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Clinical Efficacy of Piracetam in Cognitive Impairment: A Meta-Analysis

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Key Words

Piracetam · Cognition disorders · Meta-analysis · Randomised clinical trials

Abstract

A meta-analysis has been performed including nineteen double blind, placebo controlled studies with piracetam in patients suffering from dementia or cognitive impairment in the elderly. These studies had as common outcome measure a clinical global impression of change, a measure of clinically meaningful improvement. The meta-analysis of this global outcome followed the methodology set forward by the Cochrane Collaboration. This article describes the studies, the patient populations and the methods of data extraction. The results of the meta-analysis demonstrate a difference between those individuals treated with piracetam and those given placebo, both as significant odds ratio and as a favourable number needed to treat. While there may be problems in meta-analyses and the interpretation of the statistical results, the results of this analysis provide compelling evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment.

Introduction

During the last ten years four cholinesterase inhibitors have appeared on the market for the treatment of dementia. The efficacy of these compounds has been demonstrated based on current regulatory criteria and the use of modern, widely accepted outcome measures.

Nevertheless, a number of older compounds have been used for decades in the treatment of dementias and, more generally, in age-related cognitive impairment. The evidence supporting their efficacy is based upon older studies, mostly small in scale, with significant design limitations, imprecise patient selection criteria and inadequate outcome measures as seen from a current perspective. Such products continue to be widely used, but lack modern evidence-based evaluations of their efficacy.

It is therefore important to re-examine the potential efficacy of these compounds using modern methodological and rigorous statistical techniques that enable pooling of data from diverse studies. The purpose of the present review is to evaluate the clinical efficacy of one such older product, piracetam. A first attempt using systematic literature review and meta-analytical statistical techniques came from the Cochrane Collaboration in 1997 [1]. Data reported on clinical global impression of change from

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double blind, placebo controlled, parallel group studies were included in the analysis. The results, based on only five studies, showed a statistically significant superiority of piracetam over placebo, with the most conservative odds ratio being 2.89 (95% confidence interval 1.01 to 8.24). However, due to the small number of studies included, the precision of this analysis was low and the confidence intervals were large.

In the present review we were able to include a number of additional studies by using both published and unpublished reports and by applying systematic methods of data extraction. The objective was to determine the clinical efficacy of piracetam in ageing and dementia.

Piracetam (2-oxo-1-pyrrolidine-acetamide) is a cyclic derivative from GABA synthesised by Strubbe and Cyprysiak at UCB S.A., Pharma Sector, in Belgium, more than 30 years ago. It was first approved in France in 1971 for the treatment of vertigo and conditions associated with ageing, and it is currently marketed in over 120 countries world-wide for the symptomatic treatment of psycho-organic syndromes in dosages of up to 4.8 g per day, and for the treatment of cerebrovascular accidents and its sequelae, in particular aphasia, in dosages up to 12 g per day. Furthermore, piracetam is approved for cortical myoclonus in dosages of up to 24 g per day. Piracetam is a nootropic agent defined as a drug that directly enhances, in both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness, without the development of sedative or psychostimulant effects.

To evaluate the efficacy of piracetam we performed a meta-analysis of clinical studies that have been reported between 1972 and the first half of 2001. This statistical technique integrates the results of related but independent single studies. It allows an examination of heterogeneity across different studies and enables the estimation of an average effect.

One possible limitation of meta-analyses is that including only published studies (assumed to be more positive) may lead to an overestimation of the beneficial effect of the drug. Another widely discussed issue is whether the characteristics of the included studies should be carefully matched or whether a broader inclusion is desirable. A recent editorial in the British Medical Journal argued that the generalisability and usefulness of meta-analyses can be increased considerably if the individual trials include different patient populations, clinical practice settings, and concomitant routine care procedures [2].

One of the problems inherent in the review of data spanning a period of almost 30 years is the selection of outcome measures common to all studies. A variety of psychometric cognitive tests were used over the years. Only since the late 1980s were reliable and sensitive composite test batteries, such as the Alzheimer's disease assessment scale [3], consistently used in clinical trials. Previously, the most widely used instruments were clinical rating scales, such as the Gottfries Cronholm Scale [4], which also includes a global overall rating. A clinical global impression of change (CGIC) has often been used as a clinician's global rating in clinical trials since 1976 [5].

