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Physostigmine for dementia due to Alzheimer's disease (Review)

Coelho Filho JMJMC, Birks J

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[Intervention Review]

Physostigmine for dementia due to Alzheimer's disease

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ABSTRACT

Background

The main pharmacological approach for the treatment of Alzheimer's disease (AD) has been based on the use of agents potentiating cholinergic transmission, particularly by inhibiting acetylcholinesterase (AChE), the enzyme that destroys acetylcholine after it has been secreted into the synaptic clefts. Physostigmine is an AChE inhibitor originally extracted from calabar beans. It is licensed in many countries as an agent for reversing the effect of drugs and poisons causing the anticholinergic syndrome. Studies conducted more than 20 years ago suggested that physostigmine could improve memory in people with or without dementia. Investigation of this property has been limited by the very short half-life of physostigmine. Various forms of administering the drug have been tried to overcome this problem, most recently a controlled-release (CR) oral formulation, and a skin patch.

Objectives

To determine the clinical efficacy and safety of physostigmine in Alzheimer's disease.

Search methods

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 10 January 2008 using the terms: physostigmine OR syrapton OR antilirium. The CDCIG Specialized Register contains records from all major health care databases (CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trials databases and grey literature sources.

We asked Forest Laboratories and Pharmax, owners of the rights to market physostigmine for Alzheimer's disease, for additional data and reports of clinical trials but we did not receive any information.

Selection criteria

All relevant unconfounded, double-blind, randomized, placebo-controlled trials in which physostigmine was administered for more than one day to patients with dementia of Alzheimer type.

Data collection and analysis

Data were extracted independently by two reviewers (JMC and JB), pooled where appropriate and possible, and the weighted or standardized mean differences or Peto odds ratios (95% CI) were estimated. Where possible, intention-to-treat analysis was used.

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Main results

Fifteen studies were included using four different methods of administration of physostigmine. Four studies, 29 people, used intravenous infusion; seven, 131 people, used a conventional oral form; four, 1456 people, used a controlled-release oral form, and one study of 181 people used a verum skin patch.

Intravenous infusion
There are no usable results from the intravenous infusion trials,

Oral form
The few results from the trials of the conventional oral form showed no benefit of physostigmine compared with placebo.

Controlled release
The results from two of the four studies of the controlled-release physostigmine apply only to a group of patients identified as responders in a pre-randomization titration period. The best dose physostigmine was associated with improvement on the ADAS-Cog score compared with placebo at 6, 12 weeks. There were statistically significantly higher numbers of patients from the physostigmine group withdrawing from the trial (22/183 vs 2/183)(OR 5.92, 95% confidence limits 2.59 to 13.54, p<0.0001) and suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, flatulence or sweating compared with placebo at 6 weeks. There were statistically significantly higher numbers of patients from the physostigmine group withdrawing from the trial due to adverse events (13/83 vs 5/93)(OR 3.05, 95% CI 1.15 to 8.07, p=0.02) and suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, tremor, asthenia or sweating compared with placebo at 12 weeks. When no attempt was made to identify responders and all relevant patients with Alzheimer's disease were randomized, fixed dose physostigmine (mean 33 mg/day) was associated with a statistically significantly higher number withdrawing (234/358 vs 31/117)(OR 4.82, 95% CI 3.17 to 7.33, p<0.00001), withdrawing due to adverse events (196/358 vs 10/117) (OR 6.54, 95%CI 4.29 to 9.95, p<0.00001) and suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, dyspepsia, sweating, asthenia, dyspnoea or abnormal dreaming, but with no benefit on cognition compared with placebo at 24 weeks.

Verum patch
The double dose (delivering mean dose 12 mg/day) was associated with statistically significantly higher numbers suffering at least one adverse event of vomiting, nausea, or abdominal cramps, and the lower dose (delivering mean dose 5.7mg/day) was associated with statistically significantly higher numbers suffering gastrointestinal complaints compared with placebo at 24 weeks. There was no difference between physostigmine (higher and lower dose) and placebo for numbers improved (CGIC) at 24 weeks.

Authors' conclusions

The evidence of effectiveness of physostigmine for the symptomatic treatment of Alzheimer's disease is limited. Even in a controlled release formulation designed to overcome the short half-life, physostigmine showed no convincing benefit and adverse effects remained common leading to a high rate of withdrawal.

PLAIN LANGUAGE SUMMARY

Limited evidence of effectiveness of physostigmine for the symptomatic treatment of Alzheimer's disease

Physostigmine is an acetylcholinesterase inhibitor; it works by obstructing the enzyme responsible for ACh destruction in the synaptic cleft. Studies conducted more than 20 years ago suggested that physostigmine could improve memory in people with or without dementia. Investigation of this property has been limited by the very short half-life of physostigmine. Various forms of administering the drug have been tried to overcome this problem, most recently a controlled-release (CR) oral formulation, and a skin patch. An additional limiting factor has been a high incidence of adverse effects, including nausea, vomiting and diarrhoea. Physostigmine appears to have no advantage over some newer anticholinesterase drugs. The short half-life remains a serious disadvantage and requires complex forms of administration. There is no reason to recommend further research into this drug.

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BACKGROUND

Alzheimer's disease is a progressive disorder characterized by irreversible decline in intellectual abilities and by changes in behaviour and personality. It is the commonest cause of dementia in older people, and it imposes considerable burden on patients and carers. As the aged population grows, the number of individuals world wide with Alzheimer's disease is expected to rise to 34 million in the next three decades, a dramatic increase from 7.3 million today. This is an alarming prospect, particularly in the absence of effective preventive and therapeutic interventions.

Although many of the mechanisms of Alzheimer's disease remain only partially understood, impairment of the cholinergic system has been well documented (Davies 1976, Perry 1977, Sims 1980, Coyle 1983). Brains of individuals with Alzheimer's disease show a decrease in acetylcholine (ACh) neurotransmitter levels, as well as a loss of cholinergic innervation in neural areas implicated in learning and memory (Whitehouse 1982; Doucette 1986). Thus, the main pharmacological approach for the treatment of Alzheimer's disease has been based on the use of agents for potentiating cholinergic transmission, particularly by inhibiting acetylcholinesterase (AChE), the enzyme responsible for ACh destruction in the synaptic cleft.

Physostigmine is an AChE inhibitor originally isolated from the extract of calabar bean. It has been used widely for different purposes, ranging from an historical role in rituals and primitive medicine, to its present-day use for the treatment of poisoning and diseases such as myasthenia gravis. Physostigmine is approved by regulatory agencies in Europe and by US Food and Drug Administration (FDA) as an agent to reverse the anticholinergic effects of clinical or toxic dosages of drugs.

Studies conducted in the 1970s suggest that physostigmine could improve memory in normal subjects (Davis 1978), as well as in patients with dementia (Davis 1979). Several subsequent clinical trials with small numbers of patients have shown that physostigmine can improve memory, but the results have not been consistent across all the studies. Moreover, a limiting factor has been a high incidence of adverse effects, including nausea, vomiting and diarrhoea.

The development of physostigmine has been hindered by its extensive first-pass metabolism and short plasma half-life (approximately 30 minutes). The variability in the results of the physostigmine studies may reflect the different administration regimens that have been used. Both oral and intravenous routes have been explored, but both were unsatisfactory, owing to the pharmacological properties of the drug in the case of oral administration, and to its unsuitability for long-term therapy in the case of parenteral administration. Clinical trials using continuous intravenous infusion, transdermal and, more recently, oral controlled-release (CR) physostigmine and verum patch formulations, have been conducted in an attempt to yield more prolonged AChE inhibition. Adverse effects have remained common, but such trials have also claimed some beneficial effect of physostigmine on cognitive function. The application for approval of the CR formulation (physostigmine salicylate formulation named Synapton)of physostigmine is currently with regulatory agencies.

OBJECTIVES

- To determine whether there is evidence of any beneficial effect from physostigmine in Alzheimer's disease.
- To assess the incidence and severity of adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant unconfounded, double-blind, randomized, placebo-controlled trials of longer than one day were selected. Trials in which the allocation to the treatment was not randomized, or in which the allocation to the treatment was not concealed were excluded.

Types of participants

People with Alzheimer's disease as diagnosed by operational criteria such as DSM (APA 1994) and NINCDS-ADRDA (National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) (McKhann 1984).

Types of interventions

Physostigmine given at any dose for more than one day, by any means of administration and with placebo control.

Types of outcome measures

- Cognitive function (as measured by psychometric tests)
- Global impression (such as CIBIC)
- Functional performance
- Behavioural disturbance
- Mood
- Safety as measured by the incidence of adverse effects (including side-effects) leading to withdrawal
- Dependency
- Acceptability of treatment (as measured by withdrawal from trial)
- Quality of life
- Effect on carer
- Death
- Use of services including institutionalization

Search methods for identification of studies

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 10 January 2008 for all years up to 2005. 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. The following search terms were used: physostigmine OR synapton OR antilirium.

The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL were searched separately on 10 January 2008 for records added to these databases after December 2005 to January 2008. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease and mild cognitive impairment for the Group's

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Specialized Register can be found in the Group's module on *The Cochrane Library*. These search terms were combined with the following search terms and adapted for each database, where appropriate: physostigmine OR synapton OR antilirium

On 10 January 2008, the Specialized Register consisted of records from the following databases:

Healthcare databases

- CENTRAL: (The Cochrane Library 2006, Issue 1);
- MEDLINE (1966 to 2006/07, week 5);
- EMBASE (1980 to 2006/07);
- PsycINFO (1887 to 2006/08, week 1);
- CINAHL (1982 to 2006/06);
- SIGLE (Grey Literature in Europe) (1980 to 2005/03);
- LILACS: Latin American and Caribbean Health Science Literature (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F) (last searched 29 August 2006).

Conference proceedings

- ISTP (http://portal.isiknowledge.com/portal.cgi) (Index to Scientific and Technical Proceedings) (to 29 August 2006);
- INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);.

Theses

- Index to Theses (formerly ASLIB) (http://www.theses.com/) (UK and Ireland theses) (1716 to 11 August 2006);
- Australian Digital Theses Program (http://adt.caul.edu.au/): (last update 24 March 2006);
- Canadian Theses and Dissertations (http://www.collectionscanada.ca/thesescanada/index-e.html): 1989 to 28 August 2006);
- DATAD - Database of African Theses and Dissertations (http://www.aau.org/datad/backgrd.htm);
- Dissertation Abstract Online (USA) (http://wwwlib.umi.com/dissertations/gateway) (1861 to 28 August 2006).

Ongoing trials

UK

- National Research Register (http://www.update-software.com/projects/nrr/) (last searched issue 3/2006);
- ReFeR (http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home) (last searched 30 August 2006);
- Current Controlled trials: Meta Register of Controlled trials (mRCT) (http://www.controlled-trials.com/) (last searched 30 August 2006) :
- ISRCTN Register - trials registered with a unique identifier
- Action medical research
- Kings College London
- Laxdale Ltd
- Medical Research Council (UK)
- NHS Trusts Clinical Trials Register
- National Health Service Research and Development Health Technology Assessment Programme (HTA)
- National Health Service Research and Development Programme 'Time-Limited' National Programmes
- National Health Service Research and Development Regional Programmes
- The Wellcome Trust
- Stroke Trials Registry (http://www.strokecenter.org/trials/index.aspx) (last searched 31 August 2006);

Netherlands

- Nederlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) (last searched 31 August 2006);

USA/International

- ClinicalTrials.gov (http://www.ClinicalTrials.gov) (last searched 31 August 2006) (contains all records from http://clinicalstudies.info.nih.gov/);
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches http://www.controlled-trials.com/isrctn, http://www.ClinicalTrials.gov and http://www.centerwatch.com/. The ISRCTN register and Clinicaltrials.gov are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.
- The IFPMA Trial Results databases searches a wide variety of sources among which are:
- http://www.astrazenecaclinicaltrials.com (seroquel, statins)
- http://www.centerwatch.com
- http://www.clinicalstudyresults.org
- http://clinicaltrials.gov
- http://www.controlled-trials.com
- http://ctr.gsk.co.uk
- http://www.lillytrials.com (zyprexa)
- http://www.roche-trials.com (anti-abeta antibody)
- http://www.organon.com
- http://www.novartisclinicaltrials.com (rivastigmine)
- http://www.bayerhealthcare.com
- http://trials.boehringer-ingelheim.com
- http://www.cmrinteract.com
- http://www.esteve.es
- http://www.clinicaltrials.jp

This part of the IPFMA database is searched and was last updated on 4 September 2006;

- Lundbeck Clinical Trial Registry (http://www.lundbecktrials.com) (last searched 15 August 2006);
- Forest Clinical trial Registry (http://www.forestclinicaltrials.com/) (last searched 15 August 2006).

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library.*

Pharmaceutical company records

Forest Laboratories and Pharmax, owners of the rights to market physostigmine for Alzheimer's disease, were requested to provide data and reports of clinical trials but we did not receive any

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information. The Protocol for this Review was sent to them for comments as well.

Data collection and analysis

Selection of studies

A single reviewer (JMC) discarded citations deemed irrelevant on the basis of 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. Two reviewers (JMC & JB) independently selected the trials for inclusion in the review from the culled citation list. Disagreements were resolved by discussion.

Quality assessment

The same two reviewers (JMC and JB) assessed the methodological quality of each trial with particular emphasis on the allocation concealment. The trials were ranked using the Cochrane approach:

Category A (adequate) where the report described allocation of treatment by: (i) some form of centralised 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 administrated 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 provided assurance of adequate concealment.

Category B (intermediate) where the report described 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 described 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.

Empirical research has demonstrated that lack of adequate allocation concealment is associated with bias. 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; Schulz 1995).

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 (JMC and JB) and cross-checked. Any discrepancies were resolved by discussion.

For each outcome measure summary statistics were sought which included assessments from all patients. These statistics included means, standard deviations, and numbers in each treatment group for continuous variables and total numbers in each treatment group and totals experiencing the outcome for binary variables. To allow an intention-to-treat analysis, summary statistics on all patients were sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If any of the above statistics were not available in the publications, an "on-treatment" analysis was conducted using summary statistics which included patients who completed treatment according to the protocol.

For continuous variables, or ordinal variables which can be approximated to continuous variables, the main outcomes of interest are the final assessment and the change from baseline at final assessment. For some ordinal and binary outcomes, the endpoint category relative to baseline category is the outcome of interest. For others, such as the global impression of change, the endpoint itself is of clinical relevance as all patients are by definition at the same baseline score. The baseline assessment is defined as the latest available assessment prior to randomization, but no longer than two months before.

In studies where a cross-over design was used, only data from the first treatment period were included. Data from titration period prior to the randomized phase of the study, were not used to assess safety and efficacy. Data from open, follow-on phases after the randomized phase were not used to assess safety or efficacy because patients were usually not randomized, nor were treatments concealed.

Data analysis

A vast number of rating scales and tests have been devised to assess outcomes in clinical trials testing treatments for dementia. There is much duplication, as each scale purports to assess one of the five or six main characteristics of dementia but with varying procedures. 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 were the final assessment scores and the changes in score from baseline. If the analyses reported by the investigators suggest that parametric methods and a normal approximation were appropriate, then the outcome measures were treated as continuous variables. The method of weighted mean difference was used for the meta-analyses when the same outcome measure was used in all included trials, otherwise the method of standardized mean difference was used.

For binary outcomes such as institutionalization, global impression and death, the endpoint itself was of interest and the Peto method of the 'typical odds ratio' was used.

A test for heterogeneity of treatment effect between the trials was made. If no heterogeneity was indicated then a fixed effect parametric approach was taken.

The null hypotheses to be tested were that, for any of the above outcomes, physostigmine has no effect compared with placebo.

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RESULTS

Description of studies

The fifteen trials fell into four groups, according to the drug formulation used: physostigmine intravenous infusion (PI) (3 trials); conventional oral physostigmine (COP) (7 trials); controlled release physostigmine (CR) trials (4 trials) and verum skin patch (1 trial). The trial groups differed in design, formulation and administration schemes, aims, outcomes and clinical applicability. In this review, particular attention is drawn to the CR trials, as CR is the physostigmine formulation for which approval from regulatory agencies is currently being sought.

In only five of the studies were more than 30 patients enrolled; these were the CR trials and the verum patch trial. Regarding the diagnostic criteria for Alzheimer's disease, 11/15 studies adopted NINCDS-ADRDA criteria, alone or in combination with other criteria; 3/15 adopted DSM III. Three studies, carried out before 1988, established diagnoses according to different sets of clinical, laboratory and radiological characteristics. The severity of the disease was mentioned in all studies, and was mild to moderate in all cases. The criteria used to establish the severity of the disease were: MMSE score; Memory and Information Test (MIT); Dementia Rating Scale; duration of illness; and performance of activities of daily living (ADL). Baseline characteristics are summarised in Table 1.

Trials of physostigmine infusion

There are only three studies, with 29 patients in total. They all employed a crossover design, and were of short duration, between one and five days for each phase with a wash-out phase between the two treatment phases. The difficulties encountered in the administration of treatment and the short half-life of physostigmine had severely limited the design. Two studies used a dose titration phase before the randomized treatment in order to identify an optimal dose for each patient. The average dose was approximately 0.5 mg of physostigmine per hour.

Trials of oral physostigmine

There are seven included studies with 131 patients in total. Six used a cross-over design, and one a parallel group design. Six trials started with a dose titration period in order to find the optimal or highest tolerated dose for each patient. Each phase of the cross-over trials was less than one week except for Sano 1993, which used two periods of six weeks each. The drug was administered at two-hourly intervals, with a total daily dose ranging from 3.5 to 16 mg divided into four to eight doses. Four trials used wash-out periods between the titration and randomized periods and between the phases of the randomized period, but these could be as short as one day.

Trials of controlled release physostigmine

The four studies using CR formulation were the most recent studies (Thal 1996a; Thal 1996b, Thal 1999 and van Dyck 2000), the first three being carried out by the same group of researchers. In total 1456 patients were randomized.

Thal 1996a and Thal 1996b enrolled 1111 patients in an initial 4-week dose titration stage during which their cognition was assessed repeatedly using the ADAS-Cog. After completion of this stage 366 were described as responders because they had improved by 3 points on the ADAS-Cog scale at some point. The dose taken whilst displaying this improvement was defined as the patient's best dose. Those without a 3 point improvement on the ADAS-Cog (449) were described as non-responders. Two hundred and ninety six patients withdrew before the end of the initial stage on account of adverse events. Responders and non-responders were randomized to separate trials of 6 week's duration. If randomized to treatment, the responders were given their best dose, the mean dose being 24.7 mg /day divided into 2 doses, the non-responders their highest tolerated dose, the mean dose being 24.3 mg /day divided into 2 doses.

Thal 1999
The design differed from the other trials, and potentially should provide superior evidence on the efficacy of CR physostigmine for older people with AD. There was no prior division into responders and non-responders, and participants suffering adverse events were not eliminated before randomization. 475 patients were randomized. Excessive space has been devoted to the reporting of the ITT analyses which have used the LOCF methodology. Over 24 weeks, when patients suffer a progressive condition and there are differential withdrawal rates bias is likely and LOCF is not an appropriate method of dealing with missing data. The tables do not report the means of the placebo groups, only the differences between the treatment and placebo groups. A conclusive presentation of results would demand means, standard errors of means and numbers in each group for each outcome.

van Dyck 2000
An initial 3-week dose-enrichment phase was used to select potential responders to physostigmine who then entered the 12-week randomized phase after a 4-week placebo washout. During the dose-enrichment phase subjects received, in random order, placebo or 24 or 30 mg/day of physostigmine and were identified as responders if they showed at least 3 points improvement on the ADAS-Cog on physostigmine treatment compared with placebo. This also identified a best dose which was used in the randomized phase. Eight hundred and fifty patients entered the dose-enrichment phase, 546 completed it, and 196 were identified as responders, but only 176 entered the randomized, double-blind phase. The mean physostigmine dose during the randomized phase was 26.8 mg/day divided into 2 doses, 54% taking 24mg and 46% taking 30mg/day.

Verum patch trial

The transdermal system of delivery aimed to release physostigmine continuously over 24 hours. Each patch contained 30 mg of physostigmine, and released about 5.7 mg over 24 hours. One trial of this system has been reported Möller 1999. 181 patients in total with mild to moderate Alzheimer's disease were randomized to placebo, one patch per day or two patches per day for 24 weeks of treatment. At 24 weeks this was the longest trial.

Outcomes

The outcomes measured and respective scales (an acronym is given if it is well known) used in the studies are listed below. Further details about these scales, where available, are presented in Table 2 .

