulfilled Lauter's criteria for mild and moderate organic psycho-syndrome which is similar to currently used criteria for dementia but does not exclude the presence of depression.

In the German studies outcomes were primarily measured using the CGI (change in condition and degree of severity of disease) and SKT. Some other scales such as Erlangen Depression Scale, Mood Scale, Life Satisfaction Scale were also used. Safety data were presented as different descriptions of adverse events, but analysis of these data was difficult because of incomplete reports. Severe side effects or death were not reported. Included patients met criteria for mild to moderate dementia but subgroup analyses for different types of dementia or by demographic characteristics such as sex were not possible. The doses varied between 15 and 60 mg/day and comparisons using different doses were made with the same placebo group within each study. Length of treatment varied from 12 weeks to 1 year. Patients with severe organic brain disease with focal neurological symptoms, psychosis, alcohol or drug abuse, allergies and those treated with psychoactive drugs (antidepressants, neuroleptics, sedatives/hypnotics and narcotics) were excluded. Depression was not a criterion of exclusion, however.

Risk of bias in included studies

All included studies were described as randomized but without details about the randomization process, thereby meeting grade B criteria for evidence. Only completers' data were available. In the three included studies, a total number of 728 patients were enrolled, but 145 of them dropped out or were excluded because of deviations from the protocol. Fenzl 1986 noted 18 dropouts (6 on vinpocetine and 12 on placebo) and 24 exclusions due to protocol deviations from a total number of 243 patients. Blaha 1989 reported 22 dropouts (7 due to adverse effects) and 43 excluded cases due to deviations from the protocol out of the initial number of 282 patients. In the study of Hindmarch 1991, 203 patients were enrolled and 3 dropped out due to adverse effects (2 from the vinpocetine group and 1 from the placebo group). The authors

noted also 35 exclusions due either to lack of compliance or to deviation from the protocol (21 from the vinpocetine group and 14 from the placebo group). The effect of depression on cognitive performance and the effect of the drug on affect were potential confounders in all studies.

Effects of interventions

In the three included studies (Blaha 1989; Fenzl 1986; Hindmarch 1991) a total of 583 mild or moderately demented patients, who were at least 58 years old, received oral treatment with vinpocetine (n=377) or placebo (n=206). Outcome data for CGI clinical improvement (change from baseline) and SKT score-changes were available for all studies.
Comparing vinpocetine with placebo, a statistically significant improvement on CGI was obtained after a treatment with vinpocetine 30 mg/day or 60 mg/day for 12 to 16 weeks (OR 2.50, 95% Confidence Interval (CI): 1.30 to 4.82, P=0.006 and OR 2.77, 95% CI: 1.40 to 5.46, P=0.003 respectively). In the study of Fenzl 1986, after a treatment with vinpocetine 60 mg/day for one year the results were the same (OR 5.50, 95% CI: 2.76 to 10.98, P<0.00001) after either 26 and 52 weeks. The change on CGI after 15 mg vinpocetine after 12 weeks of treatment favouring vinpocetine was not significant (OR 1.42, 95% CI: 0.61 to 3.30, P=0.4).

When we calculated the number of patients who showed improvement by endpoint on CGI without regard to differences in doses or length of treatment there was a statistically significant difference favouring vinpocetine over placebo (OR 3.27, 95% CI: 2.18 to 4.91, P<0.00001).

The SKT score showed a statistically significant difference favouring 30 mg/day vinpocetine over placebo (Weighted Mean Difference (WMD) -1.18, 95% CI: -1.93 to -0.42, P=0.002) and 60 mg/day vinpocetine over placebo (WMD 0.94, 95% CI: -1.50 to -0.39, P=0.0009) but 15 mg/day of vinpocetine did not differ statistically from placebo (WMD -0.90, 95% CI: -1.90 to 0.10, P=0.08). The change from baseline at endpoint of SKT score was analysed pooling the data of all treatment groups from each trial. This favoured vinpocetine (WMD -1.19, 95% CI: -1.73 to -0.66, P=0.00001).

Two of the studies reported significant improvement favouring vinpocetine on the Erlangen Depression Scale and Mood Scale (Well-Being Scale, Befindlichtkeits-Skala (BF-S)), but statistical analysis of data was not possible. Quality of life was measured by the Life Satisfaction Scale in two included studies. Beneficial effects of vinpocetine were reported in one of them but statistical analysis was not possible. We did not analyse the effect of vinpocetine on severity of disease (part of CGI) as changes from baseline data were not available.

Safety of treatment was evaluated by calculating the number of patients with adverse effects but only completers' data were available. One of the studies was omitted from the analysis because of unclear reporting of adverse effects. More adverse effects were observed after 16 weeks of treatment with 30 mg vinpocetine versus placebo (OR 2.63, 95% CI: 1.04 to 6.64, P=0.04) favouring placebo. After one year of treatment with vinpocetine 60 mg/day, in the Fenzl 1986 study, there was no significant difference between the active drug and the placebo group with regards to adverse effects (OR 0.90, 95% CI: 0.44 to 1.84). When we analysed this dose over different lengths of treatment, the result favoured placebo but without statistical significance (OR 1.12, 95% CI: 0.60 to 2.08).