The predominant role of the CGIC in ageing and dementia trials was further reinforced in 1991 by a letter sent by the FDA to pharmaceutical companies conducting trials in Alzheimer's disease [6]. This letter requested the inclusion of a clinician's interview-based impression of change (CIBIC) in every clinical investigation, 'to determine whether the effects of a putative antidementia drug are of sufficient magnitude to allow their detection in an interview conducted by a skilled and experienced clinician'. The clinician's interview impression of change plus caregiver input was to be based upon changes in patient behaviour that have been personally observed or assessed by the clinician, assessing all domains considered part of a comprehensive clinical interview and examination: the intent was to capture a global impression, a 'holistic' assessment [7].

This emphasis on clinical assessment was motivated by the assumption that 'effects of sufficient size to be detected by clinical interview-based assessment will be readily accepted as clinically meaningful by most experts' [8].

The fact that a CGIC has been the most common outcome measure employed in clinical trials of piracetam prompted the Cochrane Collaboration to focus on this measure for their meta-analysis. This measure was also our target, particularly because it is also a required primary endpoint in present-day dementia trials [9].

Methods

Study Selection Criteria

Our analysis was restricted to trials focusing on age-related cognitive disorders and degenerative dementias in the elderly. Studies were not included on patients with cognitive impairment or dementia due to other specific causes including vascular accidents, electroconvulsive therapy and head injury.

The next important step in selecting studies was only to include studies that employed parallel groups, and that were double blind and placebo controlled. To ensure this, documents were reviewed for evidence of randomisation lists, indistinguishable placebo, sealed

Table 1. Characteristics of 19 double blind, parallel group, placebo controlled studies included in the meta-analysis

Study	Date of first publication or report	Dosage g/day	Duration weeks	N (active, placebo)	Age range	End-point	Diagnosis
Stegink (1)	1972	2.4	8	98, 98	m = 67	C	psycho-organic syndrome
Bjurwill (1)	1973	2.4	6	20, 20	64–89	C	psycho-organic syndrome
Feruglio	1973	2.6	7	30, 30	51–92	C	psycho-organic syndrome
Stegink (2)	1973	2.4	6	50, 50	52–76	C	cerebral arteriosclerosis and dementia syndromes
Bjurwill (2)	1974	4.8	6	15, 15	64–89	C	psycho-organic syndrome
Fenyvesi	1975	2.4	8	23, 25	44–93	C	disorders of senescence
Sourander	1975	4.8	6	15, 15	64–94	C	psycho-organic syndrome
Kretschmar	1976	2.4, 4.8	6	39, 39	m = 73.2	C	moderately severe organic psychosyndrome
Macchione	1976	2.6	6–8	112, 70	m = 74.6	C	psycho-organic syndrome
Trabant	1977	4.8	6	20, 20	m = 59	P	psycho-organic syndrome
Abuzzahab	1977	2.4	8	26, 30	65–80	P	mild mental deterioration
Parrisius	1978	2.4	6	30, 30	m = 85	C	cerebral sclerosis
Hronek	1979	2.4	6	22, 21	m = 75	C	dementia (senile or arteriosclerotic)
Branconnier	1980	4.8	12	21, 19	m = 70	P	mild primary degenerative dementia
Caro Mendivil	1983	3.0	8	31, 30	60–80	P	psycho-organic syndrome
Welbel	1987	2.4	8	50, 50	50–92	C	psycho-organic syndrome
Herrmann	1987	4.8	12	65, 65	65–85	P	organic brain syndrome (ICD 9: dementia)
Israel	1990	2.4, 4.8	12	54, 54, 54	m = 68	P	AAMI-NIMH criteria
Croisile	1993	8.0	52	16, 17	57–81	P	AD (NINCDS-ADRDA)

m = Mean; C = only clinical assessments performed; P = psychometric and clinical assessments performed.

code envelopes, treatment identity being unknown to both the patient and investigator, etc.

The third study selection criterion was that the data available had to include an overall clinical impression of change by the investigator and that the global measure was rated independently from psychometric testing.

Search Strategy for Identification of Studies

A search was made in UCB's continuously updated database of documents relating to each of the company's products. This database is updated weekly from several sources including Biosys, Caplus, Drugu, Embase, Kuest-Eplus, Lifesci, Medline and Scisearch. This comprehensive review of the published literature was complemented by a complete list of UCB internal reports and protocols.

Having such a comprehensive database minimised publication bias by allowing access to unpublished documents and by supplementing published information with more detailed data available in company reports.