1. Cognitive function

- Buschke Selective Reminding Test (BSRT)

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- Modified Buschke Selective Reminding Test - memory (mod BSRT)
- Verbal Paired Associate Learning - memory (VPAL)
- Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)
- Neuropsychological Test Battery (NTB)
- Digit span test
- Boston Naming Test (BNT)
- Mini-Mental State Examination (MMSE)
- Modified Mini-Mental State Examination (mod-MMSE)
- Wechsler Adult Intelligence Scale (WAIS)
- Wechsler Adult Intelligence Scale-revised (WAIS-R)
- Controlled Word Association (COWAT)
- Category naming
- Rosen Drawing Test (RDT)
- Figure copy
- Word or picture recognition
- Famous faces Test (retrieval from remote memory)
- The Squire's Memory Questionnaire (SMQ)

2. Global impression

- Clinical Global Impression of Change (CGIC)
- Clinician Interview-Based Impression of Change Plus (CIBIC-Plus)
- Geriatric Evaluation by Relatives Rating Instrument (GERRI)
- Sandoz Clinical Assessment - Geriatric(SCAG)

3. Functional performance

- Activities of Daily Living (ADL)
- Instrumental Activities of Daily Living (IADL)
- Nurses Observational Scale for Inpatient Evaluation (NOSIE)
- Performance Test of Activities of Daily Living (PADL)

4. Mood

- Brief Psychiatric Rating Scale (BPRS)
- Geriatric Depression Scale (GDS)

5. Safety as measured by the incidence of adverse effects (including side-effects) leading to withdrawal
6. Dependency
7. Acceptability of treatment (as measured by withdrawal from trial)
8. Quality of life
9. Effect on carer
10. Death
11. Use of services including institutionalization

Side effects were formally assessed in 5 (5/15) trials.

Risk of bias in included studies

Pharmax / Forest Laboratories were contacted and asked to provide information on unpublished or ongoing trials, but they decided not to release any date prior to regulatory approval. After full assessment, 15 studies were eventually classified as included and 31 as excluded. The commonest reasons for exclusion were non-randomization, and absence of double-blinding. Seven of the 15 included studies were published in more than one medical journal.

All the included studies were described as double-blind and randomized but only van Dyck 2000 gave further details on the methods.

The method of administration of physostigmine restricted the design on the trials using i.v. infusion and the first oral form (COP). Patients had to be assessed during the i.v.infusion and thus the trials were difficult to manage, and of necessity tested only a small number of patients and were of only a few days' duration. The oral form required many doses per day and these trials were also short and small.

The CR oral physostigmine trials attempted to identify responders before randomization. Responders were identified by a certain improvement measured on a cognitive test. Therefore results only apply to a selected sub group of the people with Alzheimer's disease of moderate severity. In Thal 1996a and Thal 1996b 296 (26.6%) patients discontinued before randomization, most of them (62.5%) due to adverse effects during the titration phase.

Most of the studies failed to comment on dropouts, leading to uncertainty as to which patients entered the analyses. When information was available, the reasons for dropouts were either decline of the patient's condition or adverse effects from treatment. The CR trials reported dropouts and intention-to-treat analyses were performed using the last observation carried forward (LOCF) methodology. In the Thal 1999 CR study, a comparatively well designed physostigmine trial, high rates of dropouts were reported: 26% among placebo patients; 61% among those receiving 30 mg of physostigmine; and 68% among those receiving 36 mg of physostigmine.

Effects of interventions

Physostigmine infusion

It was not possible to extract any quantitative results from any of the three included studies. Asthana 1995 reported difficulties in testing patients due to the frequent occurrence of adverse events. Davis 1982 used different scales for outcome depending on the initial severity of the patient's dementia. Gustafson 1987 only provided a narrative description of the results. Only one trial, Asthana 1995, mentioned adverse effects. Five patients experienced nausea, vomiting, dizziness, headache, nightmares or fatigue during the dose-finding phase and 5/9 patients could not tolerate their previously identified optimal dose during the randomized phase.

Oral physostigmine

In the COP trials of crossover design it was not possible to extract data relating to the first phase alone. The results derived from all phases were not considered reliable owing to problems of possible carry-over of the effects of previous treatment. The parallel group study, Thal 1989 provided results which showed no statistically significant effects.

No trials provided data on adverse effects. Two trials made no mention at all of safety monitoring. Five trials provided a description of adverse effects which were usually gastrointestinal and occurred during the dose-finding phase. They were often resolved by lowering the dose.

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Controlled release oral physostigmine

The design of the combined trial of Thal 1996a and Thal 1996b has limited the usefulness of the information. The patients initially enter a titration phase of 4 weeks from which they were eliminated if they suffered adverse events. Those retained were classified as responders if at some point they showed improvement of 3 points on the ADAS-Cog, or otherwise as non-responders before entering separate randomized trials. The report of these trials concentrates on the responders' trial. There are tables of treatment and placebo effects for each outcomes for the ITT and completers' analyses. The precise size of each group and the standard errors are not reported. The ITT analyses are based on last observation carried forward (LOCF) for the primary outcomes (ADAS-Cog and CGIC) for which assessments were made at baseline, 2, 4 and 6 weeks from baseline. It is stated that LOCF was not used for the secondary outcomes (MMSE, IADL, and PSMS) because assessments were only carried out at baseline and 6 weeks. It is unclear what the ITT analyses of the secondary outcomes represent. The ITT and completers' analyses should involve identical numbers for the secondary outcomes but do not. There is only one table of results from the non-responders trial. The sizes of the groups are missing and it is not stated whether ITT or completers' analyses are being reported. There is no information on withdrawals, or adverse events for the non-responders.

All quantitative results refer to the responders; there are no results from the non-responders' analyses. The results of the analysis of treatment effect show that there are no significant differences between physostigmine and placebo for MMSE, PSMS and IADL , but there is a significant difference in favour of physostigmine for ADAS-Cog (ITT, MD -1.75, 95% CI -2.90, -0.60) and CGIC (ITT, MD 0.26, 95% CI 0.06, 0.46) at 6 weeks. There is a statistically significant effect in favour of placebo for withdrawals by the 6-week endpoint (24/183 vs 9/183) (OR 2.71, 95% CI 1.33, 5.53).There is a statistically significant effect in favour of placebo for withdrawals due to adverse events by the 6-week endpoint (22/183 vs 2/183) (OR 5.92, 95% CI 2.59, 13.54). There are significant differences, in favour of placebo, for the number of patients suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, flatulence, or sweating, by 6 weeks.

Although it is reported by Thal 1999 that there is benefit due to 30mg and 36 mg per day compared with placebo on cognition and global measures and no benefit on activities of daily living and the GERRI, it is impossible to confirm the results because too little quantitative evidence is reported. The main investigator has not replied to a request for this essential information and therefore it is impossible to interpret the results. There is information on withdrawals and adverse events.

The 30 and 36 mg/day groups have been added together for these analyses. There is a statistically significant effect in favour of placebo compared with physostigmine for withdrawals by the 24-week endpoint (234/358 vs 31/117) (OR 4.82, 95% CI 3.17, 7.33). There is a statistically significant effect in favour of placebo for withdrawals due to adverse events by the 24-week endpoint (196/358 vs 10/117) (OR 6.54, 95% CI 4.29, 9.95). There are significant differences in favour of placebo, for the number of patients suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, dyspepsia, sweating, asthenia, dyspnoea or abnormal dreaming by 24 weeks.

The results from van Dyck 2000 are for responders and show that there are no significant differences between physostigmine and placebo for CGIC, MMSE, and IADL , but there is a significant difference in favour of physostigmine for ADAS-Cog (ITT, MD -2.02, 95% CI -3.59, -0.45) at 12 weeks. There are no significant differences between physostigmine and placebo for the number of withdrawals before the end of treatment. There is a statistically significant effect in favour of placebo for withdrawals due to adverse events by the 12-week endpoint (13/83 vs 5/93) (OR 3.05, 95% CI 1.15, 8.07). There are significant differences, in favour of placebo, for the number of patients suffering at least one event of nausea, vomiting, diarrhoea, anorexia, dizziness, stomach pain, tremor, asthenia or sweating, by 12 weeks.

Physostigmine verum patch

The results from Möller 1999 show no significant difference between physostigmine and placebo for CGIC, single and double dose at 24 weeks.There are no significant differences between physostigmine and placebo for the number of withdrawals before the end of treatment and the number of serious adverse events, single- and double-dose at 24 weeks. There are significant differences in favour of placebo compared with double dose physostigmine for the number of patients suffering at least one adverse event of vomiting, nausea and abdominal cramps, and for placebo compared with single dose physostigmine for gastrointestinal complaints at 24 weeks. The total number of adverse events was very low.

DISCUSSION

The studies of i.v. physostigmine and the original oral physostigmine are of historical interest only and provide little useful information. Physostigmine will never be used in these forms for Alzheimer's disease. Most studies were conducted in the 1980s and they reflect the initial phase of clinical trials of treatment of dementia with anticholinesterase drugs. The studies were designed to test the efficacy and safety of physostigmine, but the problems with the designs of the studies, constrained by the short half-life of the drug, resulted in the objectives being difficult to meet.

The recent controlled-release oral physostigmine trials should have taken advantage of new standards in clinical trials for Alzheimer's disease. Unfortunatley, they are marred by serious methodological limitations, and inadequate and unsatisfactory reporting of results. The true rate of adverse events will be under-estimated, when patients are withdrawn before randomization if they suffer an adverse event in the dose-titration phase. Furthermore, the identification of responders prior to entering the randomized phase hinders interpretation of the results and leaves us with a very unclear concept of the population to which the results apply.

Möller 1999 is a well-designed trial, and the patch method of administration appears to have advantages over other methods. Unfortunately the doses delivered by the single- and double-doses of patches used were too low to test efficacy. The very low level of adverse events would support this interpretation.

AUTHORS' CONCLUSIONS

Implications for practice

The net evidence of effectiveness of physostigmine for the symptomatic treatment of Alzheimer's disease is limited. Even

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in CR formulation, physostigmine showed no convincing effect and adverse effects remained common leading to a high rate of withdrawal.

Implications for research

Physostigmine appears to have no advantage over some newer anticholinesterase drugs. The short half-life remains a serious disadvantage and requires complex forms of administration. There is no reason to recommend further research into this drug.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Asthana 1995

Methods	Design: Double-blind randomized placebo-controlled crossover Washout period (minimum 1 week) between the two study phases
Participants	Country: USA Number: 9 patients Sex: 4 males, 5 females Age (mean): 68.7 years (+/- 12.1) Diagnosis Criteria: NINCDS-ADRDA Hachinski score < 4. Battery of laboratory tests to exclude other illnesses. CAT scan or MRI: normal or only cortical atrophy. Other medication stopped 3 weeks before trial entry Severity of AD: mild to moderate Duration of symptoms (mean): 4.1 years (+/- 1.6). MMSE score (mean): 22.2 (+/- 3.4). Blessed dementia score (mean): 7.7 (+/-6.7). Blessed Memory Information Concentration Test score (mean): 25.1 (+/- 5.5).
Interventions	1. placebo 2. physostigmine: continuous i.v. infusion, (0.02 to 1.041 mg/h) optimal dose During drug or placebo infusions, all patients received methscopolamine bromide (2.5mg orally every 8 h).
Outcomes	BSRT PALW GRS Stroop Color Word Interference Test

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Asthana 1995 *(Continued)*

	digit symbol figure copying COWAT category fluency TT calculations Adverse effects
Notes	Best dose of physostigmine identified in a previous dose-finding phase Psychometric performance was analyzed for all participants, but Geriatric Rating Scale (functional assessment) was for 8 subjects.

Beller 1985

Methods	Design: Double-blind randomized placebo controlled multiple phase crossover design (2 days x 4) Order of dose conditions randomized separately for each patient
Participants	Country: USA Number: 8 inpatients in a geropsychiatric unit. Sex: 4 males and 4 females Age: 58-83 years Diagnosis Criteria: DSM III for PDD Severity of AD: moderate to moderately severe Reisberg scores 3-5 MIT scores 6-13
Interventions	1. placebo 2. oral physostigmine 0.5 mg every 2 hours 7 doses per day (3.5 mg per day) 3. oral physostigmine 1.0 mg every 2 hours 7 doses per day (7.0 mg/day) 4. oral physostigmine 2.0 mg every 2 hours 7 doses per day (14.0 mg/day)
Outcomes	BSRT SCAG BPRS NOSIE
Notes	Outcomes assessed on the second day of treatment.

Davis 1982

Methods	Design: Double-blind randomized placebo controlled crossover study Two to 4 days generally separated each infusion (occurred at the same time of day)
Participants	Country: USA Number: 10 patients Sex: 8 males; 2 females

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Davis 1982 *(Continued)*

	Age: 50-68 years Severity of AD: moderate Patients with at least 1-year history of progressive memory loss Diagnosis criteria: Clinical history, physical examination, CAT scan, brain skull films, CSF analysis and serum analysis (for excluding other conditions). Not clear if all patients had such radiologic and laboratory examinations. MIT < =10 DRS > =4
Interventions	1. placebo 2. physostigmine i.v.optimal dose (0.125, 0.25 or 0.5mg dissolved in 100cc of normal saline at a constant rate over 30 min.)+2.5mg Probanthine, a cholinergic antagonist that does not cross the blood-brain barrier, i.v. 5 min before every infusion to minimize physostigmine's peripheral effects.
Outcomes	Famous faces test (retrieval from remote memory) Digit span test Word or picture recognition test (recognition memory test)
Notes	Optimal dose found in a prior dose finding phase. All patients were free of psychoactive medications for at least two weeks prior to physostigmine. Results were subjected to a technique (signal detectability analysis) which suggested that new items were more discriminable following physostigmine, and that patient's criteria for saying that they recognized an item also changed with physostigmine infusion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gustafson 1987

Methods	Design: Double-blind randomized placebo controlled crossover study One-day washout period between drug and placebo.
Participants	Country: Sweden Number: 10 patients Sex: 5 males and 5 females Age: 49-71 years. Diagnosis criteria: Clinical evaluation (focused upon differential diagnosis between AD, dementia of the Pick type, and cerebrovascular dementia). The Hachinski ischemic score and rating scales for identification of AD and of Pick's disease were used. CT scan performed in seven patients (normal in three cases and slight atrophy in four). Severity of AD: Mean duration of the disease: 3.8 years (1.5-5.4 years).
Interventions	1. placebo 2. physostigmine i.v. (bolus injection of 0.5mg followed by infusion for 2 hours; mean total amount given: 1.9 mg)+30mg propantheline bromide was given to reduce the autonomic side effects of physostigmine.
Outcomes	Neurophsychological test battery Reaction time (RT)

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Gustafson 1987 *(Continued)*

	Examination for aphasia
Notes	Outcomes assessed before infusion (RT and aphsia items), during infusion (RT, the neuropsychological battery, the aphsaia examination, and memory), and about three hours after the drug infusion (RT only).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Harrell 1990

Methods	Design: Double-blind randomozed placebo controlled crossover (2 weeks X 2)
Participants	Country: USA Number: 20 patients Sex: 9 males, 11 females Age: 51-77 years (mean age, 63+/-3.1 years) Diagnosis criteria: NINCDS-ADRDA Clinical and laboratory examination, particularly to rule out other causes of dementia. CAT scan: normal or diffuse atrophy. Hachinski Score < 4 Severity of AD: All patients had at least a one-year history of progressive cognitive impairment.
Interventions	1. placebo 2. oral physostigmine: optimal dose (1, 1.5, 2.0 or 2.5mg /dose)(six doses per day every 2 h)
Outcomes	BSRT Category generation Picture recognition Finger tapping Side effects
Notes	The best dose of physostigmine was identified in a previous dose-finding phase (two weeks). Then all patients were treated at home with physostigmine (2 weeks) up to randomization. Neuropsychological testing performed at the end of each two-week interval. One patient was excluded due to deterioration in language function prior to crossover. One patient presented cardiac toxicity (fibrillation-flutter) with physostigmine.

Jenike 1990

Methods	Design: Double-blind randomized placebo controlled crossover study (1 week X 2)

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Jenike 1990 *(Continued)*

Participants	Country: USA Number: 23 patients Sex: 12 males, 11 females Age: 53-89 years (mean of 66 years) Diagnosis criteria: NINCDS-ADRDA Other possible causes of dementia were ruled out by laboratory tests CT scans and EEGs were normal Severity of AD: Mild to moderate cognitive impairment. Patients scores on the Mattis Dementia Rating Scale (maximum possible score, 144): 81-140 (mean of 115).
Interventions	1. placebo 2. oral physostigmine optimal dose Doses: Not specified
Outcomes	Delayed Recognition Span Test (DRST) BSRT ADAS BNT Digit span Figure copy
Notes	Details on administration scheme, including doses, are not available in this paper. One patient was excluded from the analysis (missing data due to inability to carry out some of the tests)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mohs 1985

Methods	Design: Double-blind randomized placebo controlled crossover study 3-5 days X 2
Participants	Country: USA Number: 12 patients Sex: 8 males; 4 females. Age: 52-76 years (mean age: 62.3 years). Diagnosis criteria: Clinical history, CAT scans and laboratory examinations mainly to rule out other possible causes of dementia. Severity of AD: All patients had at least a 1-year history of cognitive impairment MIT scores 1-17 (mean, 9.8) DRS 0 -5.5 (mean, 2.9)
Interventions	1. placebo 2. oral physostigmine optimal dose (0.5, 1.0, 1.5 or 2.0 mg every 2 hours 8 doses/day)
Outcomes	ADAS
Notes	Preliminary dose finding phase

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Mohs 1985 *(Continued)*

	Two patients did not complete the study: one had no improvement on any dose of physostigmine in the dose-finding phase and the other was dropped out, due to delusions and hallucinations while receiving physostigmine, and excluded from analysis. Oucomes assessed on the last day of each treatment condition.

Möller 1999

Methods	Design: Double-blind randomized placebo-controlled parallel group 24 weeks
Participants	Country: Germany 27 centres Number: 181 patients Sex:52 % female Age: 69.3 +/- 8.2 years. Diagnosis Criteria: NINCDS-ADRDA DSM-III-R Severity of AD: MMSE 10-24 Mod Hachinski =< 4 Hamilton DS =< 16 Exclusion: other forms of dementia major disease history of alcohol or drug abuse vitamin deficiency
Interventions	1. placebo 2. verum patch applied once a day containing 30 mg physostigmine, releasing about 5.7mg over 24 hours 3. 2 verum patches applied once a day containing 30x2 mg physostigmine, releasing about 5.7x2 mg over 24 hours
Outcomes	ADAS-Cog CGIC NOSGER
Notes	There was a 4 week placebo phase before randomization

Sano 1993

Methods	Design: Double-blind randomized placebo-controlled crossover 6 weeks X 2
Participants	Country: USA Number: 29 patients Sex: No information Age: 69.1 +/- 9.1 years.

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Sano 1993 *(Continued)*

	Diagnosis Criteria: NINCDS-ADRDA Severity of AD: Average duration of illness: 4.2 +/- 0.3 years Mean mMMSE: 35.65 +/- 7.22 (equivalent to 18 on the MMSE)
Interventions	1. placebo 2. oral physostigmine highest tolerated dose (2-4 mg every 2 hours, 4 doses/day) Placebo - 6 weeks Route: Oral Doses: 2-4 mg every 2 hours (4 daily doses) for 6 weeks.
Outcomes	BSRT SIP SMQ Side effects
Notes	Optimal dose determined during a 2 day dose titration phase. After receiving two first doses, patients were discharged to take medication under supervision at home (compliance assessment method not mentioned) for 6 weeks. BSRT was administered before the first phase (dose-titration), six times during dose-titration phase. In the second phase (crossover) memory testing were performed twice at the end of the 6 week interval. ECG and other outcome measures were also completed at this time.

Stern 1987

Methods	Design: Double-blind randomized placebo controlled crossover (6 phases of 4-6 weeks each, placebo administered in 1 randomly selected phase)
Participants	Country: USA Number: 22 patients. Sex: No information Age: 58.7 - 75.5 years (average 67.1 years). Diagnosis criteria: NINCDS-ADRDA , DSM III Severity of AD: Average score on the modified Mini-Mental State Examination (mMMS): 41 (32.7-49.3)
Interventions	1. placebo 2. oral physostigmine highest tolerated or best individual doses 12.5-16.0mg/day taken every 2 h in 4 -6 doses) 13 patients had not the best dose and the dose used was the highest tolerated which was not reported in the paper.
Outcomes	BSRT MMSE Modified (mMMSE) WAIS-R Digit Symbol WMS COWAT Category naming RDT

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Stern 1987 *(Continued)*

	Cancelations (letters, shapes)
Notes	Best dose, or highest tolerated dose determined in a 5-day phase prior to randomization. BSRT was administered twice daily and other tests on the third day of each crossover period. 12 patients were excluded before randomisation due to inability to perform the tests. This is an extended double-blind crossover trial with 14 out of 22 patients included in the previous study by Stern 1987. Information on the remaining 8 patients was not available. The participants were: 8 out of 9 defined as responders in the previous study by the same authors; 4 out of 9 nonresponders and 2 out of 4 patients who performed worse on physostigmine than on placebo. The underlying hypothesis in this study was that extended exposure to oral physostigmine might be required for the drug to be effective. SRT and neurologic evaluation were performed at the completion of each interval.