DISCUSSION

Preclinical data of uneven quality suggest a potential beneficial effect of vinpocetine in chronic cerebrovascular diseases and on cognitive performance in a variety of animal models. Clinical trials to test these hypotheses were performed before currently used criteria for dementia had become generally accepted. The three studies included in this review totaled 583 patients fulfilling Lauter's criteria for mild or moderate organic psycho-syndrome treated with vinpocetine or placebo. The reports of these studies did not permit differentiation of effects on degenerative or vascular dementia. The results show benefit from treatment with vinpocetine 30 mg/day and 60 mg/day compared with placebo, but the number of patients treated for six months or more was small. Only one study (Fenzl 1986) extended treatment to one year. The improvement was evident on CGI and SKT scales when we pooled trials across different doses and length of treatment. Adverse effects were not consistently well reported and without adequate regard for relationship to dose. The available data do not demonstrate many adverse effects of vinpocetine. However, intention-to-treat data were not available for any of the trials. As the Lauter's criteria for "organic psycho-syndrome" do not exclude depression, the effects of depression as a confounder are not clear. We could not verify the reported beneficial effect of vinpocetine on depression and quality of life because of lack of adequate presentation of the data in the three studies.

AUTHORS' CONCLUSIONS

Implications for practice

Although the basic science is interesting, the evidence for a beneficial effect of vinpocetine for people with dementia is inconclusive and does not support clinical use. The drug seems to have few adverse effects at the doses used in the studies.

Implications for research

Large studies evaluating the use of vinpocetine for people suffering from well defined types of cognitive impairment are needed to explore possible efficacy of this treatment.

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Dymphna Hermans and Vittoria Lutje, Jacqueline Birks and John Grimley Evans from the CDCIG Editorial Board for substantial help in preparing the review.
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Szatmari 2003

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Blaha 1989

Methods	Multicentre, double-blind, placebo-controlled, randomized, method of randomization not detailed.
Participants	Degenerative and vascular dementia mild to moderate severity, fulfilling Lauter's criteria. Other types of dementia or extra/ intracranial causes excluded. The study was performed in Germany. Number of patients treated with different doses of vinpocetine: 161, and those with placebo: 56. The mean age of patients (either sex) was 74 years (range: 58-91)
Interventions	Vinpocetine or placebo 3x5 or 3x10 or 3x20 mg/day, oral route, for 12 weeks
Outcomes	CGI and SKT for efficacy
Notes	completers analysis

Fenzl 1986

Methods	Multicentre, double-blind, placebo-controlled, randomized, method of randomization not detailed.
Participants	Degenerative and vascular dementia mild to moderate severity, fulfilling Lauter's criteria. Other types of dementia or extra/ intracranial causes excluded. The study was performed in Germany. Number of patients treated with different doses of vinpocetine: 111, and those with placebo: 53. The mean age of patients (either sex) was 72.5 years in placebo group and 73.1 years in vinpocetine group (all above 60 years).
Interventions	Vinpocetine or placebo 3x20 mg/day, oral route, for 1 year
Outcomes	CGI and SKT for efficacy
Notes	completers analysis

Hindmarch 1991

Methods	Multicentre, double-blind, placebo-controlled, randomized, method of randomization not detailed.
Participants	Degenerative and vascular dementia mild to moderate severity, fulfiling Lauter's criteria. Other types of dementia or extra/ intracranial causes excluded. The study was performed in Germany. Number of patients treated with vinpocetine: 105, and those with placebo: 96. The mean age of patients (either sex) was 74.1 years in placebo group and 72.9 and 74.2 years in vinpocetine groups (range: 60-88 years).
Interventions	Vinpocetine or placebo 3x10 or 3x20 mg/day, oral route, for 16 weeks
Outcomes	CGI and SKT for efficacy

Hindmarch 1991 *(Continued)*

Notes	completers analysis

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

Study	Reason for exclusion
Balestreri 1987	Described as double-blind placebo controlled but no mention of randomization. Elderly patients with chronic cerebral dysfunction.
Filimonov 2007	No placebo group.
Ivanova 2008	Open-label study using vinpotropil in patients with chronic “vertebrobasilar insufficiency”, is-chaemic stroke in carotid territory and cerebral ischaemia after ruptured aneurism.
Kishimoto 1995	Open study, compared vinpocetine plus idebenone vs idebenone, not placebo controlled.
Kovacs no year	A review of different studies
Kuznetsov 2007	No placebo group
Manconi 1986	Described as double-blind placebo controlled but no mention of randomisation. Patients with chronic cerebral dysfunction.
Nesterova 2008	Not RCT.
Peruzza 1986	Described as double-blind placebo controlled but no mention of randomization. Elderly patients with chronic cerebral dysfunction.
Pitzus no year	Same data of Manconi 1986
Tanashyan 2007	Not RCT.
Thal 1989	Oben-label pilot trial.
Valikovics 2007	No placebo group.
Vamosi 1976	Vinpocetine vs xantinol nicotinate. Not placebo controlled. Cognitive status was not evaluated.
Wolters 1992	Double-blind placebo and piracetam controlled, not randomized study.
Zakharov 2007	No placebo group.