All retrieved articles/reports of studies were reviewed and summarised by two independent pairs of reviewers (one from an independent consultant company and one from UCB). The selection of studies was independent of their results (negative or positive). The review was particularly critical with regard to blind randomisation because subjective clinical assessments such as global change ratings are sensitive to bias. A total of nineteen studies meeting our search criteria were identified (see table 1).

Extraction of CGIC Data

Global change was assessed in a variety of ways across the nineteen studies that were evaluated.

The CGIC is generally scored on a 7-point Likert scale with three gradations of improvement (minimal, moderate and marked), the category unchanged and three gradations of worsening (minimal, moderate and marked). A number of studies only dichotomised the CGIC into improved versus unchanged/worse and hence this was the common outcome measure used for all studies in this meta-analysis. The same methodology was employed by the Cochrane Collaboration. The criteria for this dichotomisation were as follows:

Improved. The investigator had to report that the subject showed a clear improvement. Subjects whose treatment outcome was rated in other terms, e.g. 'excellent', 'very improved' and 'good' were subsumed under 'improved'.

No Change/Worse. This category includes outcome ratings such as 'no change', 'worse', 'deteriorated', and 'unfavourable'. Reports where improvements were ambiguous were also included in this category (e.g. 'doubtful improvements', 'slight improvement' and 'moderate or unchanged').

Definition of Populations

Two distinct definitions of the study populations were used for this review. The 'observed cases' population included the cases and the data as previously reported for the study. In a number of studies this was already an intention-to-treat population.

It is known that neglecting dropouts may introduce bias. To reduce this potential bias, an 'as randomised' population was also created, allocating all patients who had been excluded from the 'observed cases' analysis (including dropouts) to the category of 'no change/worse'.

Description of the Studies

In total, 54 double blind, randomised, placebo controlled studies (3,063 subjects) were identified, of which 15 used a crossover design (516 subjects) and 39 used a parallel group design (2,545 subjects). The crossover studies were excluded from the current analysis. For 19 of the parallel design studies, CGIC data could be extracted. The meta-analysis covers 1,488 subjects representing 48.6% of all randomised subjects or 58.5% of subjects in parallel studies.

Nine out of the nineteen studies in this meta-analysis have been published in scientific journals, including national journals (47% of the studies, covering 72.5% of patients). Two studies have been published as abstracts from UCB-organised symposia and data for eight studies have been derived from internal company reports. The 19 studies are detailed in table 1.

Over the years, a wide variety of diagnostic labels were used to identify cognitive impairment and dementia. The term most commonly used was senile or involutive psycho-organic syndrome (after the German 'organisches Psychosyndrom'). This broad category includes subjects with age-related cognitive impairment ranging from pre-senile or senile degenerative dementia and vascular dementia to milder forms of cognitive impairment.

Regarding outcome measures, twelve of the nineteen studies used only clinical evaluations, most commonly a Gottfries Cronholm rating [4] and a global evaluation. The Gottfries scale covers relevant symptom domains in cognitive impairment and dementia. A combination of both assessments corresponds very well with the use of a semi-structured symptom-based interview in current versions of the CIBIC plus caregiver input. In three of the studies where psychometric tests were used (Croisile, Herrmann, Israel), it is documented that the clinical global impression was performed independently.

Studies Excluded from the Meta-Analysis

Three placebo controlled, double blind studies (Chouinard, Marin Perez, Sobzik) included a clinical global impression and reported a statistically significant advantage of piracetam over placebo. However, the results of the statistical analysis were given without categorical data and therefore could not be used in the present analysis. A study by Poitrenaud used a visual analogue scale scoring of the global impression. The result favoured piracetam, but was not statistically significant. Since individual subject data were not available, the results were not included. Two studies that were considered in the Cochrane Collaboration analysis were not included in the current analysis. The study by Gallai was an open study, and the Sano study reported a global rating of neuropsychological performance which was based on a review of the psychometric testing. This does not comply with the definition of a clinical impression of change as used for this meta-analysis.

Insufficient data were available for four studies. The Kretschmar study included, in addition to the 4.8 g group, a group treated with 2.4 g/day. The publication stated only that the CGI was inconclusive ('not significant'). Solberg reported positive effects with piracetam, but the publication is confusing and it is not clear whether the study was double blind. A study by Coppinger is mentioned by Abuzzahab but reported as unpublished and negative. Extensive searching could not locate the results for this study. Wolters et al. used piracetam as a comparator in a study of vinpocetine versus placebo and found a statistical difference favouring piracetam over placebo, but did not document the CGIC data.