Thal 1989

Methods	Design: double-blind randomized placebo controlled parallel group Second phase: the best dose of physostigmine or placebo from the first phase was mantained for 6 weeks Finally all individuals were crossed over to placebo for 2 additional weeks
Participants	Country: USA Number: 16 outpatients Sex: No information Age: 56-80 years (mean 64 years). Diagnosis criteria: Research diagnostic criteria for AD (Eisdorfer and Cohen, 1980) and NINCDS-ADRDA Patients showed atrophy or no change on CT scan, and normal and diffusely slow EEG. Severity of AD: Early to moderate AD
Interventions	1. placebo 2. oral physostigmine best dose (10, 15 or 20 mg/day in 5 divided doses)
Outcomes	BSRT Rosen Construction Task NOSIE ADL IADL PADL
Notes	Patients titrated to highest tolerated dose in first 3 weeks after randomization. In addition to assessing memory, this trial attempted to assess the effect of physostigmine on other areas of cognition. It was the first trial on physostigmine assessing functional performance. All patients were begun on placebo for 1 week, and then baseline testing was carried out. The patients wre tested with 3 dise and placebo over the next 4 weeks to find the best tolerated dose. This was followed by the 6 week randomized phase using the best tolerated dose or placebo, and both groups completed with 2 weeks on placebo. Psychometric testing was performed before the first phase (baseline), at the end of each week in the first phase, every 2 weeks in the second phase, and at the end of the last study period (placebo).

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Thal 1996a

Methods	Design: Randomized double-blind placebo-controlled 6 week parallel group
Participants	Country: USA and UK 40 centres Number: 366 patients Sex: 184 males, 182 females Diagnosis criteria: NINCDS-ADRDA Severity of AD: MMSE between 10 and 26, mean 17.7 Hachinski <= 4 3 or more points improvement on ADAS-Cog during the dose titration phase (responders) No medication that affects CNS
Interventions	1. placebo 2. controlled release physostigmine best dose (18-30 mg per day divided into 2 doses) Route: Oral Doses: 9 mg (105 patients); 12 mg (137 patients) or 15 mg (124 patients) twice daily for 6 weeks.
Outcomes	ADAS-Cog CGIC MMSE ADL PSMS
Notes	The original paper deals with two randomized parallel trials: one with physostigmine responders, and other with physostigmine non-responders identified in a previous dose-titration phase. For this review, these two trials were considered separetely (Thal (a) 1996; Thal (b) 1996). A number of 1,111 patients were initially enrolled in the study: 366 were defined as physostigmine responders, 449 as physostigmine non-responders. 263 individuals withdrew from the study prior to randomisation: 185 due to adverse events in the dose-titration phase, and 78 due to multiple reasons in the placebo washout. Among the 366 responders randomized, 33 withdrew from the study due to adverse effects (24 (13.1%) with physostigmine, and 9 (4.9%) with placebo). In the completers analysis, however, the numbers showed in the table do not agree (3 more patients withdrew in each arm).

Thal 1996b

Methods	Design: Randomized double-blind placebo-controlled parallel group 6 weeks
Participants	Country: USA and UK 40 centres

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Thal 1996b *(Continued)*

	Number: 439 patients Sex: Diagnosis criteria: NINCDS-ADRDA Severity of AD: MMSE between 10 and 26, mean 18.7 Hachinski <= 4 less than 3 points improvement on ADAS-Cog during the dose titration phase (nonresponders) No medication that affects CNS
Interventions	1. placebo 2. controlled release physostigmine best tolerated dose (18-30 mg per day divided into 2 doses) Route: Oral Doses: 9 mg (105 patients); 12 mg (137 patients) or 15 mg (124 patients) twice daily for 6 weeks.
Outcomes	ADAS-Cog CGIC MMSE ADL PSMS
Notes	ADAS-Cog was administered three times before and every 2 weeks during the double-blind phase. MMSE, IADL, and PSMS were administered once before and -at the final study visit. A number of 848 patients completed the placebo washout phase, and as 439 of them were included in the non-responders trial and 366 in the responders trial, there are more 43 patients of both groups excluded before randomisation. Information about them is not avaliable in the paper.

Thal 1999

Methods	Design: Randomized double-blind placebo-controlled parallel group 12 weeks
Participants	Number: 699 patients screened and 475 enrolled in the trial. Sex: 60% females Age: 73.4 +/-6.9 years Diagnosis Criteria: NINCDS-ADRDA. Complete medical evaluation carried out to rule out another disorder that could result in cognitive impairment. Severity of AD: Mild to moderate dementia. MMSE (range): 12-26 Hamilton Scale score (range): 0-15
Interventions	1. placebo 2.controlled release physostigmine 30 mg /day in 2 divided doses 3.controlled release physostigmine 36mg/day in 3 divided doses
Outcomes	ADAS-Cog CIBIC-Plus IADL CGIC

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Thal 1999 *(Continued)*

	GERRI
Notes	

van Dyck 2000

Methods	Design: Double-blind randomized placebo-controlled parallel group 12 weeks
Participants	Country: USA 36 centres number: 176 54.7% female Age: 72.8 +/- 8.1 years. Diagnosis Criteria: NINCDS-ADRDA Severity of AD: MMSE 10-26 Mod Hachinski =< 4 Response of at least 3 points improvement on the ADAS-Cog during dose enrichment phase. Nonresponders were discontinued
Interventions	1. placebo 2. controlled release physostigmine best dose 24 or 30 mg/d divided into 2 doses
Outcomes	ADAS-Cog CIBIC-plus CGIC MMSE IADL
Notes	3-week dose enrichment phase, each patients receiving placebo, 24 and 30 mg/d for 1 week each. Responders were identified (at least 3 points improvement on the ADAS-Cog) when taking physostigmine compared with placebo and allowed to continue to randomized phase.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	

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

Study	Reason for exclusion
Agnoli 1983	It is a non randomized study.
Ashford 1981	Patients were given physostigmine and placebo with order of treatment counterbalanced across the patient group.

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Study	Reason for exclusion
Becker 1988	This is a trial using physostigmine plus lecithin with placebo plus lecithin control. There is no information on sex and age of the participants.
Bentley 2007	This is a nonrandomized trial where 16 mild Alzheimer patients and 17 age-matched healthy controls were studied. Within-subject placebo-controlled comparisons of effects of physostigmine were performed.
Bierer 1993	Not randomized
Bierer 1994	This is a single-blind study.
Blin 1998	No diagnosis criteria for Alzheimer's disease specified.
Caltagirone 1982	This is a non randomized one-arm study where neuropsychological assessment was carried out before and after treatment.
Caltagirone 1983	There was no control (placebo) group.
Christie 1981	The design is unclear.
Cummings 1993	Physostigimine compared with haloperidol, only 2 patients
Davis 1979	This is a letter reporting the preliminary results of the effect of physostigmine on 6 patients (3 nondemented elderly women, 2 with Alzheimer's disease and 1 with Huntington's disease). Data are not available.
Giuffra 1990	This is an abstract with very limited information. We wrote to the authors seeking more details but have not received a reply.
Imbimbo 2001	This is a review on efficacy and tolerability of seven cholinesterase inhibitors (tacrine, donepezil, rivastigmine, metrifonate, eptastigmine, physostigmine and galantamine) according to the results from six-month placebo-controlled trials.
Jenike 1990b	This is a nonrandomized study. Six patients treated with physostigmine in a previous study were matched with controls and followed for between 9 and 27 months.
Jotkowitz 1983	This is a nonrandomized study with non blind assessment of outcome.
Levy 1992	This is an abstract from the 3rd International Conference on Alzheimer's Disease and Related Disorders. It relates to the trial published by Levy et al. (1994) which was excluded as it is a single-blind nonrandomized study.
Levy 1994	This is a single-blind nonrandomized study. No placebo group.
Marin 1995	All patients received physostigmine.
Mitchell 1986	This an abstract with very limited information.
Muramoto 1979	It is a report of the effect of physostigmine on performance of constructional and memory tasks in a patient with Alzheimer's disease.
Muramoto 1984	This is a crossover study where half of the patients were given drug or placebo in a non-randomized order, as well as in a single blind fashion.
Peters 1979	Nonrandomized study.

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Study	Reason for exclusion
Schemechel 1984	This study is reported in abstract format. Data are not available. We sent a letter to the authors seeking more details but they did not reply.
Schneider 1993	It is a confounded study, as patients who were already receiving tacrine or physostigmine were assigned to receive either L-deprenyl or placebo.
Schwartz 1986	The description of the study design is unclear. It is a possibly randomized trial, but physostigmine appears to be confounded by lecithin.
Sevush 1991	This is a crossover study with order of treatment counterbalanced across patients (nonrandomized).
Smith 1979	This is a letter reporting the effect of physostigmine in a patient with Alzheimer's disease.
Storey 1992	This is an abstract from the 3rd International Conference on Alzheimer's Disease and Related Disorders. It is about a nonrandomized trial, where control patients were matched to the treated group on age, sex, and baseline neuropsychological performance.
Sunderland 1992	Study designed to evaluate the effect of a combination of physostigmine and lecithin versus either agent alone.
Thal 1983	There is no mention of randomization.
Tune 1991	Nonrandomized study.
Wettstein 1982	There is no mention of randomization.

DATA AND ANALYSES

Comparison 1. physostigmine (oral) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 BDS (change from baseline) at 10 weeks ITT	1	16	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-7.82, 4.82]
2 ADL (change from baseline) at 10 weeks ITT	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.6 [-1.78, 0.58]
3 PADL (change from baseline) at 10 weeks ITT	1	16	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-8.28, 3.28]
4 MDRS (change from baseline) at 10 weeks ITT	1	16	Mean Difference (IV, Fixed, 95% CI)	8.5 [-2.06, 19.06]

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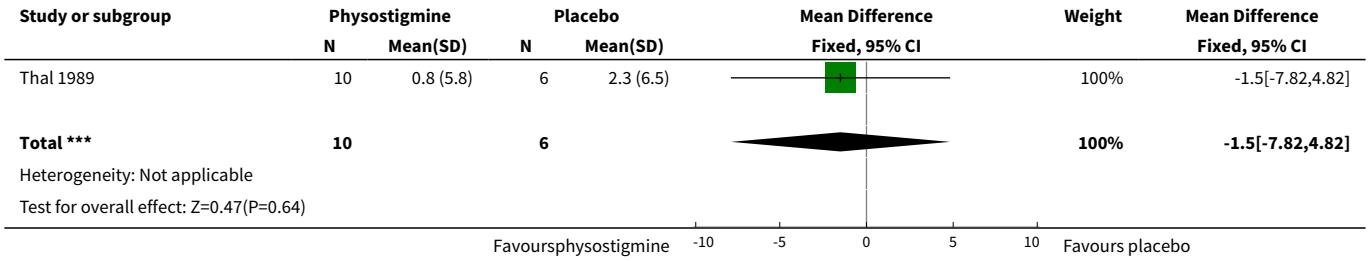
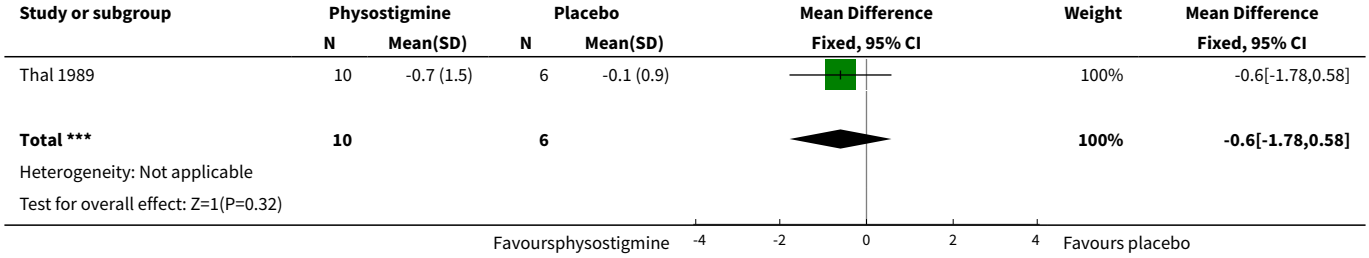
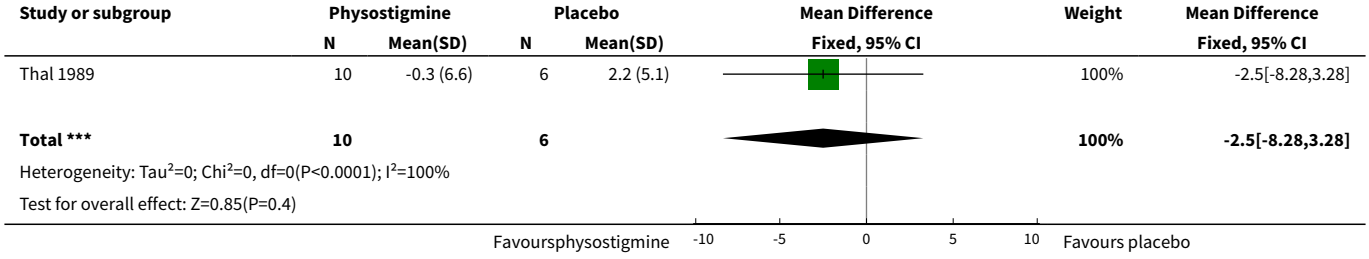
Analysis 1.1. Comparison 1 physostigmine (oral) vs placebo, Outcome 1 BDS (change from baseline) at 10 weeks ITT.



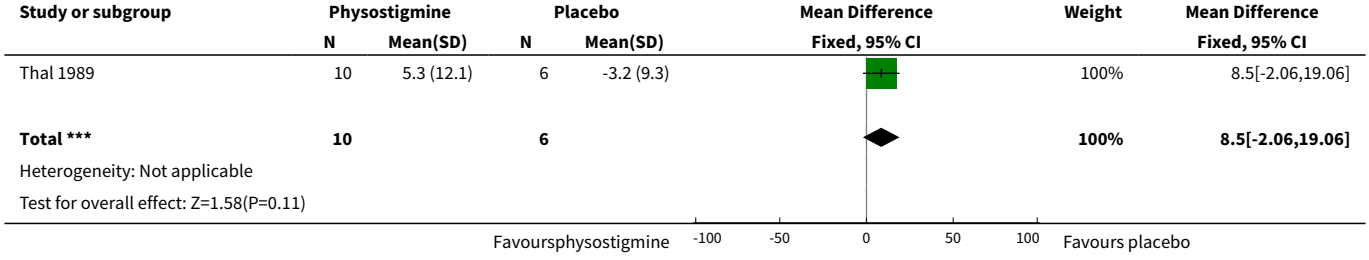
Analysis 1.2. Comparison 1 physostigmine (oral) vs placebo, Outcome 2 ADL (change from baseline) at 10 weeks ITT.



Analysis 1.3. Comparison 1 physostigmine (oral) vs placebo, Outcome 3 PADL (change from baseline) at 10 weeks ITT.



Analysis 1.4. Comparison 1 physostigmine (oral) vs placebo, Outcome 4 MDRS (change from baseline) at 10 weeks ITT.



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Comparison 2. physostigmine (CR) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of withdrawals before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.71 [1.33, 5.53]
1.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [0.85, 4.26]
1.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.82 [3.17, 7.33]
2 Number of withdrawals due to adverse events before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.92 [2.59, 13.54]
2.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.05 [1.15, 8.07]
2.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.54 [4.29, 9.95]
3 At least one adverse event of nausea before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.41 [5.24, 13.50]
3.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	13.46 [6.65, 27.21]
3.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.01 [7.19, 16.86]
4 At least one adverse event of vomiting before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.65 [5.26, 14.22]
4.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.97 [5.49, 21.92]
4.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.90 [5.20, 12.00]
5 At least one adverse event of diarrhoea before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.04 [2.68, 13.59]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.39 [2.41, 16.92]
5.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.77, 4.79]
6 At least one adverse event of anorexia before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.15 [1.82, 9.48]
6.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.01 [1.12, 14.36]
6.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.37 [1.29, 4.35]
7 At least one adverse event of dizziness before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.82 [1.29, 6.17]
7.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.78 [2.51, 13.27]
7.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.13 [1.30, 3.50]
8 At least one adverse event of headache before end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.87, 4.29]
8.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.20 [0.78, 13.20]
9 At least one adverse event of stomach pain before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.33 [2.39, 16.74]
9.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.13 [1.71, 21.92]
9.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.17, 3.78]
10 At least one adverse event of dyspepsia before end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.20 [0.78, 13.20]
10.2 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.55 [1.25, 5.19]
11 At least one adverse event of flatulence before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.77 [2.22, 27.27]
12 At least one adverse event of sweating before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.33 [2.39, 16.74]
12.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.02 [1.62, 15.52]
12.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.53 [1.94, 6.43]
13 At least one adverse event of agitation before end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
13.1 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.15, 2.13]
13.2 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.18, 0.75]
14 At least one adverse event of tremor before end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
14.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.62, 3.48]
14.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.65 [1.19, 62.66]
15 At least one adverse event of asthenia before end of treatment	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
15.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.43 [0.84, 7.07]
15.2 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.99 [1.99, 40.69]
15.3 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.36 [1.94, 5.82]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 At least one adverse event of dyspnea before end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 Responders at 12 weeks (mean dose 27mg/day)	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.21 [0.23, 21.58]
16.2 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.95 [1.29, 12.13]
17 At least one adverse event of abnormal dreaming before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
17.1 All patients at 24 weeks (mean dose 33 mg/day)	1	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.06 [1.11, 8.43]
18 ADAS-Cog (change from baseline) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-2.90, -0.60]
18.2 Responders at 12 weeks (mean dose 27mg /day)	1	170	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-3.59, -0.45]
19 CGIC (change from baseline) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Mean Difference (IV, Fixed, 95% CI)	0.26 [0.06, 0.46]
19.2 Responders at 12 weeks (mean dose 27mg /day)	1	172	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.08, 0.44]
20 MMSE (change from baseline) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
20.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Mean Difference (IV, Fixed, 95% CI)	0.65 [-0.19, 1.49]
20.2 Responders at 12 weeks (mean dose 27mg /day)	1	159	Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.34, 1.58]
21 PSMS (change from baseline) ITT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.24, 0.62]
22 IADL (change from baseline) ITT	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 Responders at 6 weeks (mean dose 24mg /day)	1	366	Mean Difference (IV, Fixed, 95% CI)	-2.46 [-5.39, 0.47]

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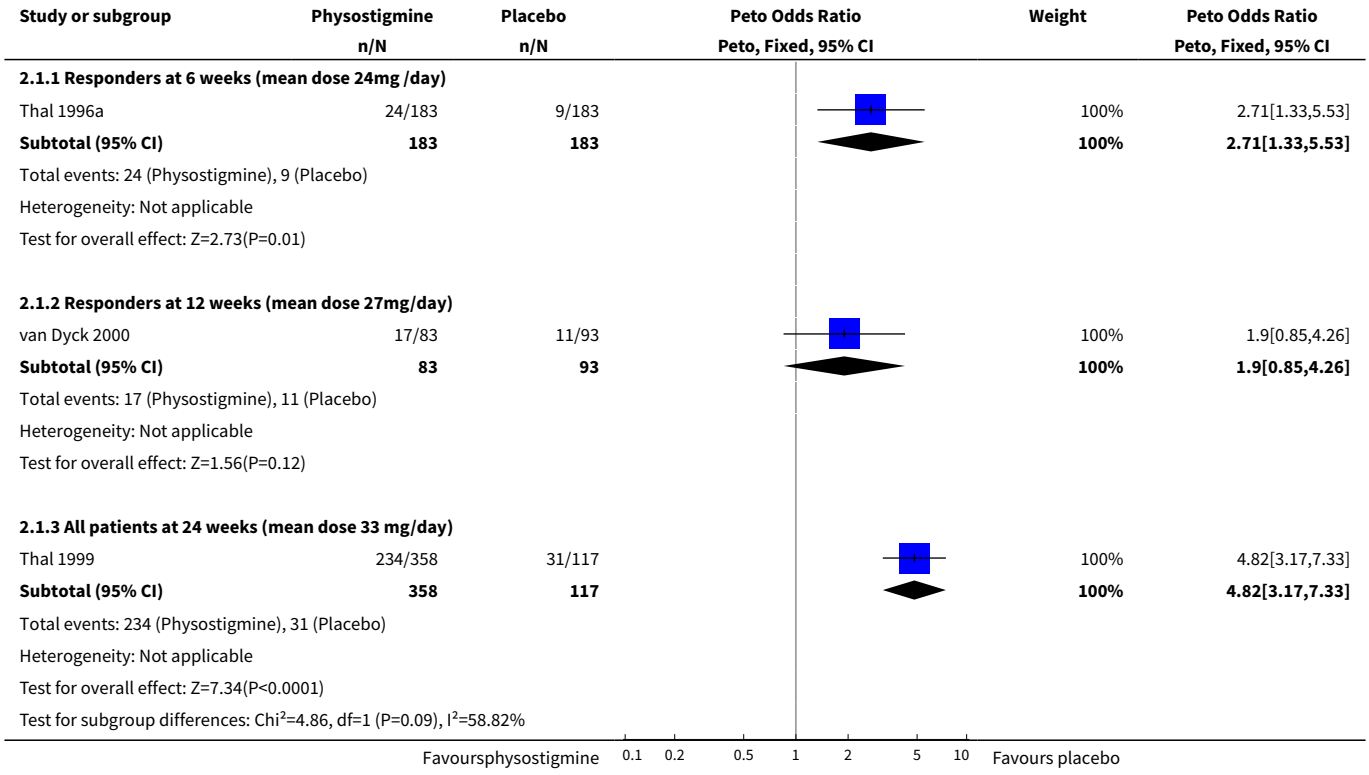
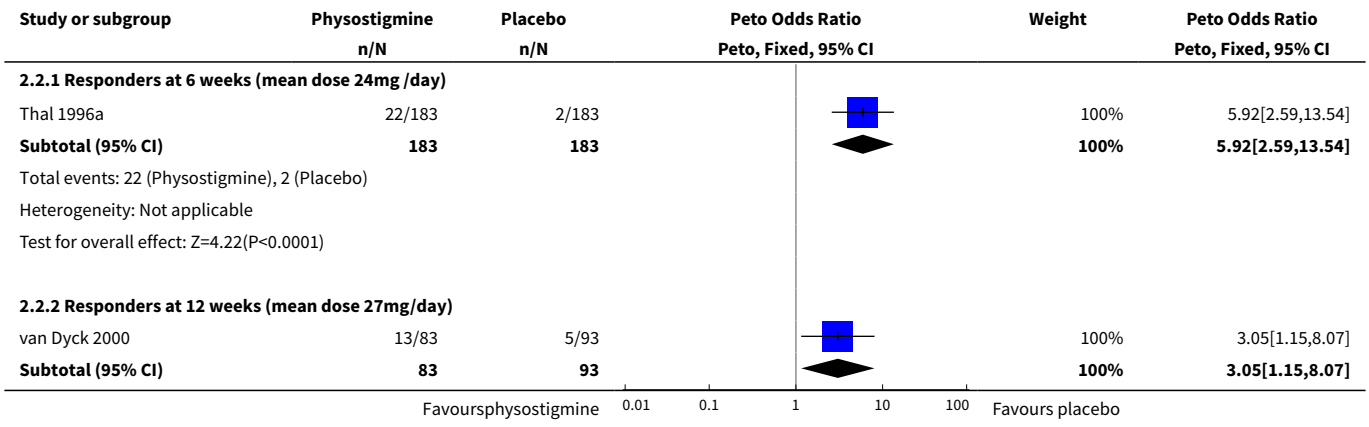
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Responders at 12 weeks (mean dose 27mg /day)	1	163	Mean Difference (IV, Fixed, 95% CI)	-2.24 [-6.08, 1.60]

Analysis 2.1. Comparison 2 physostigmine (CR) vs placebo, Outcome 1 Number of withdrawals before end of treatment.