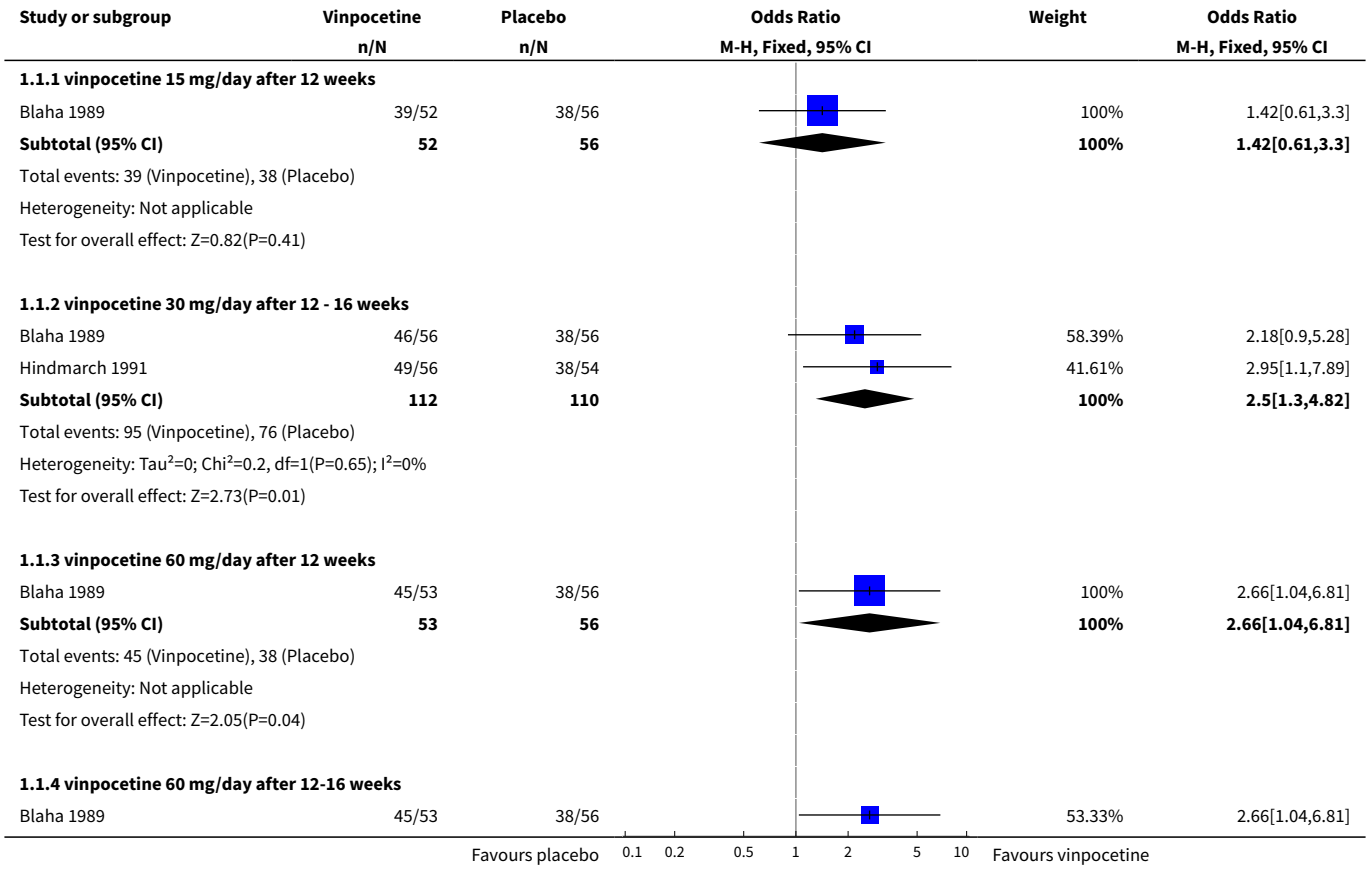
DATA AND ANALYSES

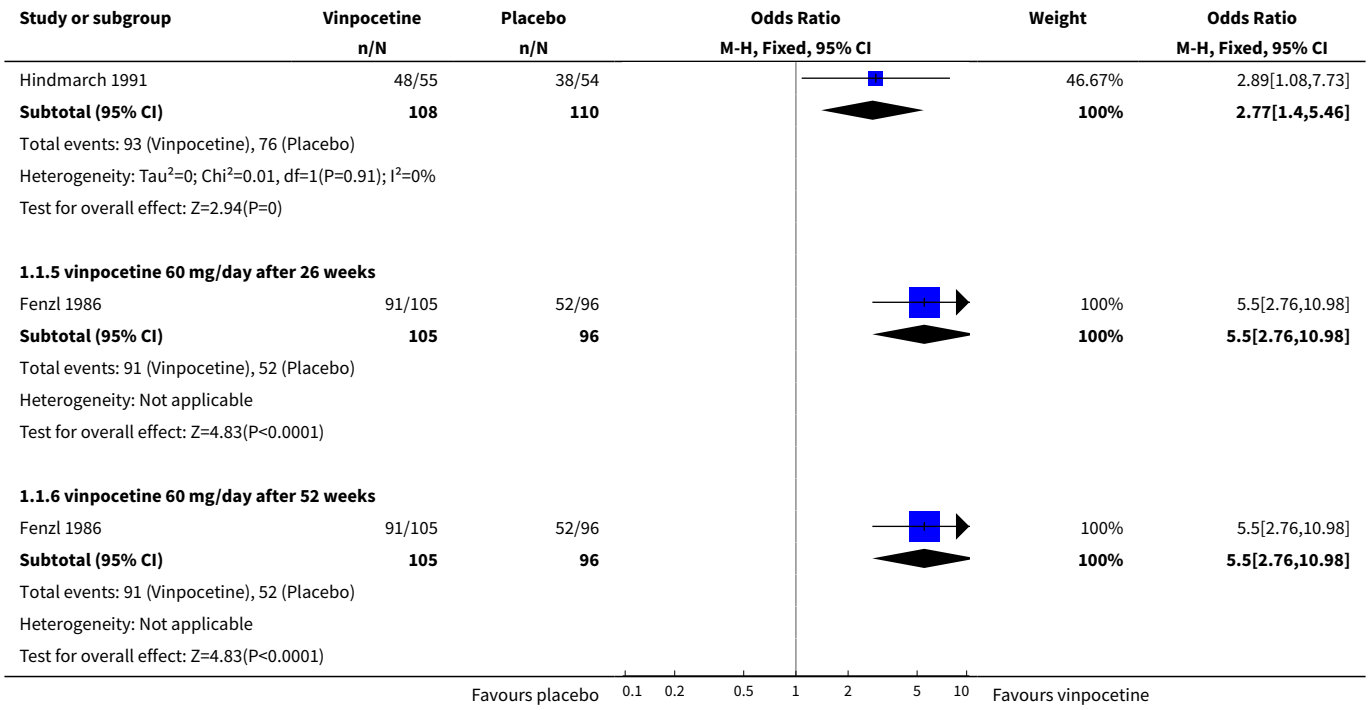
Comparison 1. vinpocetine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CGI improvement	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 vinpocetine 15 mg/day after 12 weeks	1	108	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.61, 3.30]
1.2 vinpocetine 30 mg/day after 12 - 16 weeks	2	222	Odds Ratio (M-H, Fixed, 95% CI)	2.50 [1.30, 4.82]
1.3 vinpocetine 60 mg/day after 12 weeks	1	109	Odds Ratio (M-H, Fixed, 95% CI)	2.66 [1.04, 6.81]
1.4 vinpocetine 60 mg/day after 12-16 weeks	2	218	Odds Ratio (M-H, Fixed, 95% CI)	2.77 [1.40, 5.46]
1.5 vinpocetine 60 mg/day after 26 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	5.5 [2.76, 10.98]
1.6 vinpocetine 60 mg/day after 52 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	5.5 [2.76, 10.98]
2 SKT attention and memory (change from baseline)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 vinpocetine 15 mg/day at 12 weeks	1	108	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.90, 0.10]
2.2 vinpocetine 30 mg/day at 12-16 weeks	2	222	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.93, -0.42]
2.3 vinpocetine 60 mg/day at 12-16 weeks	3	418	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-1.50, -0.39]
2.4 vinpocetine 60 mg at 52 weeks	1	200	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.58, -0.22]
3 side effects	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 vinpocetine 15 mg/day (12 weeks of treatment)	1	108	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.43, 8.29]
3.2 vinpocetine 30 mg/day (12-16 weeks of treatment)	3	224	Odds Ratio (M-H, Fixed, 95% CI)	2.63 [1.04, 6.64]
3.3 vinpocetine 60 mg/day (12-16 weeks of treatment)	2	218	Odds Ratio (M-H, Fixed, 95% CI)	2.18 [0.84, 5.64]
3.4 vinpocetine 60 mg/day (12 - 52 weeks of treatment)	3	419	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.71, 2.21]
4 CGI Numbers who show improvement by endpoint	3	583	Odds Ratio (M-H, Fixed, 95% CI)	3.27 [2.18, 4.91]

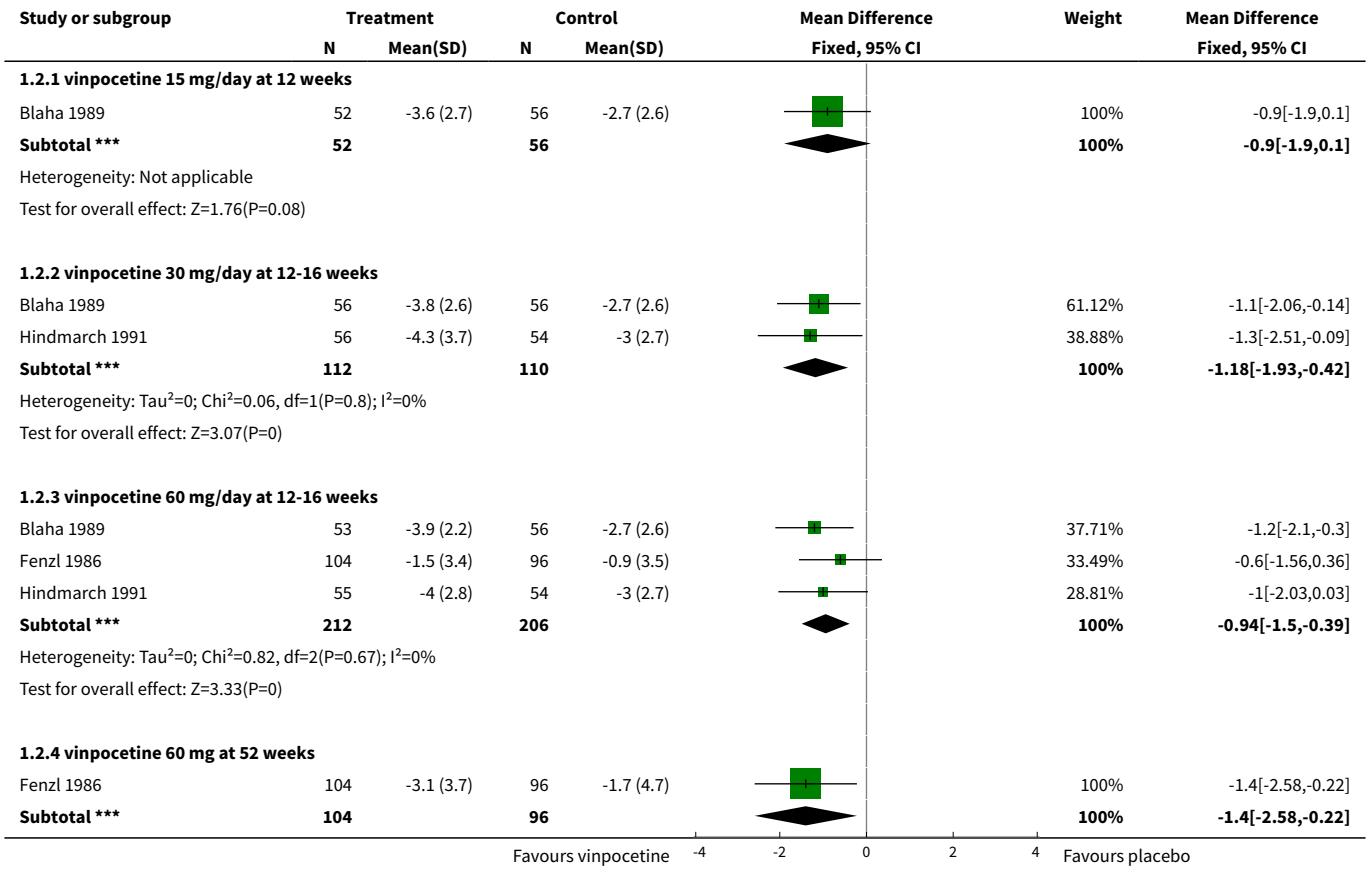
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 mean dose 30mg/day, endpoint 12 weeks	1	217	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [1.00, 3.94]
4.2 mean dose 45mg/day, endpoint 16 weeks	1	165	Odds Ratio (M-H, Fixed, 95% CI)	2.92 [1.30, 6.55]
4.3 dose 60mg/day, endpoint 26 weeks	1	201	Odds Ratio (M-H, Fixed, 95% CI)	5.5 [2.76, 10.98]
5 SKT attention and memory (change from baseline) at endpoint	3	582	Mean Difference (IV, Fixed, 95% CI)	-1.19 [-1.73, -0.66]
5.1 mean dose 35 mg/day	1	217	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.88, -0.32]
5.2 mean dose 45 mg/day	1	165	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-2.15, -0.25]
5.3 mean dose 60 mg/day	1	200	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.58, -0.22]

Analysis 1.1. Comparison 1 vinpocetine vs placebo, Outcome 1 CGI improvement.

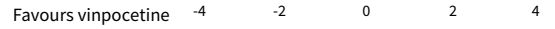




Analysis 1.2. Comparison 1 vinpocetine vs placebo, Outcome 2 SKT attention and memory (change from baseline).

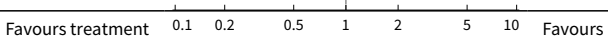


Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=2.33(P=0.02)							
Test for subgroup differences: Chi²=0.68, df=1 (P=0.88), I²=0%							

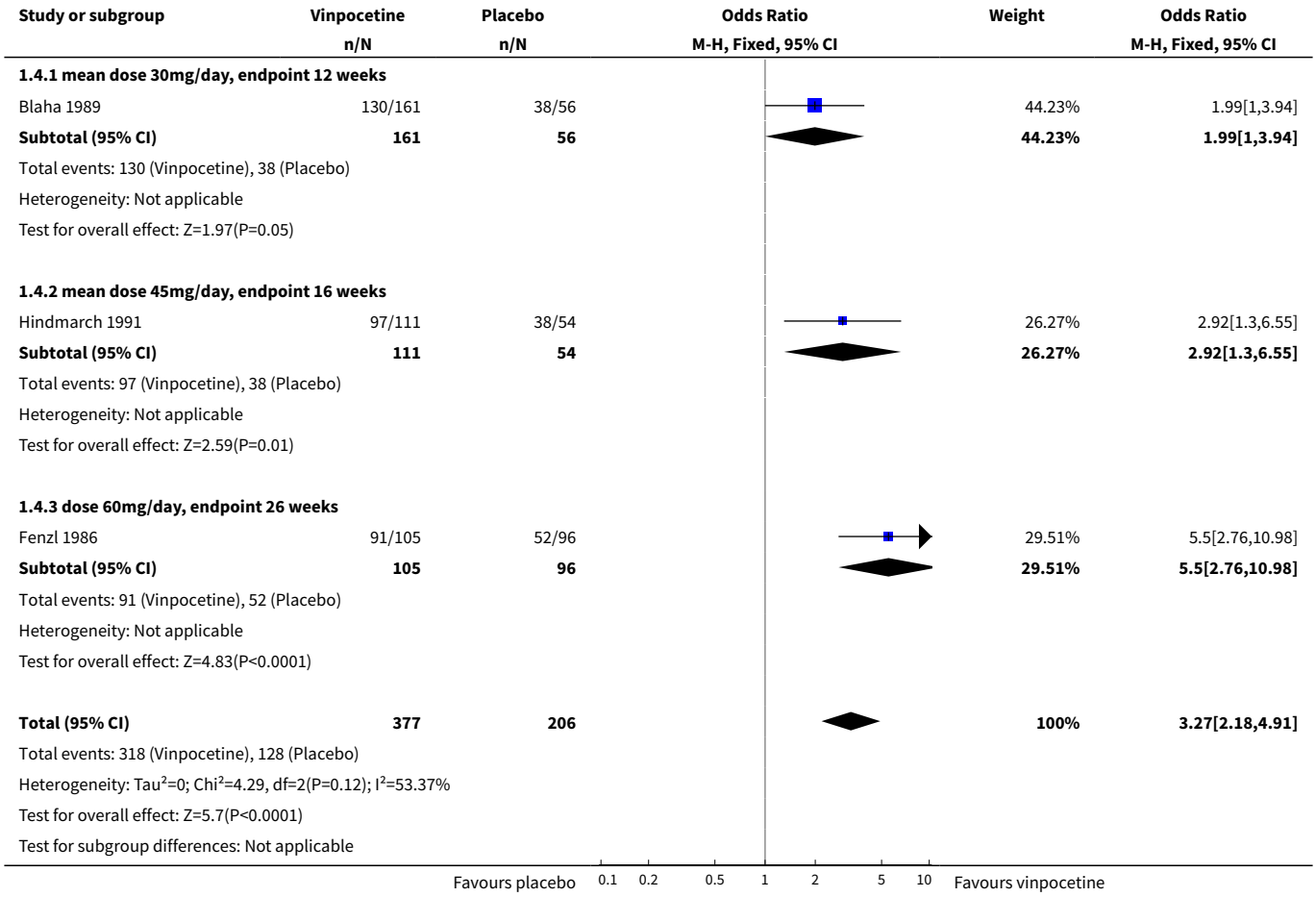


Analysis 1.3. Comparison 1 vinpocetine vs placebo, Outcome 3 side effects.

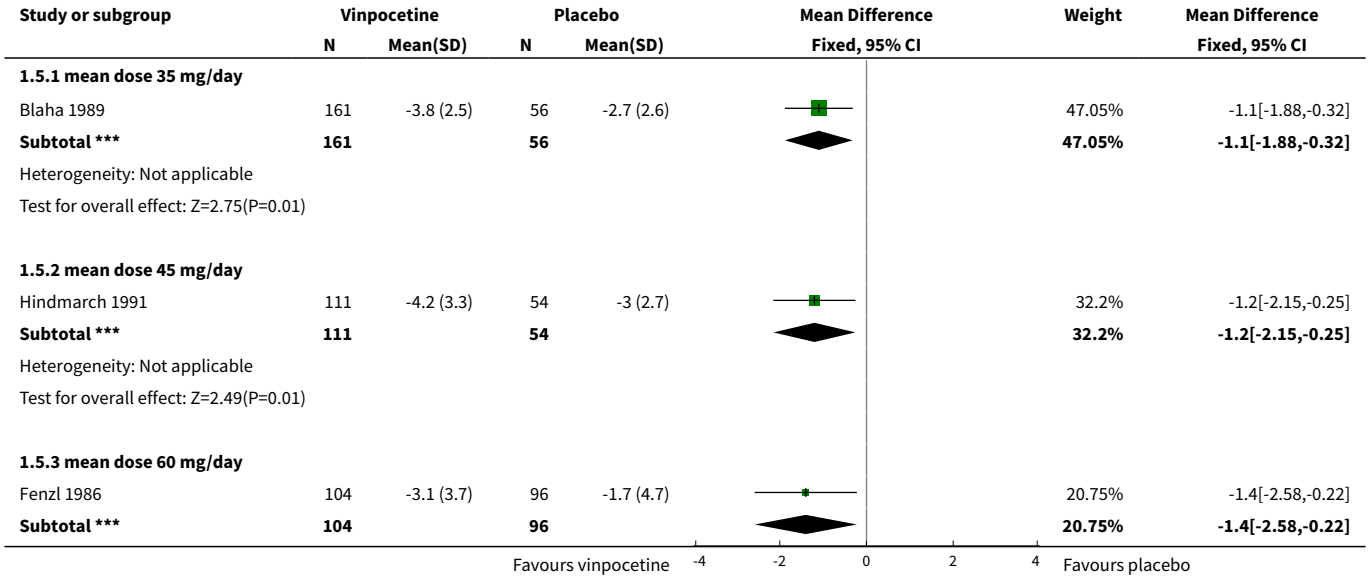
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 vinpocetine 15 mg/day (12 weeks of treatment)					
Blaha 1989	5/52	3/56		100%	1.88[0.43,8.29]
Subtotal (95% CI)	**52**	**56**		**100%**	**1.88[0.43,8.29]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.4)					
1.3.2 vinpocetine 30 mg/day (12-16 weeks of treatment)					
Blaha 1989	7/56	3/56		43.97%	2.52[0.62,10.31]
Fenzl 1986	0/1	0/1			Not estimable
Hindmarch 1991	10/56	4/54		56.03%	2.72[0.8,9.27]
Subtotal (95% CI)	**113**	**111**		**100%**	**2.63[1.04,6.64]**
Total events: 17 (Treatment), 7 (Control)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
1.3.3 vinpocetine 60 mg/day (12-16 weeks of treatment)					
Blaha 1989	6/53	3/56		42.86%	2.26[0.53,9.52]
Hindmarch 1991	8/55	4/54		57.14%	2.13[0.6,7.54]
Subtotal (95% CI)	**108**	**110**		**100%**	**2.18[0.84,5.64]**
Total events: 14 (Treatment), 7 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.95); I²=0%					
Test for overall effect: Z=1.61(P=0.11)					
1.3.4 vinpocetine 60 mg/day (12 - 52 weeks of treatment)					
Blaha 1989	6/53	3/56		11.97%	2.26[0.53,9.52]
Fenzl 1986	18/105	18/96		72.08%	0.9[0.44,1.84]
Hindmarch 1991	8/55	4/54		15.96%	2.13[0.6,7.54]
Subtotal (95% CI)	**213**	**206**		**100%**	**1.26[0.71,2.21]**
Total events: 32 (Treatment), 25 (Control)					
Heterogeneity: Tau²=0; Chi²=2.14, df=2(P=0.34); I²=6.58%					
Test for overall effect: Z=0.79(P=0.43)					

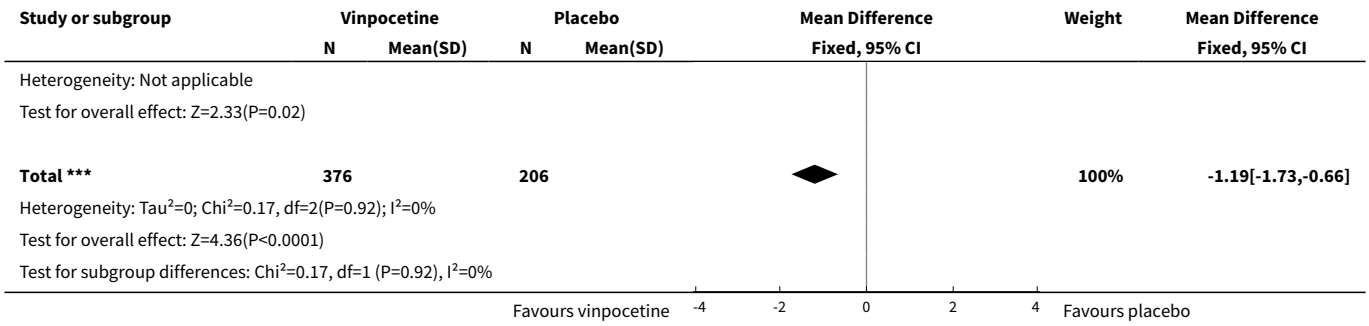


Analysis 1.4. Comparison 1 vinpocetine vs placebo, Outcome 4 CGI Numbers who show improvement by endpoint.



Analysis 1.5. Comparison 1 vinpocetine vs placebo, Outcome 5 SKT attention and memory (change from baseline) at endpoint.





APPENDICES

Appendix 1. Sources searched and search strategies used

Source	Search strategy
Medline (Pubmed)	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke) AND ((random* OR controlled OR (double blind*) OR (single blind*)
Embase (Ovid SP)	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke) AND ((random* OR controlled OR (double blind*) OR (single blind*)
PsycInfo (Ovid SP)	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke) AND ((random* OR controlled OR (double blind*) OR (single blind*)
Cinahl (Ovid SP)	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke) AND ((random* OR controlled OR (double blind*) OR (single blind*)
Lilacs (bireme)	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke) AND ((random* OR controlled OR (double blind*) OR (single blind*)
CDCIG SR	(vinpocetin* OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi)
CENTRAL (The Cochrane Library Issue 1 2009)	(vinpocetin OR cavinton OR kavinton OR "Rgh-4405" OR "Tcv-3B" OR "ethyl AND apovincaminate" OR vinRx OR periwinkle OR "myrtle AND vincapervinc" OR cezayirmeneksesi) AND (Alzheimer* OR dement* OR MCI OR cognit* or Pick* OR Huntington* OR Creutzfeldt* OR Binswanger* OR Korsakoff* OR Wernicke)
ISTP Conference Proceedings http://portal.isiknowledge.com/portal.cgi	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)

(Continued)

Australian Digital Theses Program http://adt.caul.edu.au/	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
Canadian Theses and Dissertations http://www.collectionscanada.ca/thesescanada/index-e.html	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
WHO trials register	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
Current Controlled trials: Meta Register of Controlled trials (mRCT) http://www.controlled-trials.com/	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
ISRCTN Register	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
Nederlands Trial Register http://www.trialregister.nl/trialreg/index.asp	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
ClinicalTrials.gov http://www.ClinicalTrials.gov	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
IPFMA Clinical Trials Register www.ifpma.org/clinicaltrials.html	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
UMIN Japan Trial Register http://www.umin.ac.jp/ctr/	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)
OPENsigle	(vinpocetin) AND (Alzheimer* OR dement* OR cognit*)

WHAT'S NEW

Date	Event	Description
8 April 2009	New search has been performed	An update search was performed for this review on 23 March 2009; no new studies have been included, and 7 have been excluded

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 1, 2003

Date	Event	Description
7 November 2008	Amended	Converted to new review format.
24 January 2007	New search has been performed	January 2007: an update search was performed and revealed no new references or trials in this area. The conclusions of the review remain unchanged.
8 April 2005	New search has been performed	April 2005: an update search was performed and revealed no new references or trials in this area. The conclusions of the review therefore remain unchanged.
18 November 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-SzSz: drafting of review versions, selection of trials for inclusion/exclusion; extraction of data; entry of data; interpretation of data analyses
-PW: drafting of review versions, selection of trials for inclusion/exclusion; interpretation of data analyses.

-Consumer editor: Suzie Sami
-Contact editor: J. Grimley Evans
-This review has been peer reviewed

Update search 2007: Dymphna Hermans; update search 2009: Vittoria Lutje.

DECLARATIONS OF INTEREST

Peter Whitehouse consults for a variety of pharmaceutical companies that might be competitors for this product in the market including Janssen (galantamine), Forest Labs (memantine) and Pfizer (donepezil).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIH/NIA Medical Goals in Dementia: Ethics and Quality of Life, USA.
- Shigeo & Megumi Takayama Foundation, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [drug therapy]; Cognition Disorders [*drug therapy]; Dementia [*drug therapy]; Dementia, Vascular [drug therapy]; Nootropic Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Vinca Alkaloids [*therapeutic use]

MeSH check words

Humans