Statistical Methods

We adhered to the meta-analysis methodology published by the Cochrane Collaboration. Thus, the protocol by Flicker and Grimley [1] was closely followed.

The null hypothesis of homogeneity of the treatment effect across studies was tested using a chi-square statistic. Both fixed and random effects models were used to evaluate the pooled odds ratio, along with 95% confidence intervals. Peto's estimation of odds ratio was used for calculation of the fixed effects model. A Mantel-Haenszel estimation of the fixed effects model was performed in addition to Peto's estimation in order to check the robustness of the results. For interpretation purposes, the inverse of the combined absolute risk reduction was computed to estimate the combined number needed to treat (NNT) [10]. Finally, a sensitivity analysis was performed by excluding the two studies that contributed most to the heterogeneity statistic.

The estimates were first calculated on the basis of the 'observed cases' population. A second analysis was performed on the larger 'as randomised' population.

Results

There was evidence of heterogeneity in the results from the individual studies, $\chi^2 = 58.23$ (d.f. = 18) ($p < 0.001$). Using a fixed effects model, the odds ratio for improvement in the piracetam group compared to the placebo group was 3.35 (95% CI 2.70 to 4.17). An additional Mantel Haenszel computation of fixed effects model confirmed Peto's estimation: 3.31 (95% CI 2.64 to 4.14). When a random effects model was used the odds ratio was 3.20 (95% CI 2.05 to 4.99) ($p < 0.001$) and the combined number needed to treat was 3.9 (95% CI 2.8 to 6.3). Thus, about four patients must receive piracetam if we are to achieve one additional improvement compared to placebo. If the two studies that contribute most to the heterogeneity statistic (Israel: 19.3/58.2 and Herrmann: 10.3/58.2) are excluded, there was less evidence of trial by treatment interaction, $\chi^2 = 22.69$ (d.f. = 16) ($p = 0.122$). If a fixed effects model is then applied, this yields an odds ratio of 2.50 (95% CI 1.96 to 3.17) and a number to treat of 4.6 (95% CI 3.7 to 6.1). This last estimate is a more conservative method of appraising the data and still suggests evidence of an increased chance of observing improvement in those individuals treated with piracetam as compared to placebo. These estimates were calculated on the basis of 'as observed' data. The number of subjects excluded from the 'observed cases' analysis was very small and evenly spread over piracetam (4.68%) and placebo (4.72%). The