Analysis 2.2. Comparison 2 physostigmine (CR) vs placebo, Outcome 2 Number of withdrawals due to adverse events before end of treatment.



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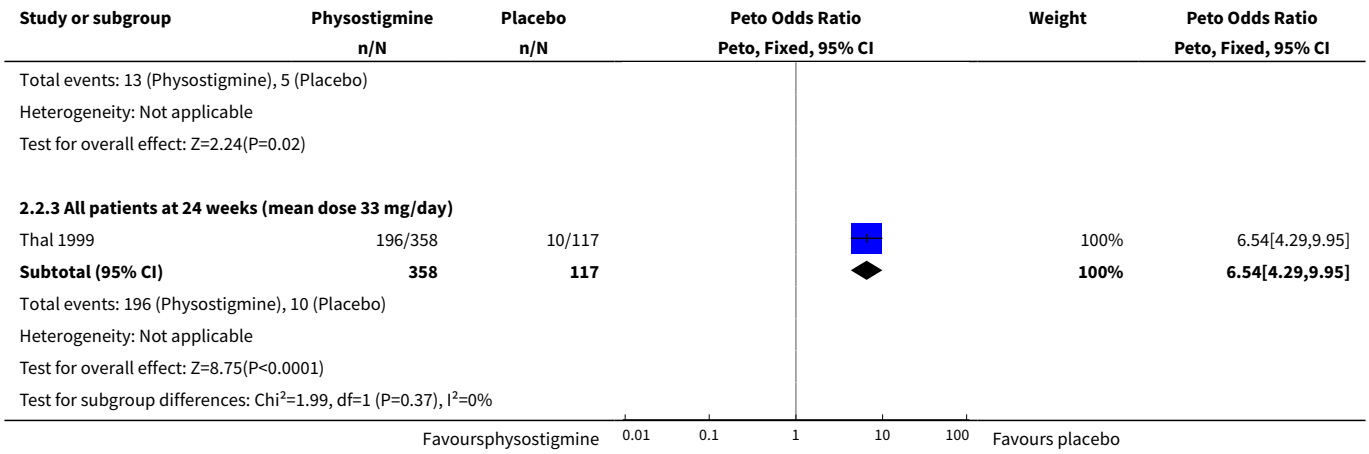
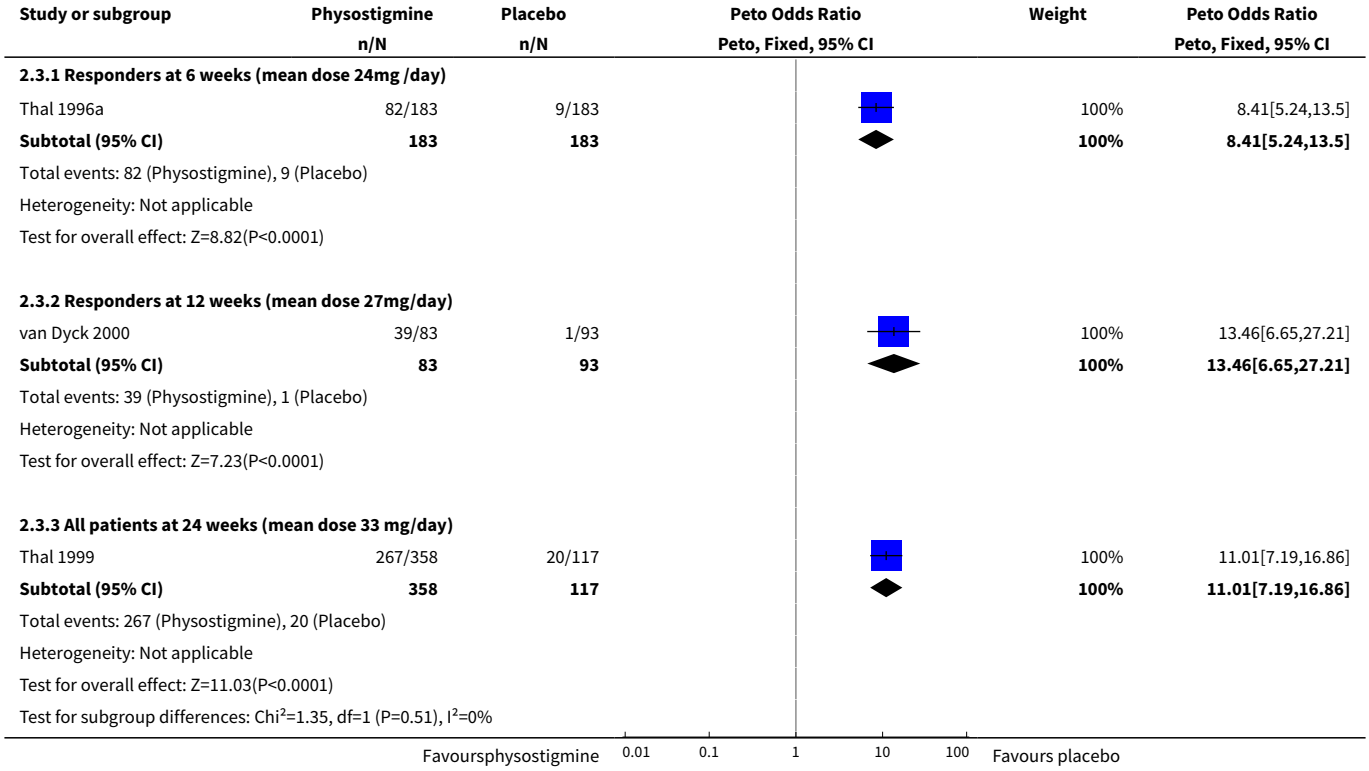
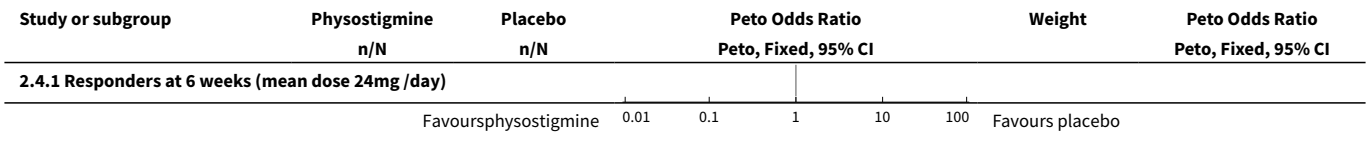


Analysis 2.3. Comparison 2 physostigmine (CR) vs placebo, Outcome 3 At least one adverse event of nausea before end of treatment.



Analysis 2.4. Comparison 2 physostigmine (CR) vs placebo, Outcome 4 At least one adverse event of vomiting before end of treatment.



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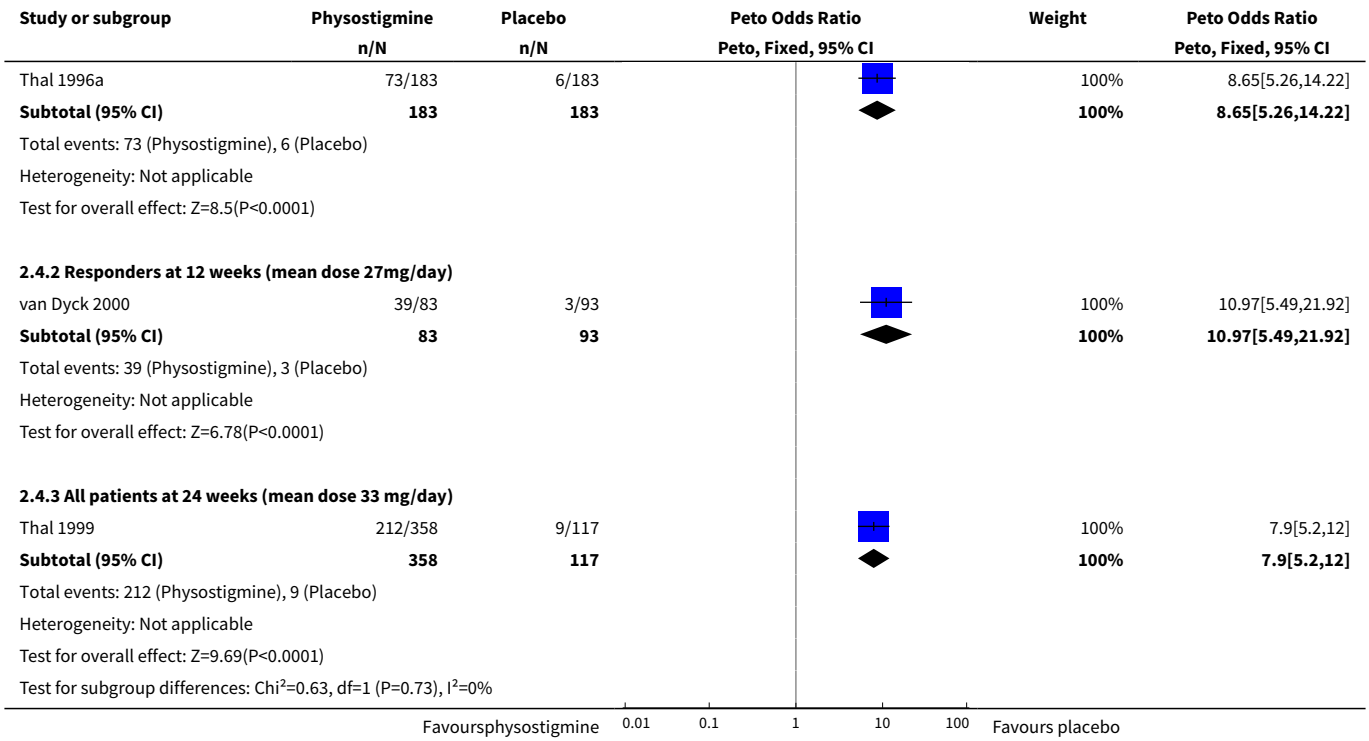
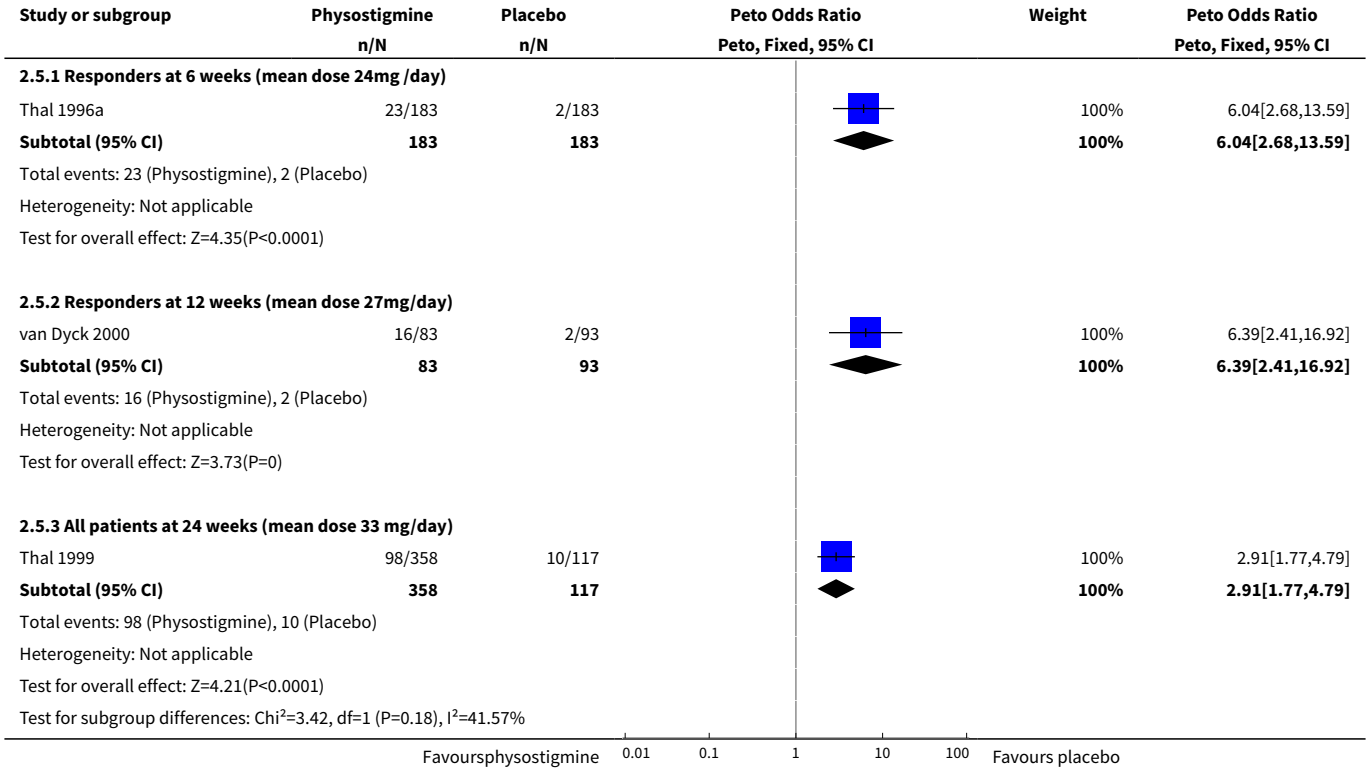


Analysis 2.5. Comparison 2 physostigmine (CR) vs placebo, Outcome 5 At least one adverse event of diarrhoea before end of treatment.



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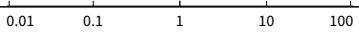
Analysis 2.6. Comparison 2 physostigmine (CR) vs placebo, Outcome 6 At least one adverse event of anorexia before end of treatment.

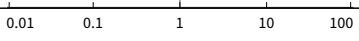
Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.6.1 Responders at 6 weeks (mean dose 24mg /day)					
Thal 1996a	20/183	4/183		100%	4.15[1.82,9.48]
Subtotal (95% CI)	**183**	**183**		**100%**	**4.15[1.82,9.48]**
Total events: 20 (Physostigmine), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.37(P=0)					
2.6.2 Responders at 12 weeks (mean dose 27mg/day)					
van Dyck 2000	8/83	2/93		100%	4.01[1.12,14.36]
Subtotal (95% CI)	**83**	**93**		**100%**	**4.01[1.12,14.36]**
Total events: 8 (Physostigmine), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.14(P=0.03)					
2.6.3 All patients at 24 weeks (mean dose 33 mg/day)					
Thal 1999	58/358	7/117		100%	2.37[1.29,4.35]
Subtotal (95% CI)	**358**	**117**		**100%**	**2.37[1.29,4.35]**
Total events: 58 (Physostigmine), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.79(P=0.01)					
Test for subgroup differences: Chi^2=1.37, df=1 (P=0.5), I^2=0%					



Favoursphysostigmine — Favours placebo

Analysis 2.7. Comparison 2 physostigmine (CR) vs placebo, Outcome 7 At least one adverse event of dizziness before end of treatment.

Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.7.1 Responders at 6 weeks (mean dose 24mg /day)					
Thal 1996a	20/183	7/183		100%	2.82[1.29,6.17]
Subtotal (95% CI)	**183**	**183**		**100%**	**2.82[1.29,6.17]**
Total events: 20 (Physostigmine), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.6(P=0.01)					
2.7.2 Responders at 12 weeks (mean dose 27mg/day)					
van Dyck 2000	22/83	4/93		100%	5.78[2.51,13.27]
Subtotal (95% CI)	**83**	**93**		**100%**	**5.78[2.51,13.27]**
Total events: 22 (Physostigmine), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.13(P<0.0001)					
2.7.3 All patients at 24 weeks (mean dose 33 mg/day)					
Thal 1999	94/358	15/117		100%	2.13[1.3,3.5]
Subtotal (95% CI)	**358**	**117**		**100%**	**2.13[1.3,3.5]**



Favoursphysostigmine — Favours placebo

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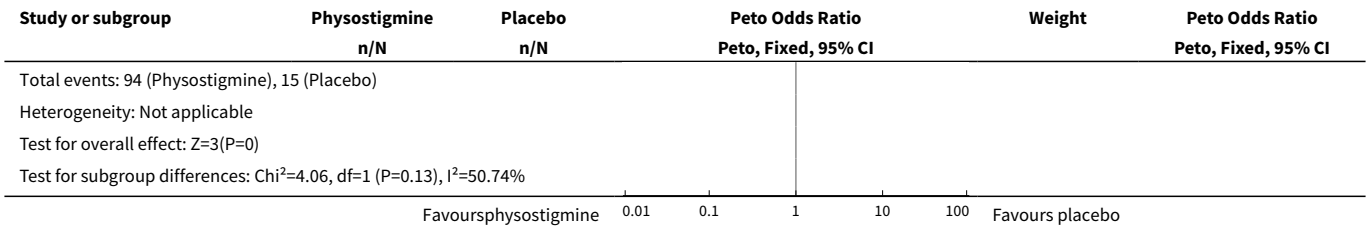
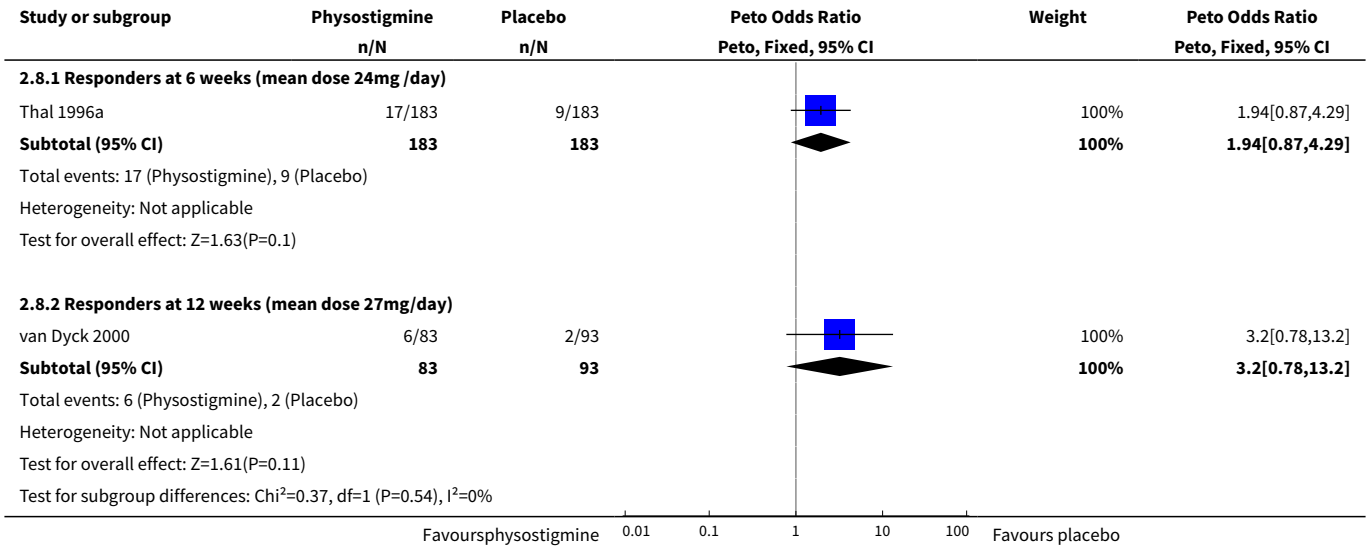
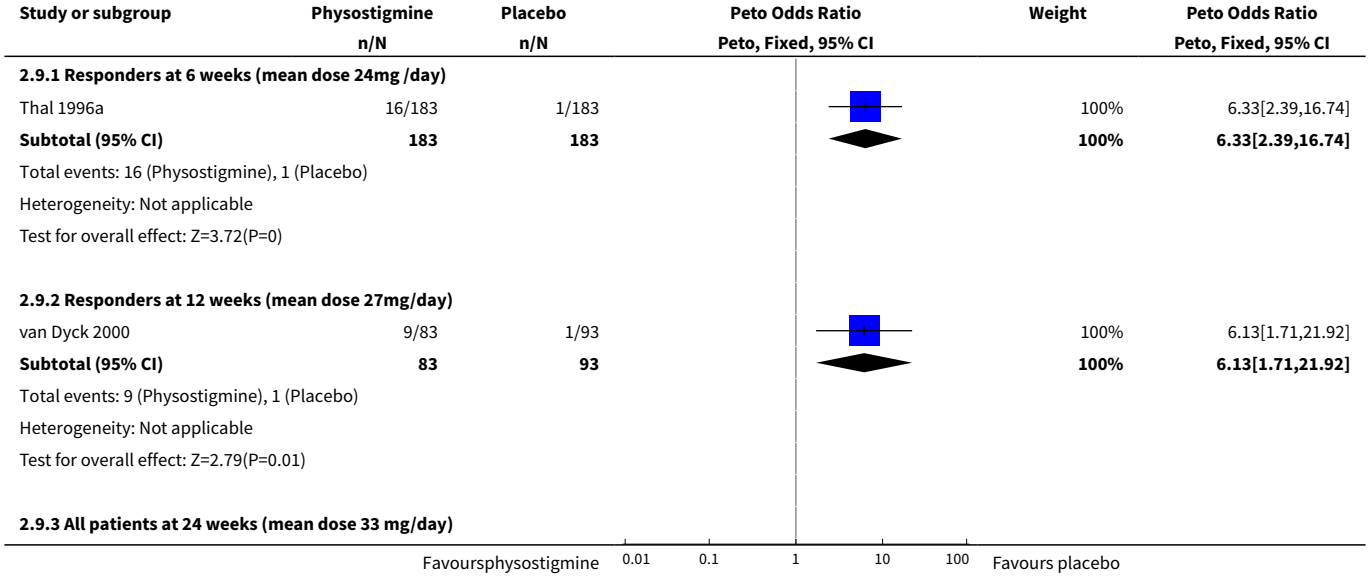


Analysis 2.8. Comparison 2 physostigmine (CR) vs placebo, Outcome 8 At least one adverse event of headache before end of treatment.



Analysis 2.9. Comparison 2 physostigmine (CR) vs placebo, Outcome 9 At least one adverse event of stomach pain before end of treatment.



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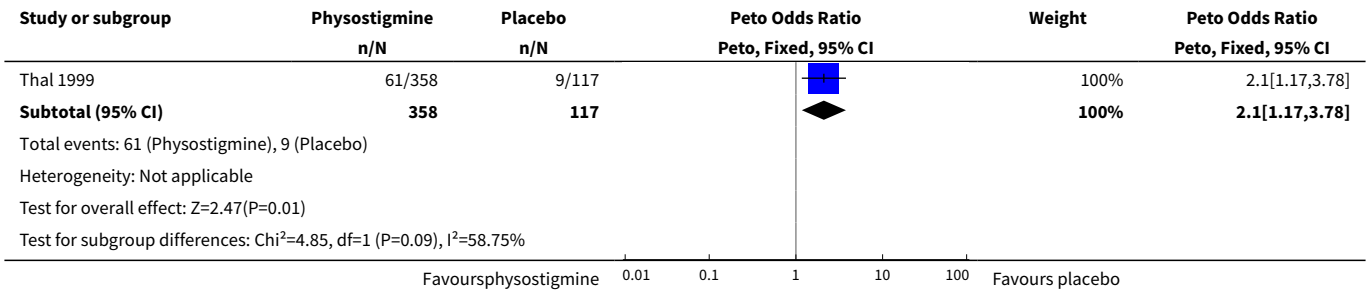
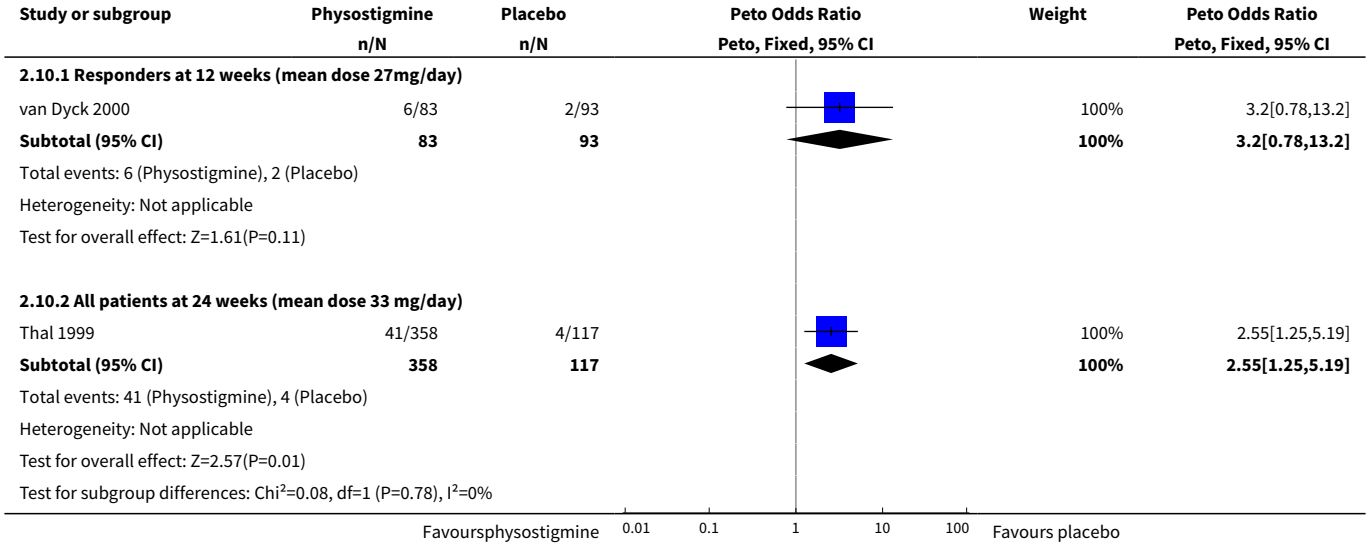
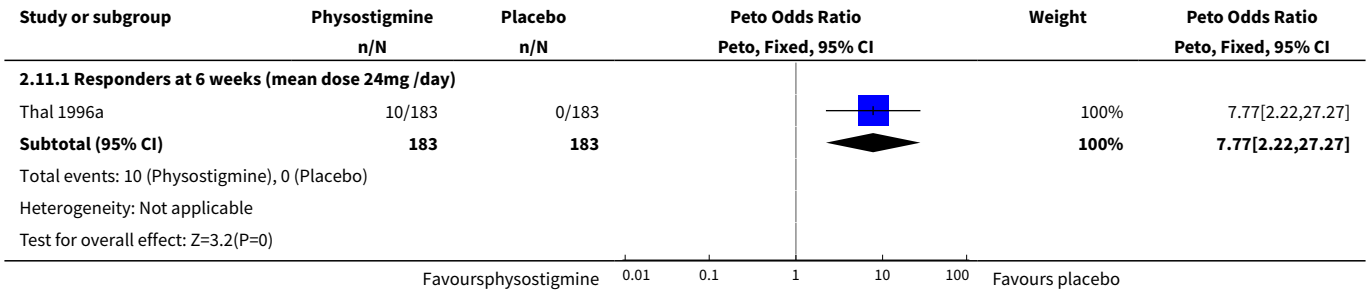


Analysis 2.10. Comparison 2 physostigmine (CR) vs placebo, Outcome 10 At least one adverse event of dyspepsia before end of treatment.



Analysis 2.11. Comparison 2 physostigmine (CR) vs placebo, Outcome 11 At least one adverse event of flatulence before end of treatment.



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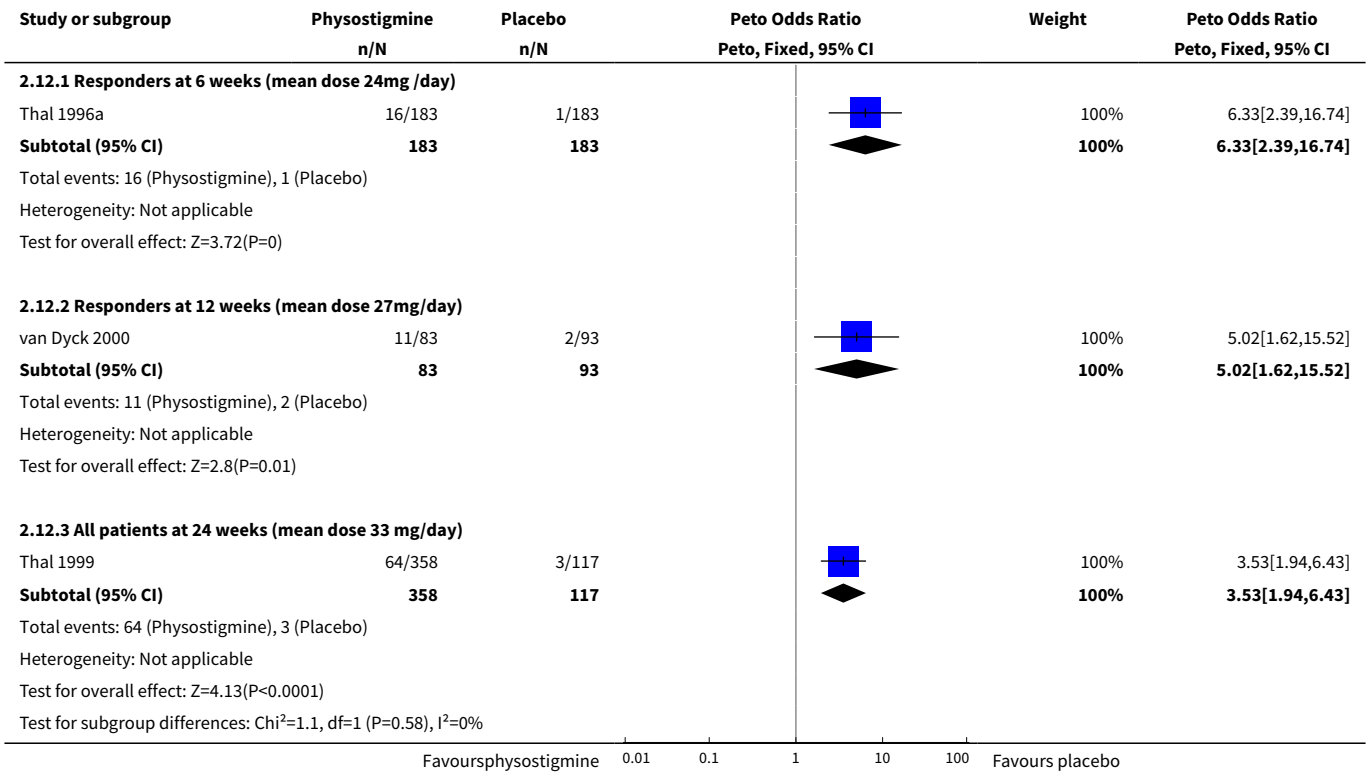
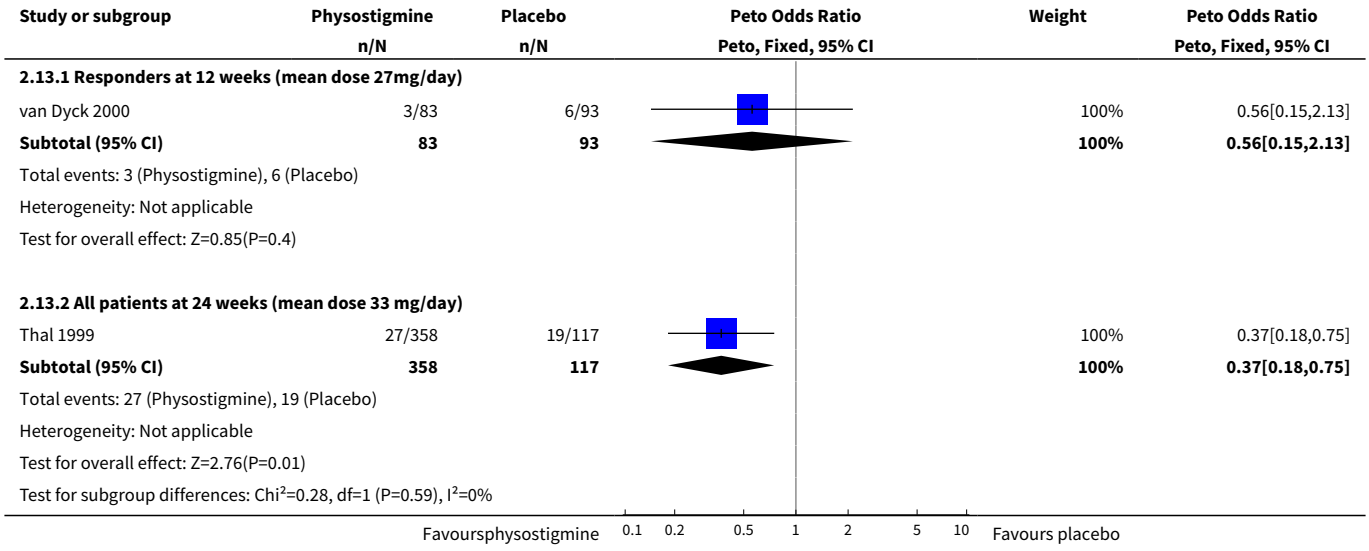
Analysis 2.12. Comparison 2 physostigmine (CR) vs placebo, Outcome 12 At least one adverse event of sweating before end of treatment.



Analysis 2.13. Comparison 2 physostigmine (CR) vs placebo, Outcome 13 At least one adverse event of agitation before end of treatment.



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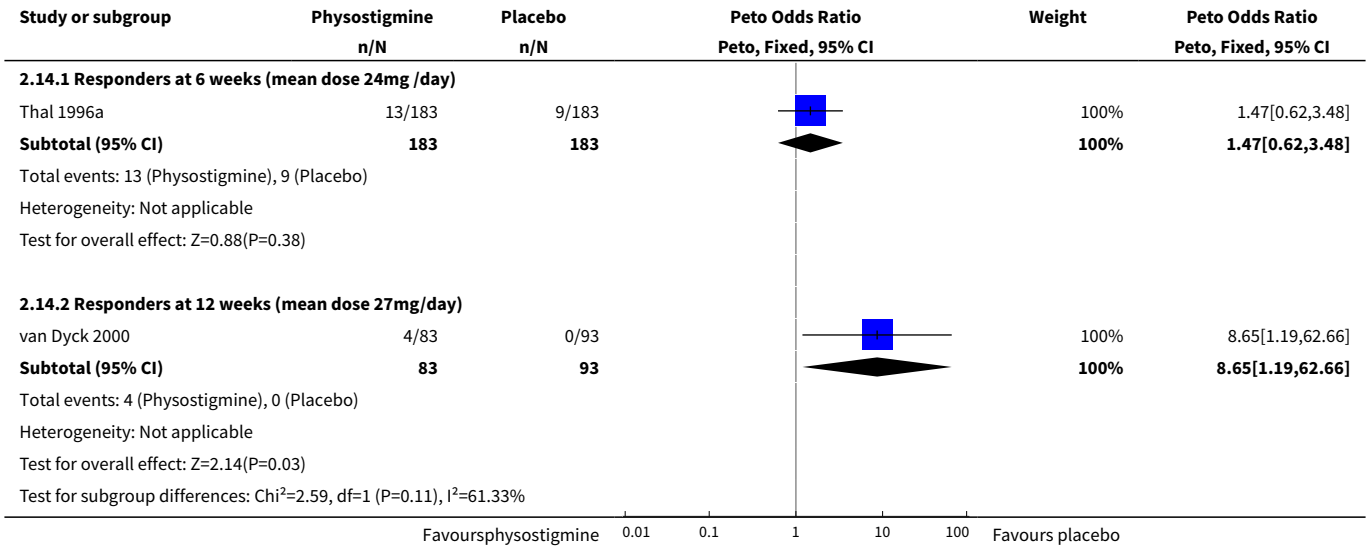
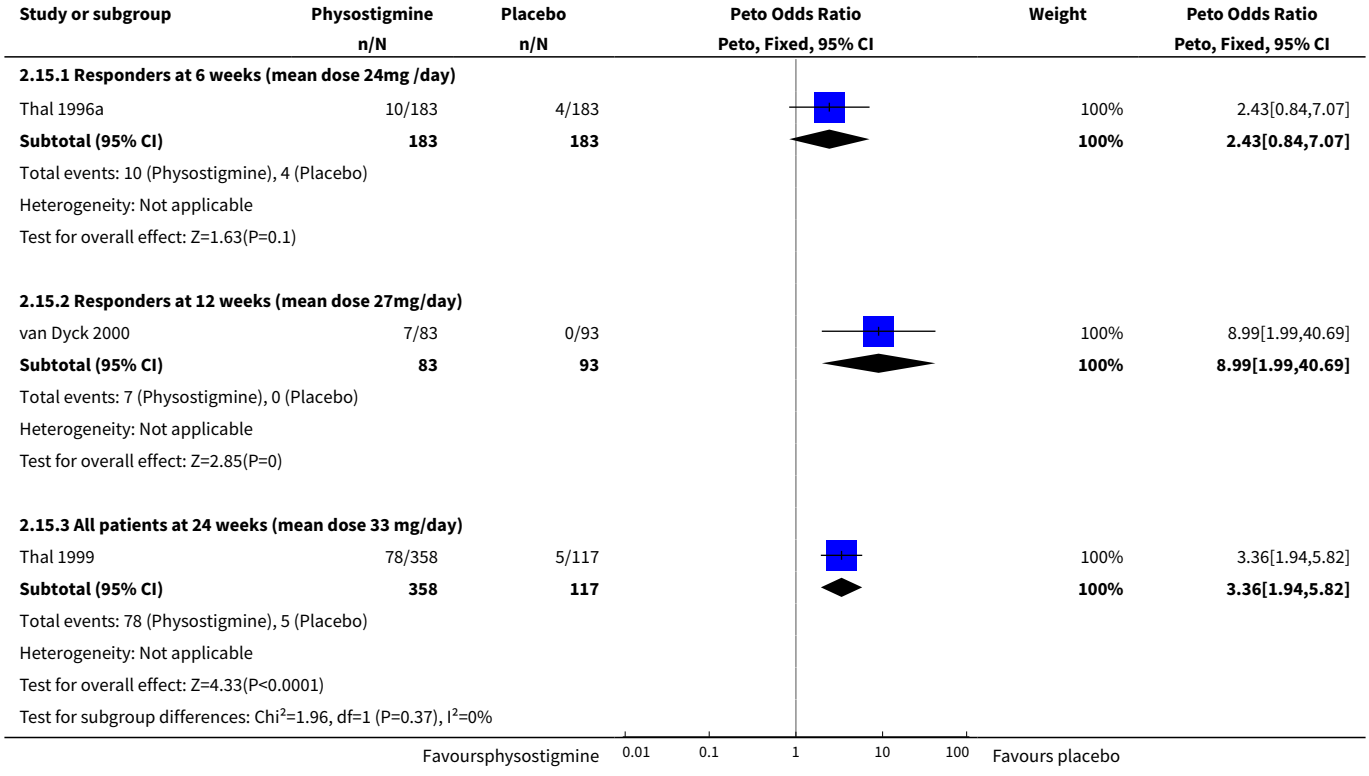
Analysis 2.14. Comparison 2 physostigmine (CR) vs placebo, Outcome 14 At least one adverse event of tremor before end of treatment.



Analysis 2.15. Comparison 2 physostigmine (CR) vs placebo, Outcome 15 At least one adverse event of asthenia before end of treatment.