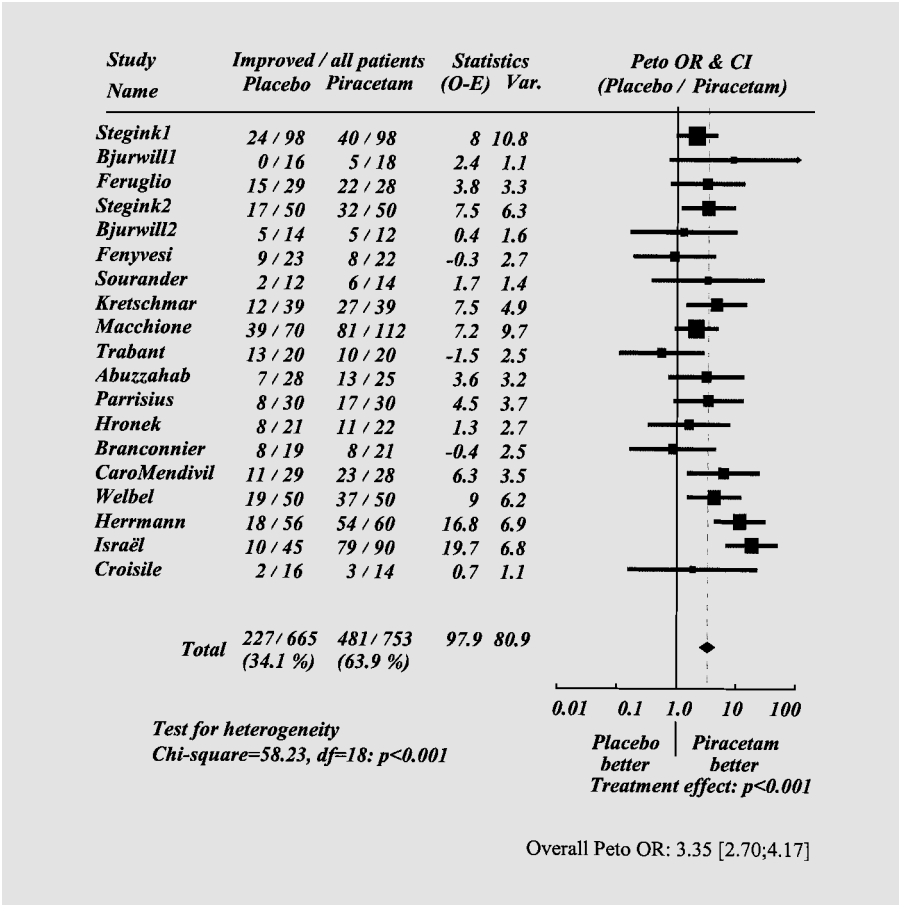

Fig. 1. Global change results for each of the 19 studies included in the meta-analysis of piracetam in dementia or cognitive impairment (fixed effects model; population of observed cases).

Table 2. Results of the meta-analysis

	Observed cases		As randomised	
	improved	no change/worse	improved	no change/worse
Placebo	227 (34.1%)	438 (65.9%)	227 (32.5%)	471 (67.5%)
Piracetam	481 (63.9%)	272 (36.1%)	481 (60.9%)	309 (39.1%)
Fixed effects model (19 studies)				
Peto OR	3.35 (2.70–4.17)		3.19 (2.58–3.94)	
Mantel-Haenszel OR	3.31 (2.64–4.14)		3.19 (2.56–3.98)	
NNT	3.3 (2.9–3.9)		3.5 (3.0–4.2)	
Random effects model (19 studies)				
Log OR	3.20 (2.05–4.99)		2.98 (2.01–4.41)	
NNT	3.9 (2.8–6.3)		4.1 (3.0–6.5)	
Sensitivity analysis: fixed effects model (17 studies)				
Peto OR	2.50 (1.96–3.17)		2.45 (1.93–3.11)	
Mantel-Haenszel OR	2.51 (1.96–3.21)		2.46 (1.93–3.14)	
NNT	4.6 (3.7–6.0)		4.8 (3.8–6.4)	

The OR (odds ratio) and NNT (number needed to treat) in both populations according to the fixed/random effects model and number of studies (19/17): odds ratio (95% CI), number needed to treat (95% CI).

results computed on the basis of the larger 'as randomised' population were very similar for each of the analyses (including sensitivity analysis). In particular, the random effects model yielded an odds ratio, for the combined nineteen studies, of 2.98 (95% CI 2.01 to 4.41) and a number needed to treat of 4.1 (95% CI 3.0 to 6.5). The results of the meta-analysis are summarised in table 2. The global change results for each of the nineteen studies included in the meta-analysis are summarised in figure 1.

Discussion

This meta-analysis is a major extension of the meta-analysis previously published by the Cochrane Collaboration. The present analysis is more extensive, covering nineteen studies versus five in the Cochrane report and 1,488 study subjects versus 747 in the previous analysis.

The findings confirm and corroborate the results of the Cochrane analysis, but with an increased robustness. The greater number of studies and patients included also result in increased precision in the estimated difference from placebo (smaller confidence intervals). For the fixed effects model (Peto's odds ratio) the Cochrane analysis yielded an odds ratio of 3.55 (95% CI 2.45 to 5.16) compared with our results of an odds ratio of 3.35 (95% CI 2.70 to 4.17). The same was true for the random effects model showing an odds ratio of 3.47 (95% CI 1.29 to 9.30) in the Cochrane analysis and 3.20 (95% CI 2.05 to 4.99) in the present analysis.

Another method is to express the results as the number of patients needed to be treated to gain one more successful outcome, compared to that expected on placebo. The most conservative number needed to treat estimation from the present meta-analysis is 4.8 (95% CI 3.8 to 6.4), which means that only five patients must receive piracetam in order to achieve one additional improvement compared to placebo.

It is important to consider the origin of the heterogeneity. Caution is warranted if very similar study protocols in comparable populations lead to varying results. In the present analysis, studies are different in duration, dosage and studied populations. The results can be seen as robust, since they are very comparable over both 'observed cases' and 'as randomised' populations, and over two statistical models.