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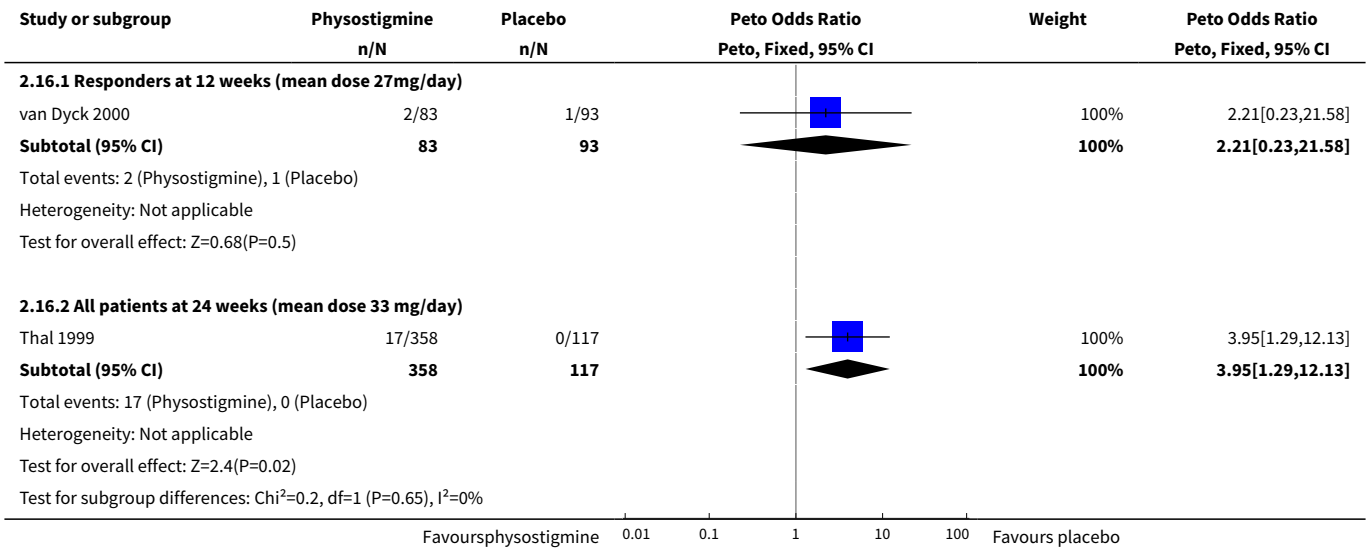
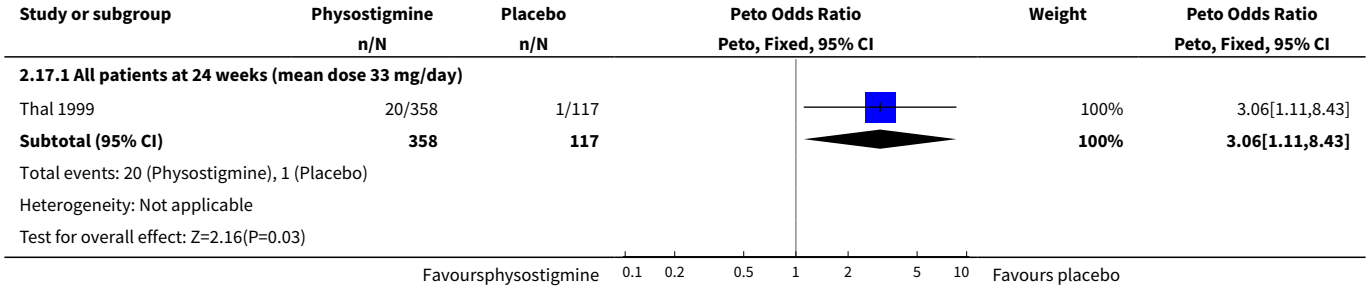
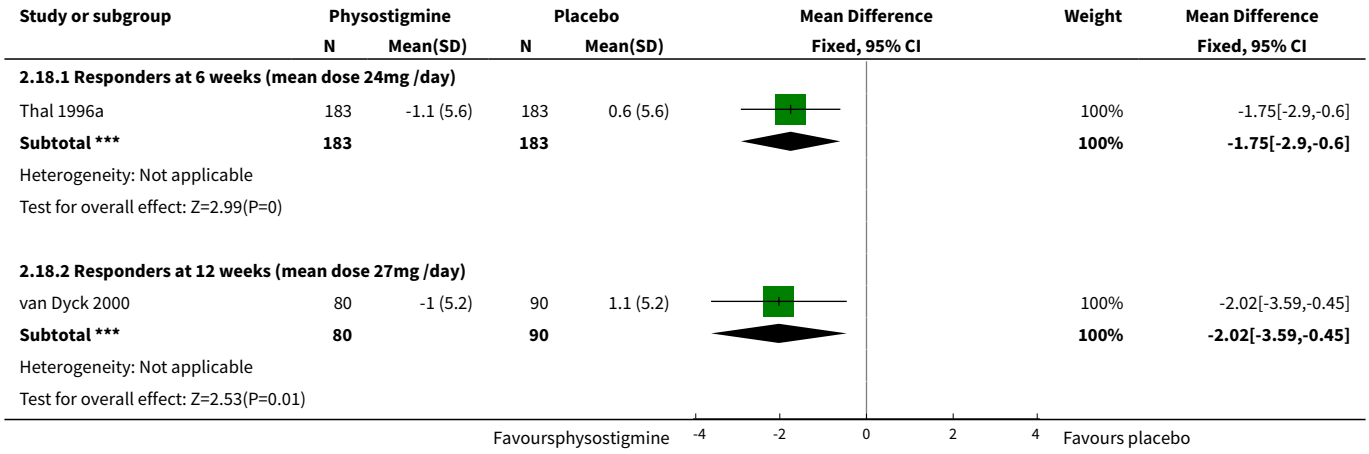
Analysis 2.16. Comparison 2 physostigmine (CR) vs placebo, Outcome 16 At least one adverse event of dyspnea before end of treatment.



Analysis 2.17. Comparison 2 physostigmine (CR) vs placebo, Outcome 17 At least one adverse event of abnormal dreaming before end of treatment.



Analysis 2.18. Comparison 2 physostigmine (CR) vs placebo, Outcome 18 ADAS-Cog (change from baseline) ITT.



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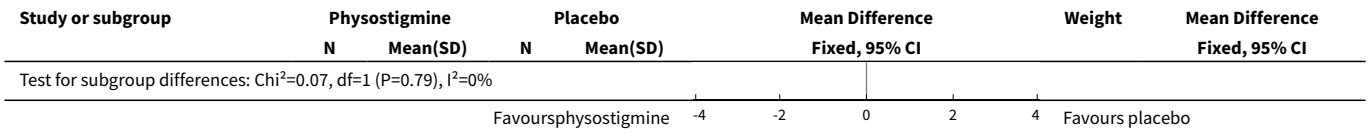
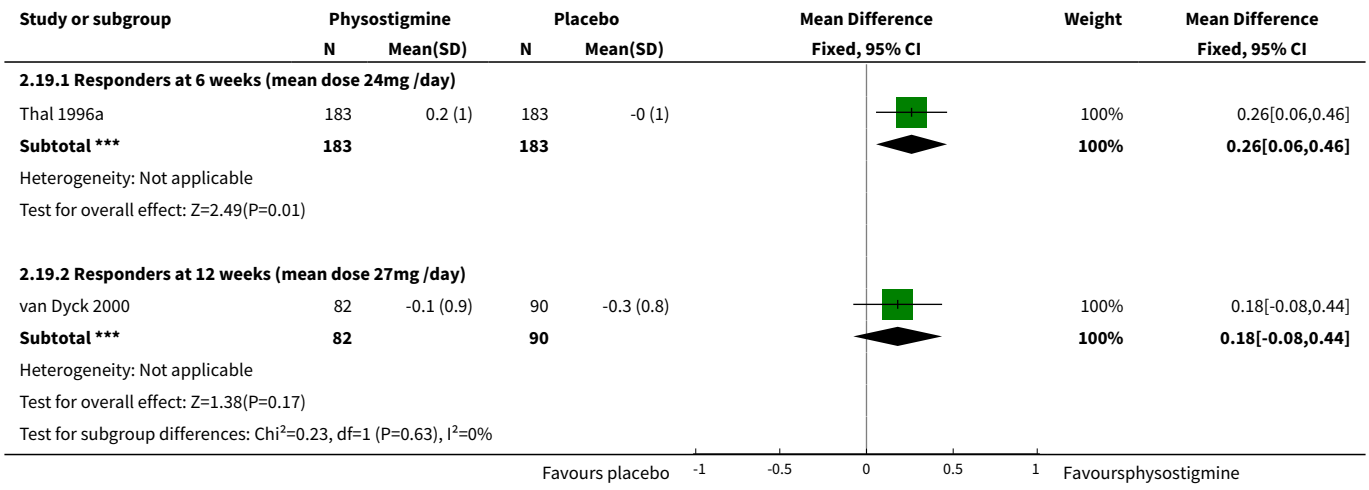
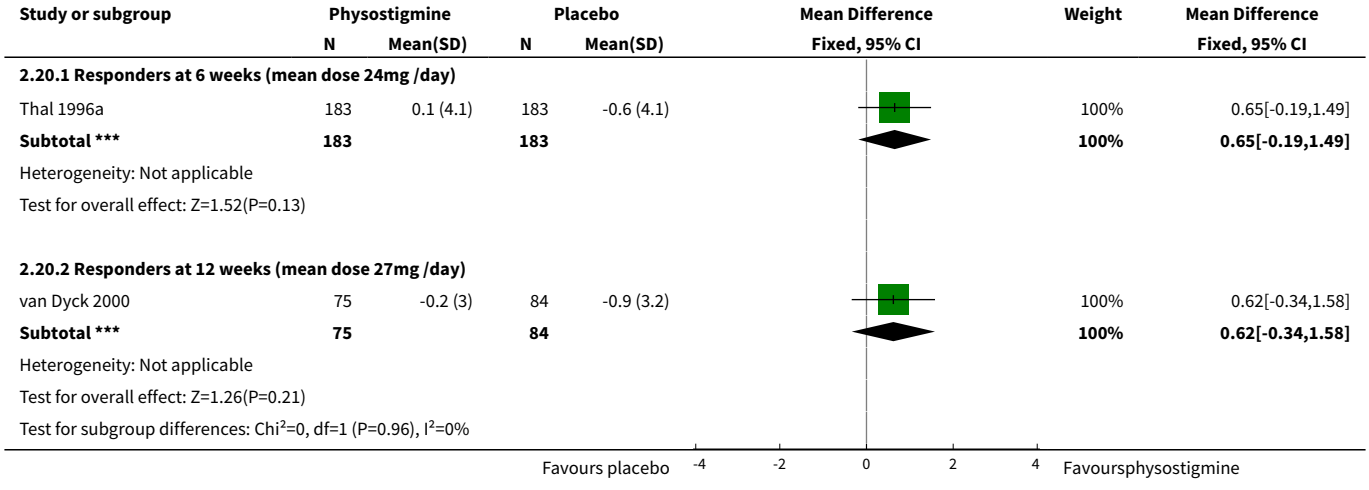


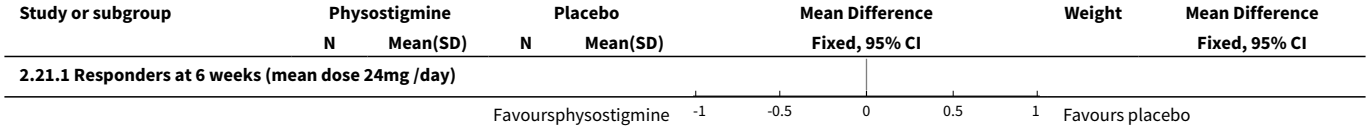
Analysis 2.19. Comparison 2 physostigmine (CR) vs placebo, Outcome 19 CGIC (change from baseline) ITT.



Analysis 2.20. Comparison 2 physostigmine (CR) vs placebo, Outcome 20 MMSE (change from baseline) ITT.



Analysis 2.21. Comparison 2 physostigmine (CR) vs placebo, Outcome 21 PSMS (change from baseline) ITT.



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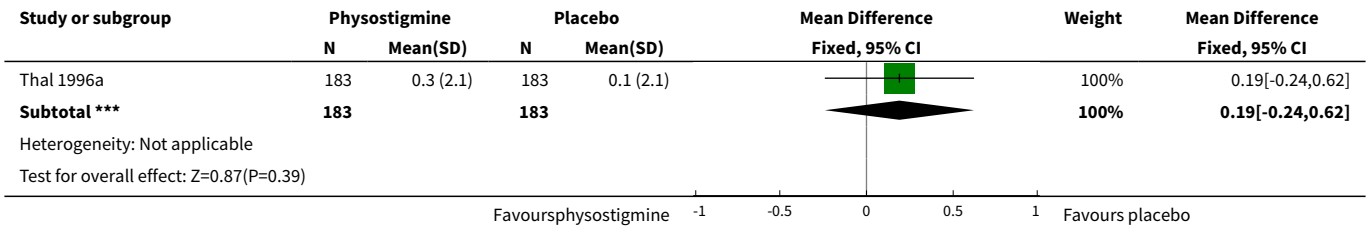
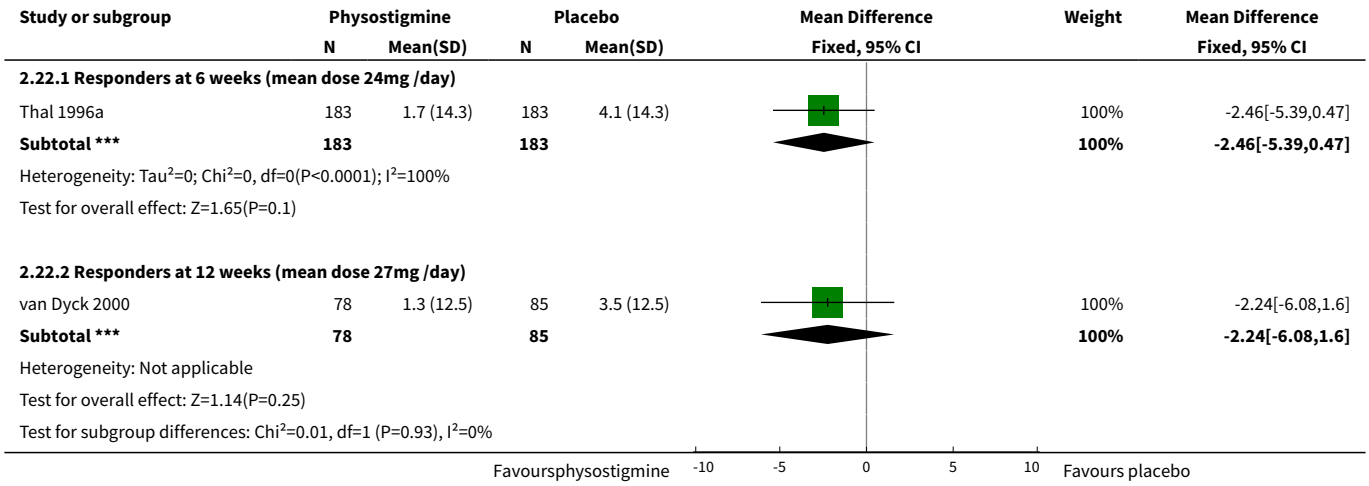


Analysis 2.22. Comparison 2 physostigmine (CR) vs placebo, Outcome 22 IADL (change from baseline) ITT.



Comparison 3. physostigmine (verum patch) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of withdrawals before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.33, 1.63]
1.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.31, 1.60]
2 A serious adverse event before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.12, 1.56]
2.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.08, 1.26]
3 At least one adverse event of eczema before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.64 [0.47, 123.52]
3.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 At least one adverse event of nausea before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.21, 3.10]
4.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.38, 4.51]
5 At least one adverse event of vomiting before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.35 [1.15, 60.87]
6 At least one adverse event of headache before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.64 [0.47, 123.52]
6.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.35 [1.15, 60.87]
7 At least one adverse event of sweating before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 1.30]
7.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.37]
8 At least one adverse event of stomach pain before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.77 [0.79, 76.10]
8.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 At least one adverse event of tremor before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 1.30]
9.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.37]
10 At least one adverse event of erythema before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.41 [0.67, 8.75]
10.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [0.57, 8.51]
11 At least one adverse event of hypersalivation before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 1.30]
11.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.37]
12 At least one adverse event of itching before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.40, 3.47]
12.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.17, 2.04]
13 At least one adverse event of abdominal cramps before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
13.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.35 [1.15, 60.87]
14 At least one adverse event of gastrointestinal complaints before end of treatment	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
14.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.90 [1.09, 57.50]
14.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 CGIC (improved compared with baseline at 12 weeks) ITT	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 At 24 weeks (dose 5.7 mg/day)	1	123	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.26, 1.27]
15.2 At 24 weeks (dose 11.4 mg/day)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.44, 2.03]
16 CGIC (improved compared with baseline at 12 weeks) OC	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
16.1 At 24 weeks (dose 5.7 mg/day)	1	91	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.20, 1.09]
16.2 At 24 weeks (dose 11.4 mg/day)	1	89	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.35, 1.85]

Analysis 3.1. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 1 Number of withdrawals before end of treatment.

Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.1.1 At 24 weeks (dose 5.7 mg/day)					
Möller 1999	14/61	18/62		100%	0.73[0.33,1.63]
Subtotal (95% CI)	**61**	**62**		**100%**	**0.73[0.33,1.63]**
Total events: 14 (Physostigmine), 18 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
3.1.2 At 24 weeks (dose 11.4 mg/day)					
Möller 1999	13/58	18/62		100%	0.71[0.31,1.6]
Subtotal (95% CI)	**58**	**62**		**100%**	**0.71[0.31,1.6]**
Total events: 13 (Physostigmine), 18 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%					

Favoursphysostigmine — Favours placebo

Analysis 3.2. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 2 A serious adverse event before end of treatment.

Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.2.1 At 24 weeks (dose 5.7 mg/day)					
Möller 1999	3/61	7/62		100%	0.43[0.12,1.56]
Subtotal (95% CI)	**61**	**62**		**100%**	**0.43[0.12,1.56]**
Total events: 3 (Physostigmine), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					

Favoursphysostigmine — Favours placebo

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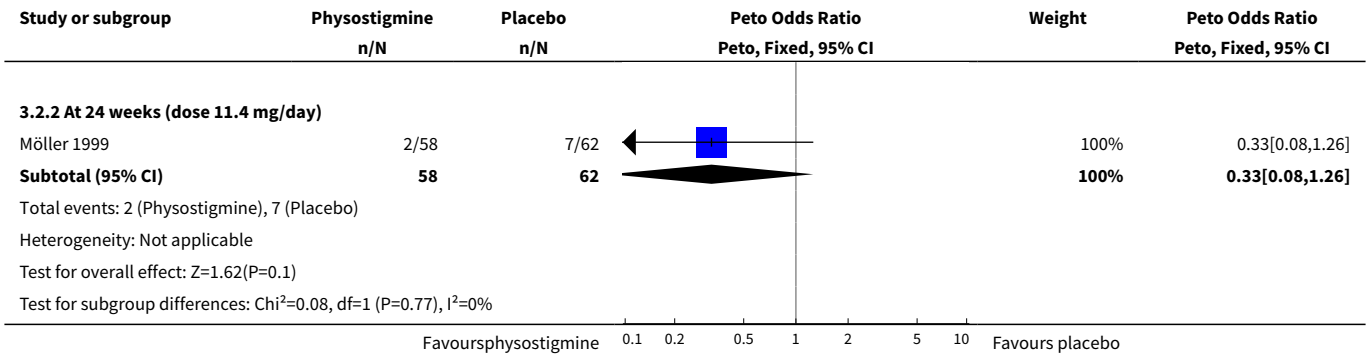
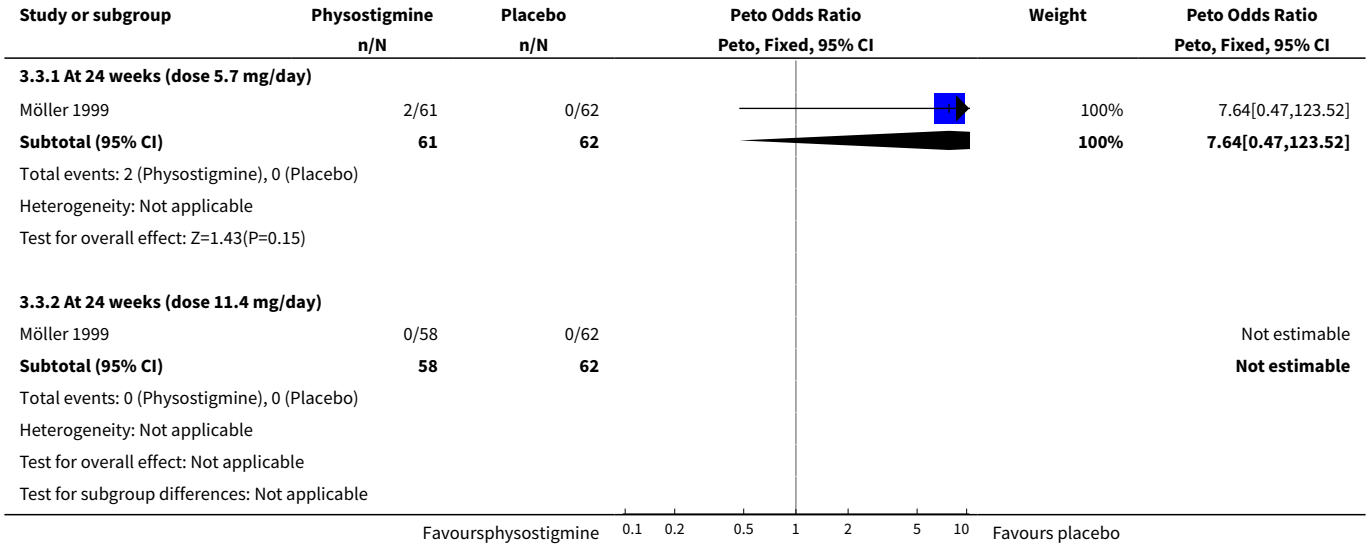
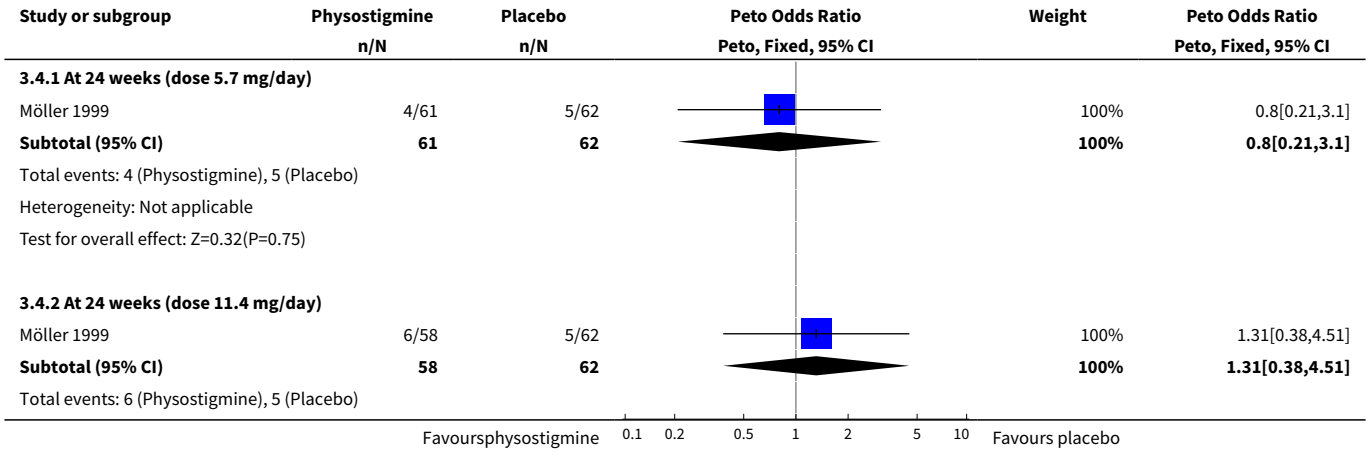


Analysis 3.3. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 3 At least one adverse event of eczema before end of treatment.



Analysis 3.4. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 4 At least one adverse event of nausea before end of treatment.



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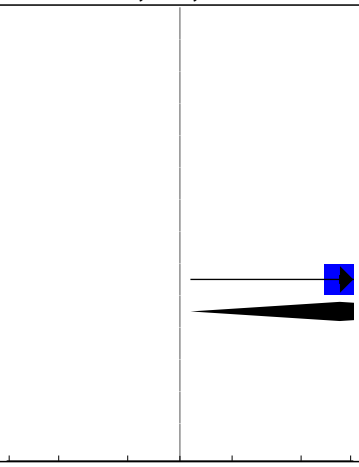
Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					
Test for subgroup differences: Chi²=0.28, df=1 (P=0.6), I²=0%					

Favoursphysostigmine Favours placebo

Analysis 3.5. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 5 At least one adverse event of vomiting before end of treatment.

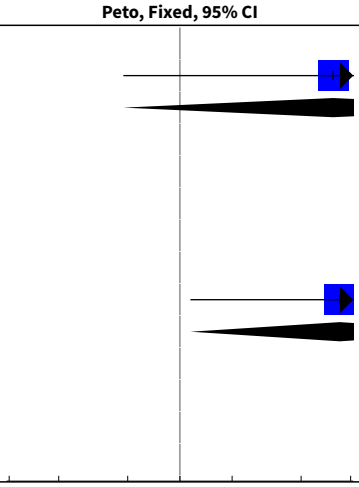
Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.5.1 At 24 weeks (dose 5.7 mg/day)					
Möller 1999	0/61	0/62			Not estimable
Subtotal (95% CI)	**61**	**62**			**Not estimable**
Total events: 0 (Physostigmine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.5.2 At 24 weeks (dose 11.4 mg/day)					
Möller 1999	4/58	0/62		100%	8.35[1.15,60.87]
Subtotal (95% CI)	**58**	**62**		**100%**	**8.35[1.15,60.87]**
Total events: 4 (Physostigmine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Not applicable					



Favoursphysostigmine Favours placebo

Analysis 3.6. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 6 At least one adverse event of headache before end of treatment.

Study or subgroup	Physostigmine n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.6.1 At 24 weeks (dose 5.7 mg/day)					
Möller 1999	2/61	0/62		100%	7.64[0.47,123.52]
Subtotal (95% CI)	**61**	**62**		**100%**	**7.64[0.47,123.52]**
Total events: 2 (Physostigmine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					
3.6.2 At 24 weeks (dose 11.4 mg/day)					
Möller 1999	4/58	0/62		100%	8.35[1.15,60.87]
Subtotal (95% CI)	**58**	**62**		**100%**	**8.35[1.15,60.87]**
Total events: 4 (Physostigmine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Chi²=0, df=1 (P=0.96), I²=0%					



Favoursphysostigmine Favours placebo

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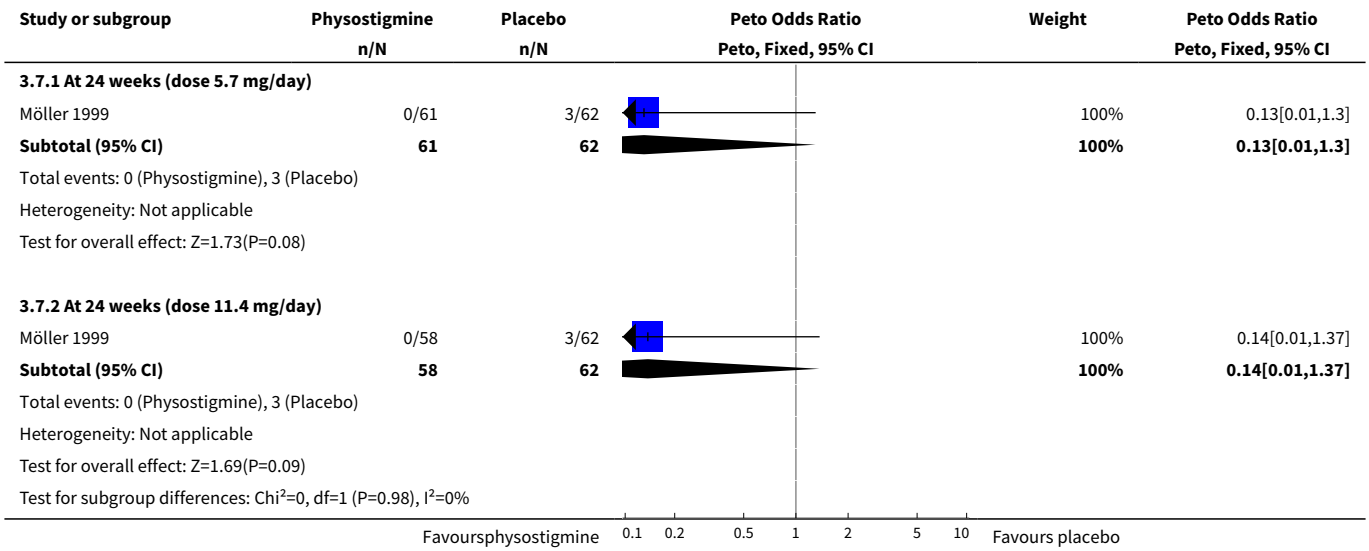
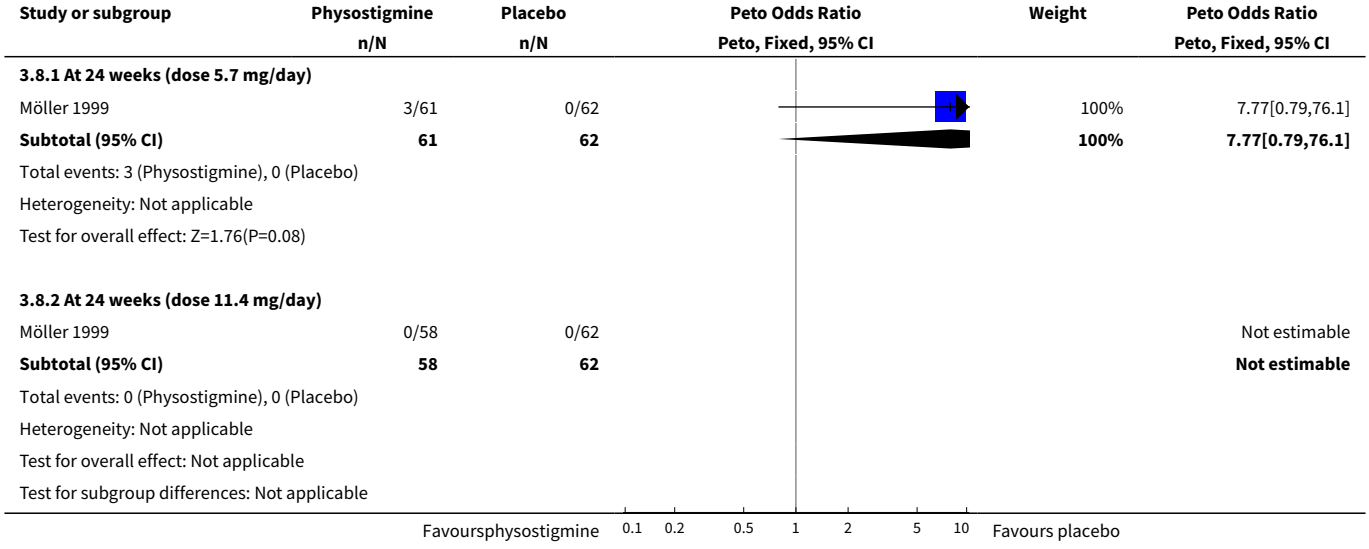
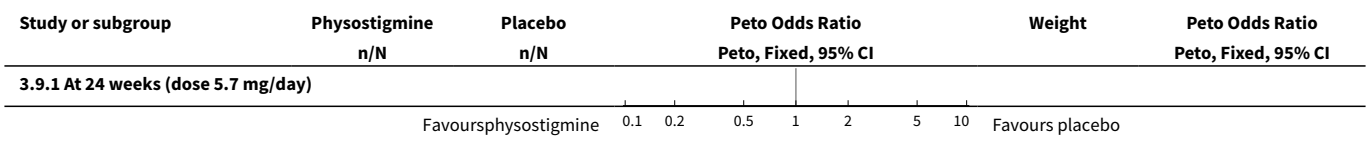
Analysis 3.7. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 7 At least one adverse event of sweating before end of treatment.



Analysis 3.8. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 8 At least one adverse event of stomach pain before end of treatment.



Analysis 3.9. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 9 At least one adverse event of tremor before end of treatment.



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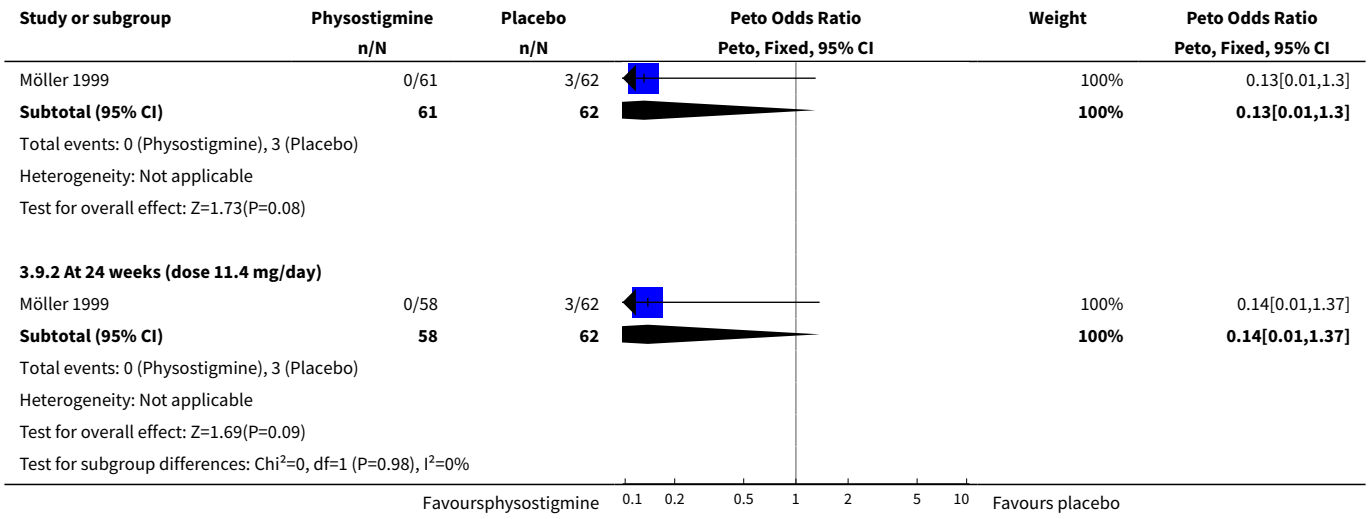
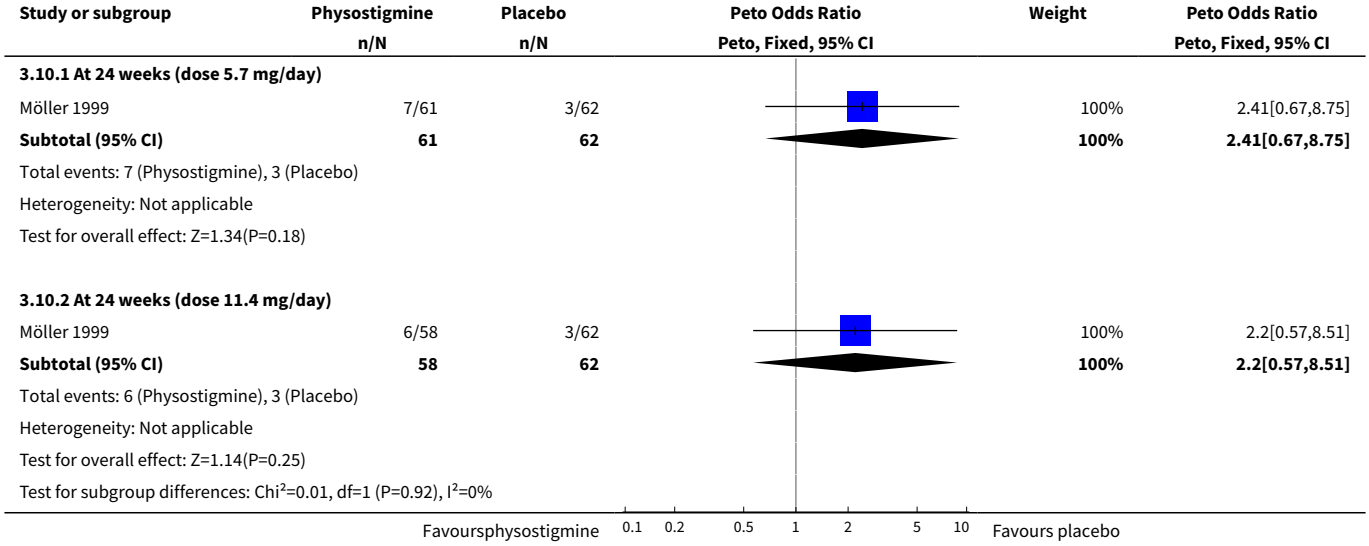
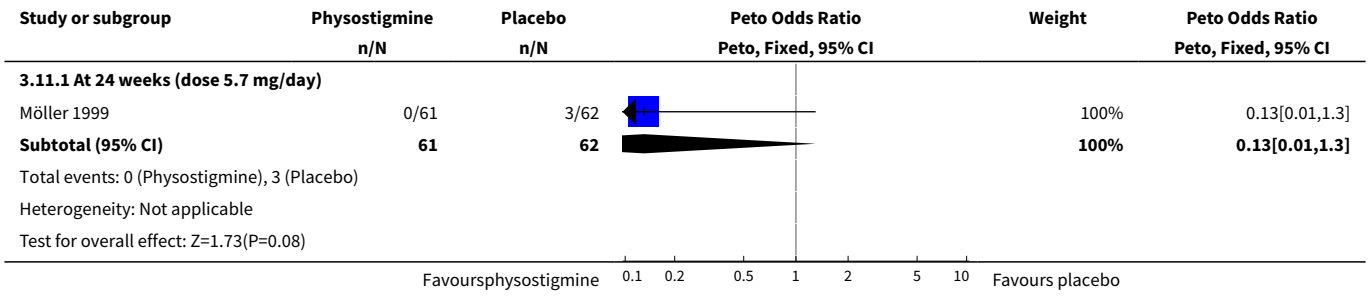


Analysis 3.10. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 10 At least one adverse event of erythema before end of treatment.



Analysis 3.11. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 11 At least one adverse event of hypersalivation before end of treatment.



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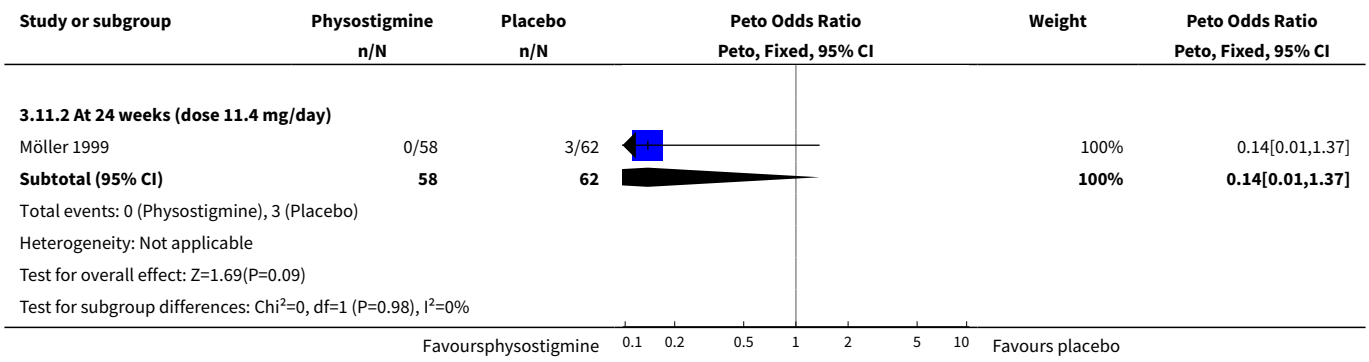
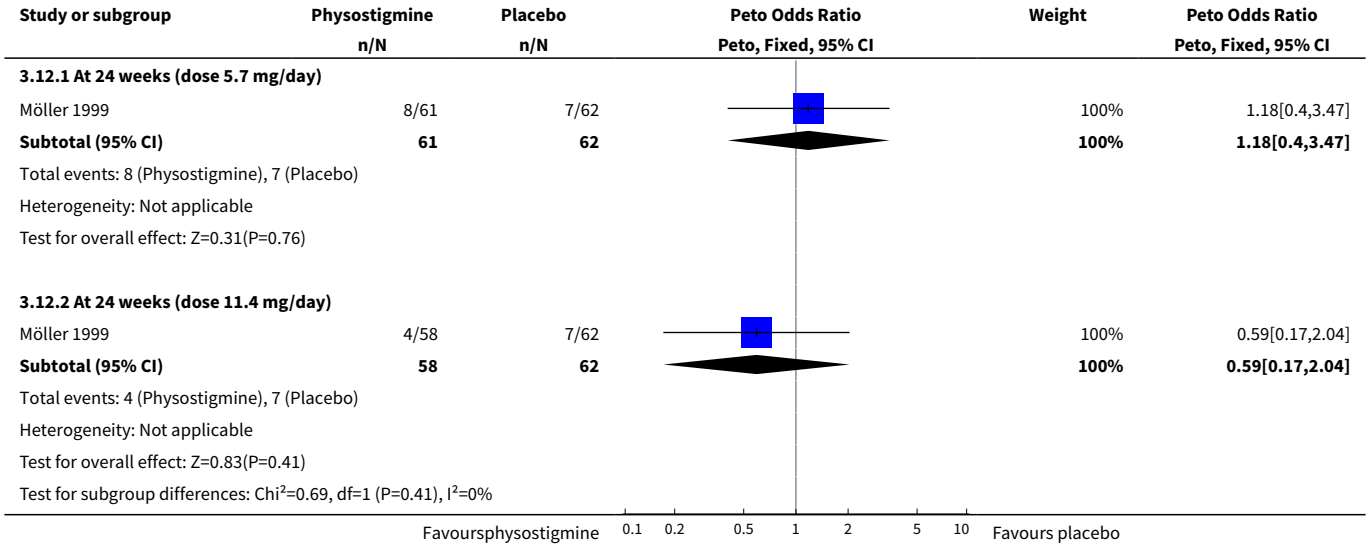
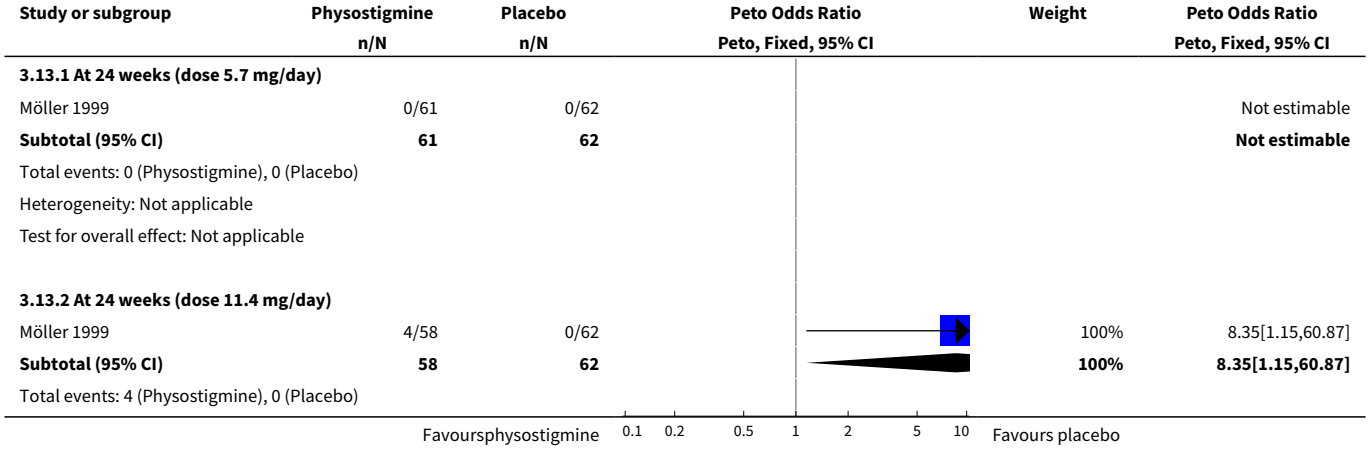


Analysis 3.12. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 12 At least one adverse event of itching before end of treatment.



Analysis 3.13. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 13 At least one adverse event of abdominal cramps before end of treatment.



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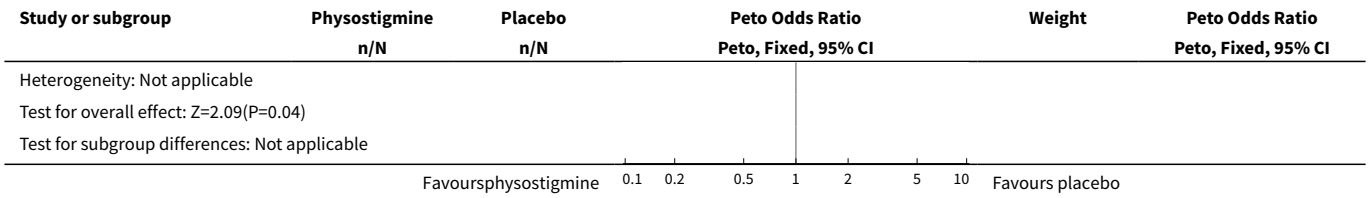
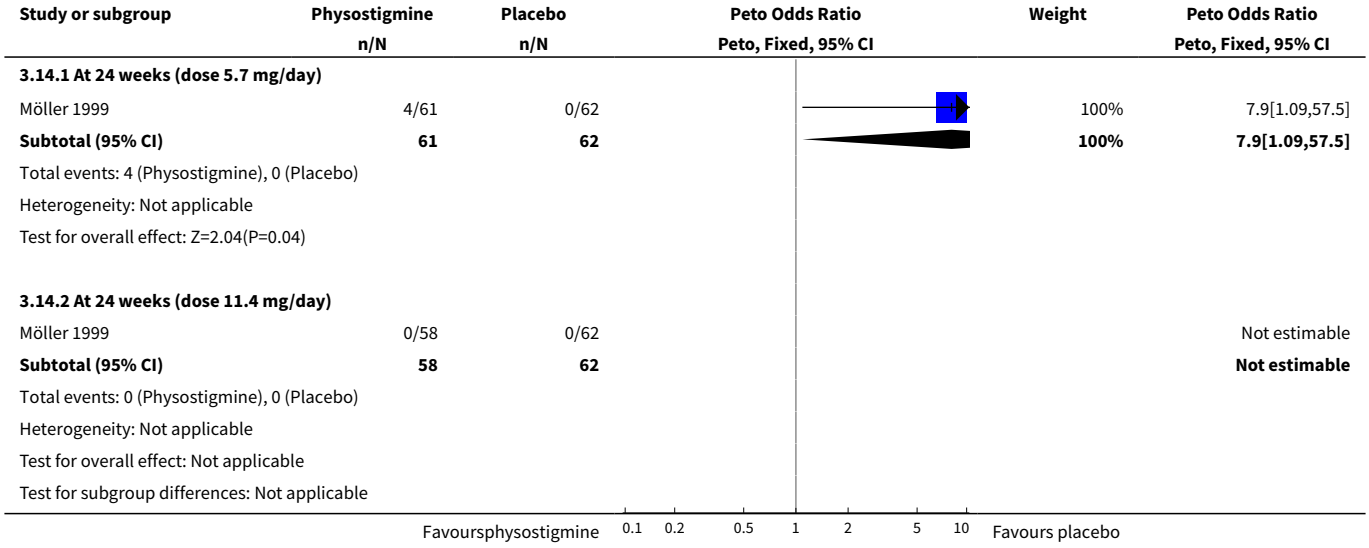
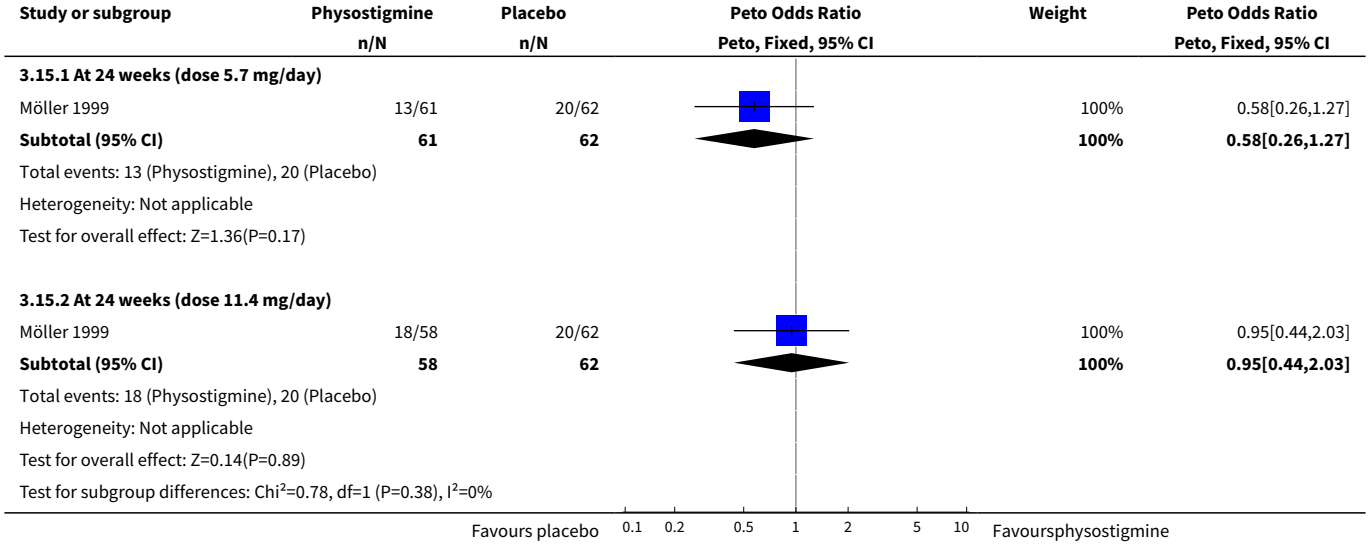


Analysis 3.14. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 14 At least one adverse event of gastrointestinal complaints before end of treatment.



Analysis 3.15. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 15 CGIC (improved compared with baseline at 12 weeks) ITT.



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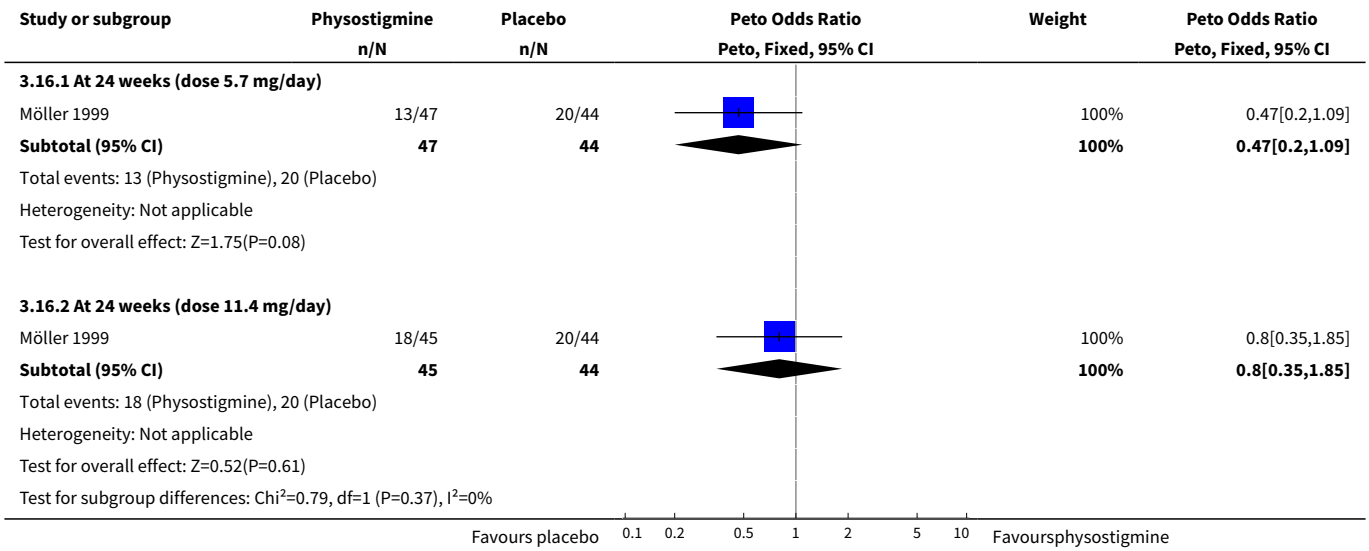
Analysis 3.16. Comparison 3 physostigmine (verum patch) vs placebo, Outcome 16 CGIC (improved compared with baseline at 12 weeks) OC.



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ADDITIONAL TABLES

Table 1. Description of included studies at baseline

Study	Design	Duration (weeks)	Number randomized	Intervention	Doses	Mean age (s.e.)	%female	Mean MMSE (s.e.)	Country
Asthana 1995a	crossover	5 days X 2	9	i.v.infusion	optimal dose (0.02 - 1.04 mg/hour)	68.7 (12.1)	56	22.2 (3.4)	USA
Beller 1985	crossover	2 days X 4 (no washout between phases)	8	oral	placebo, 3.5, 7.0, and 14 mg/day divided into 7 doses at 2 hourly intervals		50	-	USA
Davis 1982	crossover	1 day X 2	10	i.v. infusion	0.125, 0.25, or 0.5 mg over 30 minutes		40		USA
Gustafson 1987	crossover	1 day X 2	10	i.v.infusion	1.9 mg over 2 hours	61(6)	50		Sweden
Harrell 1990a	crossover	2 weeks X 2 (no washout between phases)	20	oral	highest tolerated dose (6, 9, 12, or 15 mg/day in 6 doses every 2 hours)	63 (3.1)	55		USA
Jenike 1990a	crossover	1 week X 2 (no deatils of any washout)	23	oral	optimal dose no details of quantity	66 (9)	48		USA
Mohs 1985	crossover	3-5 days X 2 (no details of any washout phase)	12	oral	highest tolerated dose (4, 8, 12, 16 mg/day divided in 8 doses every 2 hours)	62.3	33		USA
Möller 1999	parallel group	24 weeks	181	verum patch	5.7 or 11.4 mg /day delivered over 24 hours	69.3 (8.2)	52	18.1 (4.1)	Germany
Sano 1993	crossover	6 weeks X 2 (no washout between phases)	29	oral	highest tolerated dose (8-16 mg/day, divided into 4 doses every 2 hours)	69.1 (9.1)		18	USA
Stern 1987	crossover	3 days X 2 (1 day washout between phases)	22	oral	optimal or highest tolerated dose (12.5 - 16 mg/day taken every 2 hours, divided into 4-6 doses)	67.1 (8.4)			USA
Thal 1989	parallel group	10 weeks	16	oral	dose titration to 10, 15 or 20 mg per day divided into 5 doses	64			USA

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Table 1. Description of included studies at baseline *(Continued)*

Thal 1996a	parallel group	6 weeks	366	oral CR	18, 24 or 30 mg/day divided into 2 doses	68.6		17.7	USA, UK
Thal 1996b	parallel group	6 weeks	439	oral CR	18, 24 or 30 mg/day divided into 2 doses	68.7		18.7	USA , UK
Thal 1999	parallel group	24 weeks	475	oral CR	30mg/day in 2 divided doses or 36mg/day in 3 divided doses	73.4 (7.7)	60	19.5 (3.6)	USA
van Dyck 2000	parallel group	12 weeks	176	oral CR	24 or 30 mg/day divided into 2 doses	72.8 (8.1)	54.7	18.5 (4.7)	USA

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Table 2. Abbreviations, description and references for rating scales and tests

Scale	Abbreviation	Description	Reference
Alzheimer's Disease Assessment Scale	ADAS	The cognitive test consists of 11 subsets, language, comprehension, recall of test instructions, word finding difficulty, following commands, naming, construction, ideational praxis, orientation, word recall, and word recognition. The maximum score of 70 indicates severe impairment.	Rosen 1984
Activities of Daily Living	ADL		Lawton 1969
Blessed Dementia Rating Scale	BDRS	The first three sections measure changes in performance of everyday activities, habits, and personality, interests and drive as answered by the patient's close relative or carer. Each section is scored 0 (normal) -28 (severe impairment). The second three sections form the cognitive test. Information, memory, and concentration are each assessed on a score of 0(complete failure) - 37(normal).	Blessed 1968
Boston Naming Test	BNT		Kaplan 1976
Brief Psychiatric Rating Scale	BPRS	18 items, covering mood and behaviour, are each scored on a 1-7 scale, (not present to very severe)	Overall, 1962
Buschke Selective Reminding Test	BSRT	the presentation of a series of words to be remembered, followed by immediate recall of as many as possible. The subject is then reminded only of words that have not been recalled in the previous trial, and is asked again to recall as many words as possible. After six trials storage, retrieval, consistency of retrieval, intrusions and immediate memory are measured.	Buschke 1973 Buschke 1974
Cancelation Task		Detection of a specific shape within an array of shapes	
Category Fluency		Similar to COWAT, with categories fruits, animals and vegetables	Benton 1974 Batters 1987
Clinical Global Impression of Change	CGIC	A rating of global change based on a structured interview of the subject and carer by a clinician unbiased by other outcomes assessments.The patient is assessed using a 7-point Likert scale (higher score indicates improvement) where baseline is rated as 4 and the patient is assessed on a continuum from' very much worse' to 'very much better'.	Guy 1976
Clinician Interview Based Impression of Change with caregiver input	CIBIC-Plus	A rating of global change based on a structured interview of the subject and carer by a clinician unbiased by other outcomes assessments.The patient is assessed using a 7-point Likert scale (higher score indicates improvement) where baseline is rated as 4 and the patient is assessed on a continuum from very much worse to very much better.	Knopman 1994
Controlled Oral Word Association Test	COWAT	measures verbal fluency for generating words beginning with a given letter or belonging to a category within 60 seconds	Benton 1974 Batters 1987

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Table 2. Abbreviations, description and references for rating scales and tests *(Continued)*

Digit Symbol		Using a key which links the digits 1 to 9 with a symbol, the subject is timed whilst linking a list of the symbols to the correct digit.	
Digit Span		A single trial consists of two parts. The subject is given a list of digits, orally and asked to repeat them, and in the second part is asked to repeat them backwards. Each trial increases by one the number of digits in the list. The test stops after failure on both parts of a trial	Wechsler 1981
Dementia Rating Scale	DRS	Functional impairment is rated from 0 (no impairment) - 17(serious impairment) .	
Famous Faces		Designed to assess retrieval from remote memory	Albert 1981
Figure copy		drawings are copied and assessed for a number of features	Marlsen-Wilson 1975
Finger tapping		Subjects tap, using a standard finger-tapping apparatus, in a sequential manner first with the right, then the left hand.	
Geriatric evaluation by relative's rating instrument	GERRI	consists of 49 questions, each rated on a 5-point frequency scale, designed to assess the frequency of typical behavioural disturbances and complaints in cognitive functioning, social functioning and mood. The higher score indicates greater impairment. The questions are answered by a carer.	Schwartz 1988
Geriatric Depression Scale	GDS		
Instrumental Activities of Daily Living	IADL	the score ranges from 4-32, the lower score indicating better functioning	Lawton 1969
Mattis Dementia Rating Scale	MDRS	maximum total of 144	Bellock 1976
Memory and Information Test	MIT	A brief mental status test with a score from 0 (serious impairment) -20 (no impairment).	
Mini Mental State Examination	MMSE	the MMSE was developed as a short test suitable for the elderly with dementia. It concentrates on the cognitive aspects of mental function, the five sections cover orientation, immediate recall, attention and calculation, delayed recall and language. A maximum score of 30 indicates no impairment.	Folstein 1975
Modified Mini Mental State Examination	Mod MMSE		Mayeux 1981
Neuropsychological Test Battery	NTB	assessing vocabulary, inductive reasoning,verbal memory, spatial memory, reaction time and aphasia	Hagberg 1976
Nurses' Observation scale for Geriatric Patients	NOSGER	Information from the carer	Brunner 1990

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Table 2. Abbreviations, description and references for rating scales and tests *(Continued)*

Nurses' Observation Scale for Inpatient Evaluation	NOSIE	NOSIE was developed to measure therapeutic change in the older schizophrenic patient. It is based on observation of an inpatient for three days and each of 80 items is rated on a scale of 0 (never) to 4 (always). The items are categorised into 7 groups, social competence, social interest, personal neatness, cooperation, irritability, manifest psychosis, psychotic depression.	Honigfeld 1965
Performance test of Activities of Daily Living	PADL		Kurcansky 1976
Verbal and Visual Paired Associate Learning	PALW	Memory test of pairs of words or faces	
Picture copy		Pictures are copied and assessed	Haxby 1985
Picture recognition		Pictures of 7 common items shown to subject, then another 15 picturs of common items. Subjects has to identify those already seen in the first group	
Physical Self Maintenance Scale	PSMS	Range 6-30 Measures functional abilities in elderly subjects	
Recognition memory test		Measures patient's ability to learn new information	
Revised Wechsler Adult Intelligence Scale	WAIS-R	a series of brief subtests, some taken from the WMS, each measuring a different facet of memory, which are summarised into 5 composite scores and finally 2 major scores using weights prescribed by Wechsler. Some subtests of the Revised Wechsler Adult Intelligence Scale (WAIS-R) are identical to those of the WMS-R although the primary purposes of the tests are different.	Wechsler 1987
Rosen Construction Task			Rosen 1984
Sandoz Clinical Assessment Geriatric	SCAG		Hamot 1980
Sickness Impact Profile	SIP	Measures impact of illness on functional abilities in sleep and rest, home management, recreation and pastimes, physical activities, psychosocial activities	Bergner 1981
Squire Memory Questionnaire	SMQ	Memory in daily activities	Squire 1979
Stroop Color Word Interference Test		Naming of colour in which words are printed	
Token Test	TT	20 tokens, 5 each of coloured small and large circles and squares are displayed and oral commands are issued for increasingly complex manipulations of tokens	Boller 1966
Wechsler Memory Test	WMS	consists of seven subtests, information, orientation, mental control, logical memory, digit span, visual reproduction, and associate	Wechsler 1945

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WHAT'S NEW

Date	Event	Description
2 June 2008	New search has been performed	January 2008: an update search was run; two references were retrieved, both of which were excluded
2 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 2, 2001

Date	Event	Description
5 August 2005	New search has been performed	August 2005: an update search was carried out; no new references were found
26 February 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-JCF and JB extracted data, assessed methodological quality of studies and developed inclusion/exclusion criteria.
-JB did the meta-analysis
-JCF wrote the body of the text, which was edited by JB
-JCF: updates

-Consumer Editor: Corinne Cavender

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Oxford, UK.
- Universidade Federal do Ceara, Brazil, Brazil.

External sources

- CAPES Foundation, Brazil (Joao M Coelho Filho), Brazil.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Cholinesterase Inhibitors [*therapeutic use]; Physostigmine [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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