The heterogeneity in the present analysis may have resulted from the 'lumping together' of studies conducted over a time span of 30 years. Most of the older studies suffer from lack of homogeneity of the subject populations. This is due to the diversity and relative non-specificity of diagnostic classification prevalent at that time. For more recent studies, there was greater emphasis on rigorous clinical trial methodology, larger sample sizes and well-defined populations. The results of these studies are more robust and stand somewhat apart from the earlier studies.

No quality weighing of the studies was attempted. Quality assessment and weighing is recommended based upon observations that earlier, smaller, exploratory studies are less well controlled and have better results than later confirmatory studies. However, in the present case, the more recent, better-controlled studies (Israel, Herrmann) show the more favourable results. Any quality weighing would have given more weight to both these studies and hence would have increased the pooled odds ratio.

When a clinician rates a subject as changed on a clinical global change scale, he or she is affirming 'clinically meaningful and distinct change'. By definition, any change recorded on a CGIC scale is considered clinically significant. In this meta-analysis, such improvement was seen in 60.9% of patients treated with piracetam in comparison with only 32.5% under placebo. This difference is expressed as an odds ratio, defined as the odds for improvement in the treated group relative to the odds of improvement under placebo, with an odds ratio of 1 meaning equal chance. The relative magnitude of the odds ratios may be compared to studies of other compounds using comparable methods in similar treatment indications.

Clinician-rated global impression of change scales were used in all studies with cholinesterase inhibitors in Alzheimer's dementia with slightly different versions of the CGIC. A beneficial effect on the CIBIC plus caregiver input has been demonstrated for donezepil, as well as for rivastigmine, galantamine, tacrine and metrifonate. For all drugs the observed global effects were accepted as clinically relevant [11]. Although results from these studies are not directly comparable to the current results due to differences in designs and study populations, as well as somewhat different versions of the global evaluation, it may be illustrative to examine the order of magnitude of the odds ratios that were obtained in these studies. Data from two pooled (pivotal) studies with rivastigmine were retrieved from the European Public Assessment Report [12]. In these two studies, 137 patients out of 473 (29%) improved under active treatment and 85 out of 472 (18%) under placebo (intention to treat analysis). This results in an odds ratio of 1.85 (95% CI 1.36 to 2.52). In a third

study with rivastigmine there was no significant separation from placebo on the CIBIC plus caregiver input.

For galantamine, data on global clinical impression of change are documented in a meta-analysis conducted by the Cochrane Collaboration [13]. This analysis documents results according to study duration. The three month study duration which is comparable to the studies included in the present analysis yields odds ratios of 2.2 (95% CI 1.4 to 3.7) for 24 g and 3.3 (95% CI 1.2 to 9.3) for 32 g. Although differences in methodology make interpretation relative to our meta-analysis results difficult, it can be noted that odds ratios of the order of 2 or 3 have been considered as clinically relevant.

Conclusion

This meta-analysis covers all placebo controlled, parallel group, double blind studies using a global change assessment over almost a 30-year period of study of piracetam in patients with varying degrees of cognitive impairment. The statistical methodology followed the standards set by the Cochrane Collaboration. The results show a definite statistical superiority of piracetam over placebo on a global measure of clinically meaningful change. Sensitivity analyses (to investigate the validity of the statistical assumptions) confirm that the results are robust. These results provide compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment. In order to confirm the findings of this meta-analysis, prospective, double blind, placebo controlled studies, using modern diagnostic and efficacy measures, should be conducted.

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Contributors

T.W. and C.W. participated in the design and execution of the systematic review and data collection, interpretation of the data and writing of the paper.

A.D. participated in analysing and interpreting the data.

S.F., A.K. and B.W. participated in interpreting the data and commenting on the paper.

T.W. will act as guarantor for the paper.

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What is already known on this topic:

- A number of older drugs are used in dementia and age-related cognitive impairment without modern evidence-based evaluation.
- Global clinical impression of change is a measure of clinically meaningful effect of treatment.
- In spite of uncertainties about its efficacy in dementia and age-related cognitive impairment, piracetam is a widely prescribed drug in several countries.

What this study adds:

- Piracetam shows a significant difference between piracetam and placebo on a global measure of clinically meaningful change, both expressed as a significant odds ratio and a favourable number needed to treat.
- The odds ratio obtained has been considered as relevant for this measure.
- This study provides evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment.