Technology *Report*

Issue 58 September 2005

Cholinesterase Inhibitors for Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials

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CCOHTA
600-865 Carling Avenue
Ottawa ON Canada K1S 5S8
Tel. (613) 226-2553
Fax. (613) 226-5392
Email: pubs@ccohta.ca

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Cite as: Perras C, Shukla VK, Lessard C, Skidmore B, Bergman H, Gauthier S. *Cholinesterase inhibitors for Alzheimer's disease: a systematic review of randomized controlled trials* [Technology report no 58]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

Production of this report is made possible by a financial contribution from Health Canada's Health Care Strategies and Policy, federal, provincial and territorial partnership grant program.

CCOHTA is funded by Canadian federal, provincial and territorial governments.

Legal Deposit - 2005
National Library of Canada
ISBN: 1-894978-68-4 (print)
ISBN: 1-894978-69-2 (online)

PUBLICATIONS MAIL AGREEMENT NO: 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT
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Canadian Coordinating Office for Health Technology Assessment

Cholinesterase Inhibitors for Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials

Christine Perras BSc Phm MPH[1]
Vijay K. Shukla BPharm MSc PhD[1]
Chantale Lessard BPharm MSc[2]
Becky Skidmore BA MLS[1]
Howard Bergman MD[3]
Serge Gauthier MD FRCPC[4]

September 2005

[1] Canadian Coordinating Office for Health Technology Assessment, Ottawa ON
[2] Doctoral student, Public Health Section, Department of Health Administration, Faculty of Medicine, Université de Montréal, Montréal QC
[3] Division of Geriatric Medicine, Department of Medicine, McGill University and Jewish General Hospital, Montréal QC
[4] McGill Center for Studies in Aging, McGill University, Montréal QC

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Janice Graham, PhD
Associate Professor
Dalhousie University
Halifax NS

James L. Silvius, BAOxon MD FRCPC
Head and Chief, Division of Geriatric Medicine
University of Calgary, Calgary Health Region
Calgary AB

CCOHTA Scientific Advisory Panel Reviewers

Gina Bravo, PhD
Professor, Department of Community Health Sciences
Faculty of Medicine, University of Sherbrooke
Sherbrooke QC

David Persaud, MSc MHSA PhD
Associate Professor
School of Health Services Administration
Dalhousie University
Halifax NS

Authorship

Christine Perras was responsible for the extraction, analysis and quality assessment of the data. She wrote the draft reports, responded to reviewers' comments and completed the final report.

Vijay Shukla was responsible for the coordination of the project, the protocol development and the selection of trials. He provided guidance regarding the data analysis. He made comments on all drafts and final reports.

Chantale Lessard was responsible for the protocol development, the selection of trials and the data extraction. She provided comments on the draft and final reports.

Becky Skidmore was responsible for the design and execution of the literature search strategies, for writing the methods section and associated appendix on literature searching; and for verifying and formatting bibliographic references.

Howard Bergman gave clinical input on the protocol and provided comments on the draft and final reports.

Serge Gauthier gave clinical input on the protocol and provided comments on the draft and final reports.

Acknowledgements

The authors are grateful to Marie Sirdevan, BScPhm (MS) for data extraction from the Japanese article; Zhiliu Tang, MSc, MD (ZT) for data extraction from the Chinese articles; and Abdallah Tahr MD, PhD (AT) for assistance with the quality assurance and quality assessment of the data.

Conflicts of Interest

There were no conflicts of interest reported for the following people: Christine Perras, Vijay Shukla, Chantale Lessard, Becky Skidmore, Janice Graham and James L. Silvius.

Howard Bergman received a grant to carry out clinical trials involving medications that are discussed in this report. In the past, he served on advisory boards for Novartis, Pfizer and Janssen.

Serge Gauthier received research grants from Pfizer/Eisai and Janssen-Cilag. He has participated at Pfizer-sponsored symposia; and at Pfizer and Janssen-Cilag national advisory boards. He was compensated for writing publications with Novartis.

REPORT *IN BRIEF*

September 2005

Cholinesterase Inhibitors for Treatment of Mild to Moderate Alzheimer's Disease

Technology

Cholinesterase inhibitors (ChEIs): donepezil, galantamine and rivastigmine.

Disease

Alzheimer's disease (AD) is a form of dementia. Its most common symptom is memory loss. People with AD may forget simple words, misplace items and become disoriented regarding time and place. In 1991, approximately 5% of individuals older than 65 years met the criteria for AD. Societal costs of care can range from $9,451 per patient annually for mild AD to $36,794 for severe AD.

Issue

There is a demand to use ChEIs in the community and in institutions. It is estimated that in Canada, $129 million was spent on these drugs last year. It has never been shown, however, that these drugs prevent or cure AD.

Methods and Results

The benefit and harm of ChEIs to manage mild to moderate AD was determined by examining changes in functional performance, global improvement, quality of life (QoL), adverse events (AE) and serious AE. The effect of using ChEIs on the rates of institutionalization and persistence with therapy, was also examined.

Implications for Decision Making

- **For patients, the long-term benefit of using ChEIs remains to be determined.** Studies show that ChEIs can lead to modest short-term decreases in functional disability and global impressions of disability. The clinical significance of these changes is difficult to predict.
- **There is no clear advantage to choosing one ChEI in place of another.** Studies that compared a ChEI to another ChEI showed that the drugs have comparable benefits. However, the studies were of poor quality, which prevents the formation of definitive conclusions.
- **Between 8% and 25% of patients will not continue taking therapy.** Compared with placebo, patients on galantamine and rivastigmine experienced AE that led to a greater chance of stopping treatment. ChEIs did not cause an increase in the number of deaths; or of patients requiring hospitalization or emergency room visits (serious AE).
- **QoL and rates of institutionalization, measured in studies comparing donepezil with placebo, did not show a difference.** There is insuffficient information to comment on time to institutionalization. It is unknown if this effect will occur with the other ChEIs.
- **The economic implications of using ChEIs require consideration.** Decision makers will need to determine if the funds dedicated to ChEIs are warranted despite small to modest benefits in the short term and largely unknown clinical benefits after one year.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Perras C, Shukla VK, Lessard C, Skidmore B, Bergman H, Gauthier S. *Cholinesterase inhibitors for Alzheimer's disease: a systematic review of randomized controlled trials.*

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
600-865 Carling Avenue, Ottawa, ON, Canada K1S 5S8 Tel: 613-226-2553 Fax: 613-226-5392 www.ccohta.ca

EXECUTIVE SUMMARY

The Issue

The treatment of dementias such as Alzheimer's disease (AD) is a challenge that is arising in health care. Three cholinesterase inhibitor (ChEI) drugs are available in Canada for AD: donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®). They have been subject to health technology assessments (HTA), including three reports that were done by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), although most of these have focused on cognitive outcomes. This systematic review was undertaken to supplement CCOHTA's previous publications and to update information using the current literature (e.g., functional, global and harm outcome data).

Objective

The primary objective of this report is to provide relevant clinical information to decision makers through a systematic review of the literature. This report will critically examine existing evidence for the efficacy of ChEIs, based on functional performance and a global clinical impression of change. It will also investigate harm in individuals with mild to moderate AD. ChEI therapy is also evaluated in terms of acceptability, effect on quality of life (QoL) and impact on rates of mortality and institutionalization.

Methods

A comprehensive search strategy was developed to identify published and unpublished (grey) literature. Published and unpublished studies, including abstracts, were selected if they reported on randomized, parallel group design trials of at least 12 weeks. Trial participants had evidence of mild to moderate, possible or probable AD, based on established diagnostic criteria. There were no language restrictions. Meta-analysis was performed when sufficient quantitative data were provided. Sensitivity analyses were performed for quality of trials and language of publications where applicable.

Results

From 1,004 identified citations, 198 were potentially relevant. Of these, 69 citations met inclusion criteria, for a total of 25 unique trials. Trials measured functional outcomes (21), global impression of change (21) and QoL (4). All trials reported adverse events (AE) or harm data. The mean age of participants ranged from 68.8 years to 85.9 years and $\geq$50% were female.

Functional outcomes, measured using the AD Cooperative Study/Activities of Daily Living inventory (ADCS/ADL) and Alzheimer's disease Functional Assessment and Change Scale (ADFACS), showed that treated and placebo groups had deterioration in function, although deterioration was less with treatment. The Disability Assessment for Dementia (DAD) and Progressive Deterioration Scale (PDS) showed that some patients improved whereas others deteriorated, but overall the results of treatment favoured employing active treatment, rather than with placebo. The Instrumental Activities of Daily Living (IADL), Mental Function Impairment Scale (MENFIS) and Unified Activities of Daily Living (Unified ADL) demonstrated no statistical differences in scores between active treatment and placebo.

Global outcomes, measured as Clinical Dementia Rating-Sum of the Boxes (CDR-SB), Clinicians' Interview-Based Impression of Change Plus (CIBIC-plus) and Clinical Global Impression of Change (CGIC), improved in the treated groups compared with placebo. Overall treatment effect was in favour of drug therapy. For CIBIC-plus/CGIC, the number needed to treat (NNT) ranged from five to 11.

Analyses revealed that patients perceived a net improvement in their QoL when they were taking donepezil 5 mg for 12 weeks, but not at 24 weeks. In total, three trials reported rates of institutionalization, with no statistical differences found between donepezil and placebo.

Compared with placebo, discontinuation due to AE was higher with galantamine and rivastigmine. No significant difference was found between placebo and the following drugs, for the AE cited: diarrhea with rivastigmine, weight loss with galantamine or agitation with galantamine and donepezil. There was no significant difference in the number of patients experiencing a serious AE for all three drugs. All other comparisons demonstrated significantly more AE in treated patients than in placebo. There was no difference in death rates associated with any of the drugs.

In head-to-head trials, no statistically significant differences were observed with the exception of DAD scores at 12 weeks (in favour of donepezil, although the difference is unlikely to be clinically important) and nausea, vomiting and discontinuation rates (less with donepezil). Preliminary results suggest that galantamine and rivastigmine confer similar clinical benefits as donepezil, although nausea and vomiting may be greater with rivastigmine. As there are not enough comparative trials, definite conclusions cannot be reached.

Definitive conclusions were limited by the diversity of scales used to measure functional outcomes, use of only published trials, lack of consistency in reporting results and lack of a standard definition for AE. The fact that many trials did not present measures of dispersion for continuous variables, the wide variety of trial designs and the poor quality of head-to-head trials further complicated the analyses.

Conclusions

ChEIs were found to have a modest impact on functional performance and global outcomes. The clinical significance of this improvement is difficult to predict. Patients on galantamine and rivastigmine experienced AE that led to a greater likelihood of treatment discontinuation, although ChEIs did not cause an increase in the number of patients experiencing serious AE or death. Donepezil did not improve QoL or prevent institutionalization, but whether this is a class effect remains to be determined. The few head-to-head comparisons suggest that ChEIs have comparable efficacy, but methodological limitations prevent the formation of definitive conclusions.

ABBREVIATIONS

ACh	acetylcholine
AD	Alzheimer's disease
ADCS/ADL	AD Cooperative Study/Activities of Daily Living inventory
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
ADL	activities of daily living
AE	adverse events
BDS	Blessed-Roth Dementia Scale
BrADL	Bristol Activities of Daily Living scale
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of the Boxes
CGI	clinical global impression
CGIC	Clinical Global Impression of Change
ChEI	cholinesterase inhibitor
CI	confidence interval
CIBIC-plus	Clinicians' Interview-Based Impression of Change Plus
DAD	Disability Assessment for Dementia
DAT	dementia of the Alzheimer's type
DSM-III	Diagnostic and Statistical Manual of Mental Disorders (3rd edition)
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders (3rd edition revised)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
FDA	Food and Drug Administration
GBS	Gottfries-Bråne-Steen scale
GDS	Global Deterioration Scale
HTA	health technology assessment
IADL	Instrumental Activities of Daily Living scale
IDDD	Interview for Deterioration in Daily living activities in Dementia
ITT	intention to treat
MENFIS	Mental Function Impairment Scale
MMSE	Mini-Mental State Examination
NHS	National Health Service
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Strokes-Alzheimer's Disease and Related Disorders Association
NNH	number needed to harm
NNT	number needed to treat
NS	not statistically significant
PDS	Progressive Deterioration Scale
PSMS	Physical Self Maintenance Scale
QoL	quality of life
QoL-C	quality of life interviews with caregivers
QoL-P	quality of life interviews with patients
RR	relative risk
SD	standard deviation
SE	standard error
SMD	standard mean difference
sMMSE	standardized Mini-Mental State Examination
WMD	weighted mean difference

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1 INTRODUCTION

1.1 Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the aged. It is characterized by the loss of short-term memory and immediate recall. It is associated with declines in higher cognitive abilities such as executive function, language, orientation and judgment.[1] Changes in functional autonomy are recognized as a part of the disease process and are often the first clinical sign of AD.[2]

The treatment of dementias, such as AD, poses a challenge in health care, because of the aging population and the high costs of managing the disease. According to a 1991 survey, prevalence estimates in Canada suggest that approximately 8.0% of the population aged 65 and older met the criteria for dementia (i.e., 252,000 cases);[3] and of these, approximately two-thirds had AD (i.e., 161,000 cases).[3] If prevalence estimates remain constant, the number of Canadians with dementia is expected to almost triple by 2031. A Canadian cross-sectional study suggests that the societal costs of care per patient per year increase with the severity of AD, ranging from C$9,451 for mild AD, to C$36,794 for severe AD.[4]

There is no treatment available to prevent or cure AD. There are, however, three drugs approved in Canada for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. The drugs are donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®). Most provincial government-sponsored drug programs provide coverage for these drugs, albeit in a restricted manner (i.e., there is a requirement to fulfil specific clinical criteria before approval is obtained for reimbursement).

1.2 Technology Overview

Acetylcholine (ACh) is a neurotransmitter that is used for memory, attention and concentration. It is synthesized in the presynaptic neurons and liberated at the synaptic cleft when a nerve impulse passes. Some ACh binds to the postsynaptic neurons and the neurotransmission continues. Some ACh remains unbound in the synaptic cleft and is then hydrolized by an enzyme called acetylcholinesterase. The drugs that are approved in Canada for AD inhibit the acetylcholinesterase enzyme and are known as cholinesterase inhibitors (ChEIs). By inhibiting the breakdown of ACh, more ACh becomes available in the synaptic cleft.[5]

The first ChEI to become available was tacrine, but this drug was never approved in Canada because of reports of liver toxicity.[6] Donepezil, rivastigmine and galantamine were then introduced. In Canada, they are all indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type (details appear in Appendix 8, Table 1). Information about utilization and expenditure appears in the health services impact section of this report.

While there are no alternative drug treatments indicated for mild to moderate AD, memantine (Ebixa®) was approved as monotherapy or as adjunctive therapy with ChEIs for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type.[7]

Newer pharmacologic therapies are being investigated for mild to moderate and moderate to severe AD. There are more than 30 drugs in pre-marketing clinical trials worldwide.[8] Approved drugs, such as conventional non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, vitamin E and estrogens have been studied with mixed results.[9,10]

2 THE ISSUE

When this report was started, functional, global and harm outcomes had not been studied in a meta-analysis; and no Canadian economic evaluation had been performed incorporating these outcomes. A systematic review of the trials reporting these outcomes was thought to be of benefit. While these drugs neither prevent nor cure AD, they are extensively used in the community and in institutions for slowing the progression of the disease. Given that there are no alternative therapies available, the additional information provided in this report may assist with decisions regarding appropriate access to these medications.

3 OBJECTIVES

It is expected that knowledge about the impact of drugs for AD, in terms of functional, global and harm outcomes, will be of use to health care providers; and government policy and decision makers.

The objective of this report is to provide relevant clinical information to decision makers through a systematic review of the literature and the existing evidence from randomized controlled trials, by addressing these questions.

- What is the clinical efficacy of ChEIs with respect to functional performance and global clinical impression of change in the treatment of individuals with mild to moderate AD?
- What is the harm of ChEIs in individuals with mild to moderate AD?
- What is the acceptability of ChEI therapy in individuals with mild to moderate AD?
- What is the effect of ChEIs on the QoL of individuals with mild to moderate AD?
- What is the impact of ChEIs on the mortality rate of individuals with mild to moderate AD?
- What is the impact of ChEIs on the rate of institutionalization of individuals with mild to moderate AD?

4 METHODS

4.1 Literature Search Strategy

A comprehensive search strategy was designed to identify published and unpublished (grey) literature (Appendix 1). MEDLINE®, EMBASE®, PsycINFO®, AgeLine, BIOSIS Previews®, Pascal and ToxFile were searched on DIALOG® on May 5, 2003. This search was systematically updated and results incorporated on a biweekly basis until December 7, 2004. In addition, parallel searches on PubMed and CINAHL were conducted; and a secondary search (with a looser clinical trial filter used to capture harm and adverse events information) was run on PubMed only. Where possible, all search results were limited to human studies without language or publication date restrictions. The Cochrane Library was searched and results updated to 2004, Issue 4.

Grey literature was identified through searching the web sites of HTA and related agencies and their databases in June 2003 and again in August 2004. Search engines included Google™ and other Internet tools. Searches were supplemented by manual searches of the bibliographies and abstracts of selected publications and conference proceedings; and through contact with selected experts and agencies. In addition, the regulatory approval packages for donepezil, galantamine and rivastigmine were requested from the US Food and Drug Administration (FDA). The manufacturers of the ChEIs (i.e., Pfizer, Novartis and Janssen-Ortho) were contacted directly for information pertaining to unpublished studies.

4.2 Selection Criteria and Methods

4.2.1 Selection criteria

A study was eligible for inclusion in the review if it fulfilled all selection criteria.

a) Study design

All published and unpublished randomized clinical trials of parallel group design, of at least 12 weeks duration, were considered. Trial reports published as abstracts were also included if additional data could be obtained. The authors of selected abstracts were contacted to obtain details of the trials. In the case of non-responders, two follow-up requests were sent.

Clinical trials may have included a titration period before randomization. The data from the non-randomized titration periods were not used to assess harm and efficacy in this review. Similarly, data from any open follow-up phase (i.e., subsequent to the randomization phase of the trial) were not used.

b) Population

Trials were included if they enrolled participants with diagnostic evidence of mild to moderate, possible or probable AD based on the:

- Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R or DSM-IV)[11]
- National Institute of Neurological and Communicative Disorders and Stroke ─ Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[12]

c) Interventions and comparators

Trials compared a ChEI with placebo or with another treatment.

d) Outcomes

The outcomes of interest were:

- functional performance
- global clinical impression of change (i.e., by clinician or caregiver)
- AE or serious AE
- AE leading to withdrawal from the clinical trial
- acceptability of ChEIs (i.e., as measured by treatment discontinuations such as withdrawals and drop-outs), including timing of discontinuation
- QoL
- mortality rate
- rate of institutionalization, including time to institutionalization.

4.2.2 Selection method

Two reviewers (CL and VS) independently examined citations, to exclude those that were irrelevant based on the title and abstract of the report. The full texts of potentially relevant reports were retrieved for further assessment. The reviewers independently made the final selection of relevant studies to be included in the systematic review, based on the selection criteria. Agreement between reviewers was noted and differences were resolved by discussion (Appendix 2).

4.3 Data Extraction and Abstraction Strategy

Using the data extraction form, two reviewers (CP and CL) independently extracted data from each article that was selected for inclusion (Appendix 3). An exception was made for foreign language trials, of which there were three. One reviewer (ZT) extracted data from the two trials that were published in Chinese. One reviewer (MS) extracted data from the trial published in Japanese. Information on trial design, participant characteristics and outcome measures were collected for all selected trials. In addition, data on AE, withdrawals and drop-outs were recorded. Reviewers discussed discrepancies and reached a consensus.

4.4 Strategy for Quality Assessment

Quality assessment of the selected trials was conducted (CP and AT) using the Jadad scale (Appendix 4). Allocation concealment was also noted.

4.5 Data Analysis Methods

4.5.1 Measures of effect

Numerous instruments were used to assess outcomes in the selected trials. Only validated scales were considered in this review (Appendix 5):

- for functional disability, AD Cooperative Study/Activities of Daily Living inventory (ADCS/ADL), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), Blessed-Roth Dementia Scale (BDS), Bristol Activities of Daily Living Scale (BrADL), Disability Assessment for Dementia (DAD), Instrumental Activities of Daily Living (IADL), Mental Function Impairment Scale (MENFIS), Progressive Deterioration Scale (PDS) and Unified ADL
- for global functioning, Clinical Dementia Rating-Sum of the Boxes (CDR-SB), Clinical Global Impression of Change (CGIC), Clinicians' Interview-Based Impression of Change Plus (CIBIC-plus), Gottfries-Bråne-Steen Scale (GBS) and Global Deterioration Scale (GDS)
- for QoL, interviews with patients (QoL-P) and interviews with caregivers (QoL-C).

In trials with multiple treatment groups (i.e., low and high doses of drug versus placebo) or if various treatment durations were reported, data were analyzed according to dose and duration. Examples of doses are donepezil 5 mg, donepezil 10 mg, galantamine 24 mg, galantamine 32 mg and rivastigmine high-dose (6 mg to 12 mg). Duration of treatments are 12 weeks, 24 weeks and study endpoints. In some trials, investigators titrated patients to tolerated doses, with the possibility of increasing or decreasing the dose during the trial. In these trials, the results for combined data were reported. In this report, a series of analyses using different dose combinations were done.

4.5.2 Statistical analysis

Standard deviations (SD) were calculated when standard error (SE), probability values (p values) or confidence intervals (CI) were available or could be measured from the SE bar in graphs. Analyses were performed according to intention to treat (ITT), when possible. Meta-analysis was performed when sufficient quantitative data were provided and trials were sufficiently similar. The software Review Manager® 4.2 was used.[13] To calculate the number needed to treat (NNT) or the numbers needed to harm (NNH), the software CIA® 2.1.0 was used.[14]

Relative risk (RR) and NNT or NNH with 95% CI were calculated for dichotomous variables. This included data collected on success rate for CIBIC-plus, CGIC and AE. The change in score from baseline to the final assessment was used in the analyses of all continuous variables (with the exception of CIBIC-plus and CGIC) to calculate the weighted mean difference (WMD) with 95% CI. For CIBIC-plus and CGIC, final scores (with global impression of change, all patients are at the same baseline score) were analyzed together and the standard mean difference (SMD) calculated.

a) Statistical heterogeneity

For pooled data, statistical heterogeneity was measured using I^2. This new quantity, which was developed for The Cochrane Collaboration's Revman Analyses software, measures inconsistency of results across studies. For this report, the data were pooled under a fixed-effects model for $I^2 \leq 20\%$. The quantity I^2 is expressed as a percentage, with higher values indicative of heterogeneity. It describes the variation across studies not due to chance. The advantage of I^2 is that it does not depend on the number of studies included in the meta-analysis. Therefore, it can be used when pooling data from a small number of studies.[15] Otherwise, a random-effects model can be used to determine the impact of heterogeneity on the results. The data were re-analyzed to explore potential sources of heterogeneity when there were >4 pooled trials.

b) Sensitivity analysis

Sensitivity analyses were performed for the quality of trials and language of publication, where applicable.

5 RESULTS

5.1 Quantity of Research Available

Of the 1,004 citations identified in the original electronic search, 813 were excluded. Seven citations were identified from other sources, resulting in 198 potentially relevant reports. These reports were retrieved for a full text review. The level of agreement between reviewers was 0.65 (95% CI: 0.54; 0.76) using a kappa (κ) statistic. A total of 173 reports did not meet the selection criteria, leaving 25 reports that were used for the systematic review. A total of 69 relevant reports had been identified based on the selection criteria, but 44 were duplicate publications of the individual trials contained in the 25 selected reports (Appendix 8 Table 2). The excluded trials are listed in Appendix 6. A description of the flow of documents is found in Appendix 9 Figure 1.

5.1.1 Publication characteristics

All articles used in this report come from published literature. Requests for unpublished data were either refused or no response to the request was received. Insufficient data were available for extraction from abstracts. All reports were published in English, except two reports in Chinese and one in Japanese.

Of the 25 trials selected for this review, 16 unique trials were reported in 60 publications as original reports, abstracts or duplicate publications. The remaining nine trials were the original publications of the unique trials.[16-24]

5.2 Trial Characteristics

The characteristics of the 25 selected trials are summarized in Appendix 7. Most of the trials were randomized, placebo-controlled and of parallel design (21). The remainder were randomized, head-to-head, open-label trials of parallel design (four). Sample sizes ranged from 64 to 978 participants and study durations from 12 to 54 weeks. Drug manufacturers sponsored 20 trials and four trials had no sponsorship stated. The National Health Service (NHS) sponsored one trial.

All trial participants were diagnosed with mild to moderate AD. One trial[25] included patients with severe AD, but the results of a subgroup analysis of patients with mild to moderate AD were also available in the report. Although one trial[24] included patients with vascular dementia, this group constituted <18% of the study population. The mean age of participants ranged from 68.8 to 85.9 years and ≥50% of the participants were female.

In total, 21 trials measured functional outcomes and 21 measured global impression of change; whereas four assessed QoL. All selected trials reported AE or harm outcomes.

5.3 Data Analyses and Synthesis

5.3.1 Summary of results

The overall results of the analyses are summarized in Appendix 8 Tables 26 and 27.

5.3.2 Quality assessment

Information on the quality of each selected trial can be found in Appendix 7; results are summarized in Appendix 8 Table 3.

5.3.3 Results for functional outcomes

An analysis was performed for each functional outcome. We could only describe the results of one trial or pool data from two trials. The results should be interpreted in light of this limitation.

The overall treatment effect was measured as the difference in change of score from baseline between treatment and placebo (i.e., treatment difference = change in score for drug − change in score for placebo). In some trials, patients receiving placebo and those on active treatment experienced a decline in function. The differences in score, however, demonstrated an overall benefit with treatment. Sensitivity analyses were not performed for these results.

In instances where the data could not be meta-analyzed, the results are presented in a table. In those instances where the data could be meta-analyzed, the results are presented in forest plot.

a) Donepezil versus placebo

ADFACS (the higher the score, the greater the impairment)
In one trial,[26] donepezil 10 mg and the placebo groups demonstrated an increase in score after 12 and 54 weeks of treatment when compared to baseline (Appendix 8 Table 4). The deterioration, however, was worse with placebo; and overall treatment effect resulted in favour of donepezil, which was statistically significant.

DAD (a higher score indicates better function)
In one trial,[27] scores for donepezil (5 mg to 10 mg dose, titrated according to a clinician's judgement) were increased at 12 weeks and remained unchanged at 24 weeks (Appendix 8 Table 5). Patients receiving placebo had a decrease in function at both periods. The net treatment difference was in favour of treatment; and results were statistically significant.

MENFIS (the higher the score, the greater the functional deficit)
Pooling the results of two trials[16,22] showed that the mean difference in score was not statistically significant for donepezil 5 mg compared with placebo at 12 weeks (Appendix 9 Figure 2); or at the endpoint (Appendix 9 Figure 3).

Unified ADL (the higher the score, the greater the impairment)
In one study,[28] the difference in ADL score for donepezil 5 mg compared with placebo after 12 weeks of treatment was not statistically significant (Appendix 8 Table 6).

b) Galantamine versus placebo

ADCS/ADL (a decrease in score indicates deterioration)
One trial used ADCS/ADL as an outcome measure (Appendix 8 Table 7).[29] In this study, it was shown that after five months of 16 mg and 24 mg of galantamine, all groups had deteriorated. Nonetheless, the treatment effect was in favour of galantamine and this finding was statistically significant for both dosages.

DAD (a higher score indicates better function)
One trial at 12 weeks[30] (Appendix 8 Table 8) showed that galantamine, 24 mg to 32 mg, and placebo patients had a decrease in score (i.e., worsening of function). Treatment effect was found to be in favour of galantamine and this finding was statistically significant.

At endpoint, similar results were obtained for galantamine (Appendix 9 Figure 4).

c) Rivastigmine versus placebo

IADL (a higher score indicates better performance)
The pooled results of two studies, one of which considered rivastigmine 6 mg daily for 12 weeks;[19] and the other an average dose of rivastigmine 10 mg daily for 18 weeks,[17] showed no statistical difference with placebo in IADL (Appendix 9 Figure 5).

PDS (a higher score indicates better performance)
Based on two studies,[21,31] high-dose rivastigmine (6 mg to 12 mg daily) was found to be better than placebo at 26 weeks and results were statistically significant (Appendix 9 Figure 6).

d) Galantamine versus donepezil

BrADL (an increase in score indicates functional decline)
BrADL was measured in one head-to-head trial of 52 weeks (Appendix 8 Table 9).[32] Patients were titrated to 24 mg for galantamine and 10 mg for donepezil, if they tolerated the dose. Scores increased for galantamine and donepezil, demonstrating a functional decline in both groups. The difference in score was not significant.

DAD (a higher score indicates better function)
In one head-to-head trial, galantamine fared statistically worse than donepezil after 12 weeks of treatment (Appendix 8 Table 10).[33] Patients were titrated to 24 mg for galantamine and 10 mg for donepezil, if they tolerated the dose (Appendix 9 Figure 4). The treatment difference was 1.9 out of a possible score of 100 (i.e., this difference is unlikely to be clinically important).

e) Rivastigmine versus donepezil

BDS (an increase in score indicates functional decline)
One head-to-head trial used BDS as an outcome measure (Appendix 8 Table 11).[20] For rivastigmine at 6 mg and donepezil at 10 mg, patients showed improvement after 16 weeks of treatment, with no statistical difference in treatment effect between the two groups.

5.3.4 Results for global outcomes

For global outcomes (except CDR-SB), the analyses and results are based on $\leq$4 trials. Sensitivity analyses were performed for CDR-SB when the number of trials used to pool the results was >4.

Results for CIBIC-plus and CGIC were combined, because these are considered to be essentially the same instrument. Similarly, the results were derived from $\leq$4 studies. Sensitivity analyses were not performed because of the low number of studies included.

The interpretation of these results is limited by the small number of studies using each of these scales.

a) Donepezil versus placebo

CDR-SB (an increase in score indicates deterioration)
Patients receiving donepezil 5 mg and 10 mg showed an improvement as measured by a CDR-SB change in scores. The net treatment effect was statistically significant at 12 weeks (Appendix 9 Figures 7 and 8), 24 weeks (Appendix 9 Figures 9 and 10) and endpoints (Appendix 9 Figures 11 and 12).

Sensitivity analyses: Six studies[16,18,22,28,34,35] were used to pool the results for donepezil 5 mg versus placebo at 12 weeks and at the endpoint (Appendix 9 Figures 7 and 11). Sensitivity analyses took into account the quality of the study and the language of the publication.

Quality of study: When the study with a Jadad score of two was removed from the analysis[22] [with donepezil 5 mg and placebo in CDR-SB scores after 12 weeks of treatment (Appendix 9 Figure 13)], the base case analysis result did not change (Appendix 9 Figure 7).

Language of publication: The removal of the one study published in Japanese[22] did not change the results of the base case analysis for donepezil 5 mg versus placebo at the study endpoint.

Heterogeneity: Heterogeneity was high for the results obtained for the donepezil 5 mg versus placebo group at 24 weeks (three trials[16,34,35]) and at the study endpoint (six trials[16,18,22,28,34,35]). Heterogeneity was also high for donepezil 10 mg versus placebo at study endpoint (four trials[18,25,34,35]).

For the donepezil 5 mg versus placebo endpoint analysis, removing the two studies conducted in Japan[16,22] decreased the reported heterogeneity from 71.5% to 56%. Homogeneity was obtained when the Rogers *et al.* trial[18] was also removed. This finding could not be explained by the study duration, sample size, quality of the trial or the individual study results.

CIBIC-plus/CGIC (an increase in score indicates deterioration)
Final scores: Final scores were lower for donepezil when compared with placebo. The mean differences were statistically in favour of donepezil 5 mg and 10 mg at 12 weeks (Appendix 9 Figures 14 and 15); at 24 weeks (Appendix 9 Figures 16 and 17) and at the study endpoint (Appendix 9 Figures 18 and 19).

Success rates: Successful treatment was obtained if a patient improved compared with baseline. Success rates were measured using a Likert scale of one to seven, with one being very much improved, four meaning no change; and seven being very much worse. More donepezil patients improved at 12 weeks [i.e., success rate <4 (Appendix 8 Table 12)], 24 weeks (Appendix 9 Figures 20 and 21) and at the study endpoint (Appendix 9 Figures 22 and 23). The NNT ranged from five to eight.

The results were not statistically significant for donepezil 5 mg versus placebo in a 12-week study[28] that reported a success rate of <5 (i.e., patients improved or no change from baseline). At 24 weeks, another study[27] comparing donepezil 5 mg to 10 mg versus placebo reported a statistically significant difference. When pooling the results of these two studies, the difference was not significant (Appendix 8 Table 13 and Appendix 9 Figure 24).

GBS (an increase in score indicates deterioration)
In one study,[36] donepezil (5 mg to 10 mg dose titrated according to the clinician's judgement) and placebo patients had clinical deterioration as seen in increasing scores compared with baseline (Appendix 8 Table 14). There were no significant differences between donepezil and placebo at 12 weeks or at 52 weeks.

b) Galantamine versus placebo
CIBIC-plus/CGIC (an increase in score indicates deterioration)
Final scores: The pooled final scores of three studies (Appendix 9 Figure 25) showed that galantamine 24 mg was statistically better than placebo. Two studies[37,38] were conducted for 24 weeks and one study[29] lasted 20 weeks. Similar results were obtained for galantamine 32 mg versus placebo at 24 weeks (Appendix 9 Figure 26), but these results were based on two trials.[37,38]

Success rate: Two trials reported a success rate of <4 at 12 weeks. In one trial,[30] the galantamine dose could be titrated between 24 mg to 32 mg according to the patient's tolerance and the investigator's discretion. The results for the 24 mg dose were used for the other study.[39] There was no statistical difference between galantamine 24 mg to 32 mg; and placebo (Appendix 9 Figure 27). At 24 weeks, there were no statistical differences between galantamine 24 mg and placebo (Appendix 9 Figure 28); and galantamine 32 mg and placebo (Appendix 9 Figure 29).[37,38]

There were no statistical differences between galantamine 24 mg to 32 mg and placebo at the study endpoint when combining 12 and 24 week studies (Appendix 9 Figure 30).

One study,[29] which compared galantamine 16 mg and 24 mg versus placebo, showed a statistical difference in the success rate of <5 (i.e., patients improved or no change from baseline) after 20 weeks of treatment (Appendix 8 Table 15).

c) Rivastigmine versus placebo

CIBIC-plus/CGIC (an increase in score indicates deterioration)
Final scores: Based on one trial,[31] final scores were lower for high dose rivastigmine (i.e., 6 mg to 12 mg) than for placebo (Appendix 8 Table 16). Treatment effect favoured rivastigmine at 26 weeks, but showed no difference at 12 weeks.

Success rates: Patients were considered to have significantly improved (i.e., success rate was <4) for rivastigmine 6 mg to 12 mg versus placebo at 26 weeks[21,31] and at study endpoints combined[17,21,31] (Appendix 9 Figures 31 and 32), but not at 18 weeks (Appendix 8 Table 17).[17]

d) Rivastigmine versus donepezil

GDS (an increase in score indicates deterioration)
One head-to-head trial[20] used this outcome measure. There was insufficient information provided in the publication to complete an analysis on this outcome.

5.3.5 Results for QoL

a) Donepezil versus placebo

QoL-C (a higher score indicates improvement)
Based on one study, from the perspective of the caregiver,[28] the difference in QoL scores between donepezil 5 mg and placebo was not statistically significant at 12 weeks (Appendix 8 Table 18).

QoL-P (a higher score indicates improvement)
From the patient's perspective, QoL was measured in four studies[18,28,34,35] and results were reported in three.[18,28,35] At 12 weeks, patients perceived a net improvement in QoL with donepezil 5 mg compared with placebo (Appendix 9 Figure 33). For donepezil 10 mg versus placebo, the difference was not statistically significant at 12 weeks (Appendix 9 Figure 34) or at 24 weeks (Appendix 8 Table 19).

5.3.6 Results for institutionalization

a) Donepezil versus placebo

Based on the pooled results of three donepezil studies,[22,24,26] there was no significant statistical difference in the number of patients institutionalized compared to placebo (Appendix 9 Figure 35). This result should be interpreted in light of a few limitations. One trial[22] had a duration of 12 weeks with donepezil 5 mg and a Jadad score of two. The second trial[26] had a duration of 54 weeks with donepezil 10 mg and a Jadad score of three. The third trial[24] lasted 48 weeks with donepezil 5 mg to 10 mg and had a Jadad score of four.

The results remain non-significant if the 12-week study[22] is excluded from the analysis (Appendix 9 Figure 36).

5.3.7 Results for timing of institutionalization

There was insufficient information on the timing of institutionalization to complete an analysis on this outcome.

5.3.8 Results for discontinuation rates

In the 25 selected trials, reasons for withdrawals and drop-outs included entry into a nursing home; cessation of treatment; withdrawal; adverse events; serious adverse events, death; intercurrent illness; a request by patient, investigator or family; non-compliance; protocol violation; withdrawal of consent and other. The total number of patients reported as withdrawn or dropped out for any reason was used for these analyses.

a) Donepezil versus placebo

The differences in withdrawals and drop-outs were not statistically significant for donepezil 5 mg versus placebo at 12 weeks, 24 weeks, 54 weeks and for all weeks combined (Appendix 9 Figures 37 to 39 and Appendix 8 Table 20); for donepezil 10 mg versus placebo at 24 weeks and for all weeks combined (Appendix 9 Figures 40 and 41); and for donepezil 5 mg to 10 mg versus placebo in studies $\geq$48 weeks (Appendix 9 Figure 42). Based on one study,[18] the donepezil 10 mg versus placebo at 12 weeks was the only analysis for which there was a statistical significant difference (Appendix 8 Table 21).

Heterogeneity

Heterogeneity was noted for donepezil 10 mg versus placebo at study endpoints (four studies). The 12-week study[18] seems to contribute to some of the heterogeneity.

b) Galantamine versus placebo

One study[39] considered discontinuation rates for galantamine 24 mg versus placebo at 12 weeks. Results were not significant (Appendix 8 Table 22). At 20 to 24 weeks and for all endpoints combined, patients receiving galantamine 24 mg were more likely to discontinue treatment compared with placebo (Appendix 9 Figures 43 and 44). These findings were statistically significant. All comparisons for which patients received galantamine 32 mg were also statistically significant compared to placebo (Appendix 9 Figures 45 and 46). In one study,[30] the investigator could titrate the dose of galantamine from 24 mg and 32 mg, according to a patient's

response. The results at 12 weeks are shown in Appendix 8 Table 23. The results for that study are included in the analysis of galantamine 32 mg at combined endpoints (Appendix 9 Figure 46).

c) Rivastigmine versus placebo

A statistically greater number of patients receiving rivastigmine 6 mg to 12 mg withdrew from treatment compared with placebo at 12 weeks to 18 weeks, 26 weeks and at combined endpoints (Appendix 9 Figures 47 to 49).

d) Galantamine versus donepezil

The difference was not statistically significant between galantamine 24 mg and donepezil 10 mg at the study endpoint [12 weeks[33] and 52 weeks[32] combined (Appendix 9 Figure 50)].

e) Rivastigmine versus donepezil

In two head-to-head trials,[20,40] statistically more patients on rivastigmine 6 mg to 12 mg withdrew from the studies compared with donepezil 10 mg after 12 weeks and 16 weeks of treatment (Appendix 9 Figure 51).

5.3.9 Results for timing of discontinuation

There was insufficient information on the timing of treatment discontinuation to complete an analysis on this outcome.

5.3.10 Results for harm

Among 25 trials, 24 reported the different types of AE experienced by the participants. Some trials reported treatment-emergent signs and symptoms; others reported AE experienced by at least 5% of the participants. The AE could not be separated into different periods of interest, such as 12 weeks, because these AE were experienced during the entire the trial. Results were combined for trials that evaluated >1 dose.

AE reported in the trials include cardiovascular (12), central nervous system (nine), dermatological (eight), digestive (11), infections (10), musculoskeletal (six) and other (15). In this report, AE are not presented according to system, as this would represent incidence and not the number of participants with a particular AE. Instead, the results for agitation, anorexia, diarrhea, dizziness, headache, nausea, vomiting and weight loss are presented. Deaths, number of patients withdrawn due to AE and the number of participants with serious AE are also analyzed.

In this report, death is counted as an AE and was included in the analyses for participants with serious AE and for participants withdrawn because of AE. The World Health Organization defines serious AE as a medical occurrence that at any dose is life-threatening or results in death; requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability or incapacity.[41]

a) Donepezil versus placebo

There was no difference in agitation for donepezil versus placebo. A statistically greater number of patients experienced anorexia [NNH: 30 (95% CI: 21; 53)], diarrhea [NNH: 15 (95% CI: 11; 20)], dizziness [(NNH: 40 (95% CI: 23; 157)], headache [NNH: 27 (95% CI: 16; 27)], nausea [NNH: 49 (95% CI: 26; 266)], vomiting [NNH: 31 (95% CI: 19; 73)] and weight loss [NNH: 38 (95% CI: 19; 1,182)] compared with placebo (Appendix 9 Figures 52 to 59).

There was no statistically significant difference in the number of participants withdrawn due to AE, in the number of deaths or in the number of participants with serious AE compared with placebo (Appendix 9 Figures 60 to 62). When death was excluded as an AE, however, the number of participants withdrawn because of AE became significant.

Sensitivity analyses

For comparisons that included >4 trials, sensitivity analyses were conducted for the language of the publication (i.e., excluding articles published in a language other than English). This resulted in sensitivity analyses being performed only for trials that compared donepezil versus placebo.

Language of publication: When comparing donepezil versus placebo, the exclusion of the one article published in Japanese[22] did not affect any of the conclusions. This study provided data for the analyses of dizziness; participants with serious AE, death; and participants withdrawn due to other AE.

Heterogeneity: High heterogeneity was noted for participants withdrawn due to AE for donepezil versus placebo (11 studies). The exclusion of one trial with a smaller sample size (n<100)[28] did not affect the results, although heterogeneity was still high (49.8%).

b) Galantamine versus placebo

There was no difference in agitation and weight loss for galantamine versus placebo. Compared with placebo, statistically more patients taking galantamine experienced anorexia [NNH: 11 (95% CI: 10; 15)], diarrhea [NNH: 29 (95% CI: 7; 83)], dizziness [NNH: 16 (95% CI: 11; 28)], headache [NNH: 15 (95% CI: 10; 28)], nausea [NNH: 5 (95% CI: 4; 6)] and vomiting [NNH: 9 (95% CI: 7; 11)] (Appendix 9 Figures 63 to 70).

There was no significant difference in the number of deaths or in the number of participants with serious AE compared with placebo. A statistically greater number of participants withdrew from galantamine treatment compared with placebo due to AE [NNH: 8 (95% CI: 7; 11)] (Appendix 9 Figures 71 to 73).

Heterogeneity

High heterogeneity was noted for participants who withdrew because of AE for galantamine versus placebo. The removal of two trials[29,30] decreased the heterogeneity from 74.9% to 29.2%, without changing the results. This finding cannot be explained by the study duration, sample size, quality of trial or the individual study results.

c) Rivastigmine versus placebo

The RR of developing diarrhea was not significant for rivastigmine when compared with placebo. There were, however, a statistically greater number of patients who experienced

anorexia [NNH: 8 (95% CI: 6; 11)], dizziness [NNH: 7 (95% CI: 5; 9)], headache [NNH: 10 (95% CI: 7; 17)], nausea [NNH: 3 (95% CI: 3; 4)] and vomiting [NNH: 5 (95% CI: 4; 6)], compared with placebo (Appendix 9 Figures 74 to 79).

There were no statistically significant differences in the number of deaths or in the number of participants with serious AE compared to placebo. A statistically greater number of participants withdrew from rivastigmine treatment compared with placebo as a result of AE [NNH: 6 (95% CI: 5; 7)] (Appendix 9 Figures 80 to 82).

d) Galantamine versus donepezil

In two studies,[32,33] all comparisons were found to be statistically non-significant (Appendix 8 Table 24 and Appendix 9 Figures 83 to 87).

e) Rivastigmine versus donepezil

Statistically fewer patients had nausea or vomiting with donepezil versus rivastigmine [NNH: 11 (95% CI: 6; 53)]. All other comparisons were non-significant (Appendix 8 Table 25 and Appendix 9 Figures 88 to 90).

6 DISCUSSION

6.1 Main Findings

In total, 25 clinical trials that collectively measured 29 outcomes were used in this systematic review. The numbers of individual outcomes evaluated, according to the objectives of the review, are nine for functional performance; five for global impression of change; two for QoL; and 10 for AE, discontinuation rates, institutionalization and mortality. Overall, 11 comparison groups at various study durations were investigated. This made the analyses complex and the pooling of data challenging. Four of the 25 trials were attributed a Jadad score of two (low quality).

Sensitivity analyses for the quality of trials and the language of publications were performed where feasible. This allowed for the testing of the robustness of the results.

An attempt was made to explain heterogeneity when I^2>20%. Heterogeneity is likely to be obtained if there are differences between trials such as the duration of study and the types of participants. This may affect the conclusion of the analysis. If heterogeneity was noted and could not be removed by excluding certain studies, then the results should be interpreted with caution (i.e., the results may have occurred because of a difference in studies).

Although the results of this review appear favourable for ChEIs, the clinical relevance of statistically significant results of anti-dementia treatments is still unclear.[42] A review of this is warranted, but is beyond the scope of this report.

6.1.1 ChEIs versus placebo

a) Functional performance

Functional performance was measured using one of nine scales (i.e., ADFACS, DAD, MENFIS, Unified ADL, ADCS/ADL, IADL, PDS, BrADL and BDS) for eight comparison groups. The pooling of individual trial results for the different scales could only be done using a maximum of one to two trials. Results must be interpreted with caution.

For the ADCS/ADL and ADFACS scales, active treatment and placebo groups experienced functional deterioration, but the magnitude of the deterioration was shown to be statistically less for active treatment. For the DAD and PDS scales, some patients receiving active treatment improved whereas others deteriorated. Overall treatment effects were in favour of active treatment. For the IADL, MENFIS and Unified ADL scales, there were no statistically significant differences in scores between placebo and active treatment groups. Sensitivity analyses were not performed because one or two trials were used in the review.

b) Global impression of change

Global impression of change was measured using one of three scales (i.e., CDR-SB, CIBIC-plus/CGIC and GBS) for eight comparison groups. Although not all comparisons were statistically significant, patients receiving active treatment displayed better results in CDR-SB and CIBIC-plus/CGIC final scores than did those receiving placebo. Overall effects were in favour of active treatment. For results investigated using the CIBIC-plus/CGIC scale, the NNT ranged from five to 11.

A sensitivity analysis was conducted on CDR-SB for the donepezil 5 mg versus placebo comparison at 12 weeks. The removal of a lower quality trial[16,22,34] (i.e., Jadad score of two) did not affect the result. Heterogeneity investigations could not be extensively conducted because of the small number of studies used to pool the results. The high heterogeneity observed for the CDR-SB analysis of donepezil 5 mg versus placebo comparisons was attributed to the inclusion of a study by Rogers *et al.*[18]

c) Quality of life

The QoL of patients with AD was assessed based on the perspective of the caregivers (QoL-C) and of the patients (QoL-P). This was measured in one (QoL-C) [28] and three (QoL-P) trials[18,28,35] for donepezil 5 mg and 10 mg versus placebo. Results indicated that caregivers did not perceive a change in QoL for patients receiving donepezil 5 mg treatment for 12 weeks. In contrast, patients perceived a net improvement in their QoL with donepezil 5 mg for 12 weeks. Results for donepezil 10 mg at 12 weeks and at 24 weeks were found to be non-significant. These results must be interpreted with caution, because this scale has not been validated specifically for AD patients.

d) Institutionalization

Three trials[22,24,26] reported institutionalization rates. No statistical differences were found between patients receiving donepezil and placebo. There was insufficient information on the timing of institutionalization to complete an analysis on this outcome.

e) Treatment discontinuations

In general, treatment discontinuations were significant with galantamine and rivastigmine, but not with donepezil, when each were compared with placebo. Sensitivity analyses were not performed because ≤4 studies were used in the base case analyses. High heterogeneity for the donepezil 10 mg versus placebo group was explained, in part, by a 12-week study.[18]

In the analysis of treatment discontinuations due to AE, more patients treated with galantamine and rivastigmine withdrew from the studies compared with placebo patients.

f) Adverse events

Analyses of the most common digestive and central nervous system AE that occurred with the ChEIs, were conducted. Results showed that patients receiving ChEIs, compared with placebo, experienced significantly more nausea, vomiting, diarrhea, anorexia, weight loss, dizziness and headache for donepezil; nausea, vomiting, diarrhea, anorexia, dizziness, and headache for galantamine; and nausea, vomiting, anorexia, dizziness and headache for rivastigmine.

There were non-significant differences for diarrhea (rivastigmine versus placebo), weight loss (galantamine versus placebo) and agitation (galantamine or donepezil versus placebo). Agitation and weight loss were not reported for rivastigmine. When serious AE of all three drugs were compared with placebo, the results were not statistically significant.

g) Deaths

There were no differences in death rates for any of the drugs when compared with placebo. Sensitivity analyses conducted with donepezil also did not change these results.

6.1.2 Head-to-head comparisons

There were four trials comparing ChEIs that were included in this review: galantamine versus donepezil[32,33] and rivastigmine versus donepezil.[20,40] The comparisons revealed non-significant differences between ChEIs, except for DAD scores at 12 weeks in one trial. The difference is unlikely to be clinically important. There was less nausea in one trial, less vomiting in two trials and a lower discontinuation rate in two trials, with donepezil. These preliminary results suggest that galantamine and rivastigmine confer similar clinical benefits as donepezil, except for more nausea and vomiting with rivastigmine.

There were too few trials to make a definitive conclusion. In addition, these trials were not blinded; had small sample sizes; and with the exception of one trial of 52 weeks,[32] were of short duration. Jadad scores varied between two (for rivastigmine versus donepezil trials), indicating lower quality; and three (for galantamine versus donepezil trials), indicating higher quality. One trial[32] had adequate allocation concealment. A recent article[43] provides an assessment of the methodological limitations for three[32,33,40] of the four head-to-head trials. It is suggested that the studies are subject to performance, ascertainment and comparator biases.

6.2 Limitations

Interpretation of the results from this review was limited by several factors:

- the leap between statistical and clinical significance (i.e., how to give a clinical interpretation to a result that is statistically significant)
- the diversity of scales used to measure functional outcomes (i.e., resulting in one or two studies that could be used in the analysis for each outcome)
- the use of published trials only (it was impossible to obtain non-published data if they existed; requests for abstract data that could have been useful were either refused or not acknowledged)
- the exclusion of measures of dispersion for continuous variables in some trials (e.g., standard deviations), necessitating the exclusion of some results from the analysis
- the lack of consistency between trials for the values reported (e.g., final scores, change in scores or mean treatment difference for continuous variables), which in turn necessitated the exclusion of some results from the analysis
- the lack of a standard definition for AE (i.e., rare but significant AE may have been missed)
- the variety of trial designs used (e.g., varied duration of treatment or multiple treatment groups), which often made comparisons difficult.

6.3 Findings in Relation to Other Reviews

ChEIs have been the topic of health technology assessment (HTA) reports in which a variety of clinical trial inclusion criteria have been used and a number of clinical and economic outcome measures evaluated. In 2000, CCOHTA published three reports of drug treatments for AD.[44-46] The first is a comparative analysis of clinical trials for the drugs donepezil, rivastigmine and metrifonate.[44] It was concluded that the three agents have similar modest benefits on cognitive performance and global functioning. The second report is a review of the outcome measures used in the clinical trials included in the first report.[45] The third report is a review of pharmacoeconomic evaluations of donepezil and rivastigmine. It found that both agents are associated with either a slight increase or decrease in overall treatment costs while producing a better clinical outcome for patients with mild to moderate AD.[46] The models used in the economic evaluations are based on short-term efficacy data and cognitive outcomes.

In addition to the CCOHTA reports, three HTA reports of AD drug therapy were published between 1998 and 2002 in the Basque Country,[47] the United Kingdom[48] and the Netherlands.[49]

All report similar conclusions (i.e., ChEIs produce marginal benefits in outcome measures, although such modest improvements may not be reflected in changes in the daily lives of individuals with AD).[47-49] It was concluded that uncertainty remains about the cost-effectiveness of the drug therapies because of the nature of the economic evidence reviewed.[48] Specific issues that were noted were uncertainty pertaining to the duration of the drug effect; omission of AE and drop-out rates in most analyses; and use of the Mini-Mental State Examination (MMSE)[50] to model outcomes and quality of economic modelling.[46,48]

Since the publication of the CCOHTA reports, galantamine has been approved in various countries, including Canada. In addition, new studies utilizing functional outcome measures, such as ADL[51] and IADL,[52] have appeared in the literature.

Changes in the levels of ADL may not parallel changes in cognition. The loss of functional autonomy increases caregiver burden and could be a determinant factor for early institutionalization.[2] A recent economic analysis finds that the cost of a one-point decline in a functional outcome measure, such as the Barthel ADL Index,[53] is >10 times the cost of a one-point decline in a cognitive outcome measure such as MMSE.[54] It was found that both measures predict time to institutionalization and cost of care, but changes in the levels of ADL are better predictors of costs outside institutional care.[54] As a result, it may be inappropriate to develop economic models based solely on measures of cognitive change.

In the last two years, three other systematic reviews were published. The methods used in each review are compared with those used in this report in Appendix 8 Table 28.

A systematic review of the efficacy of ChEIs on neuropsychiatric and functional outcomes in the treatment of AD was published in early 2003.[55] The meta-analysis included 29 randomized clinical trials with a parallel or a cross-over design; and treatment duration of at least one month. Limitations were the inclusion of clinical trials of short-term duration or of crossover design. Because of the progressive nature of AD and the intra- and inter-variability in the progression of individuals, the draft guidelines of the US Food and Drug Administration (FDA) for the clinical evaluation of antidementia drugs, recommend that only parallel group design trials of at least three months duration be considered.[56,57] The existing evidence on the safety of ChEIs was not evaluated in this review.

In September 2003, a systematic review of the safety and efficacy of ChEIs on global and cognitive functions in the treatment of AD was published.[58] In total, 16 randomized, double-blind, placebo-controlled, parallel group trials of $\geq$12 weeks duration that used therapeutic doses of the three marketed ChEIs, were included. The review has been criticized for including data on dosages outside the recommended range and for comparing trials with varying treatment durations.[59] The review excluded trials published in a foreign language; did not provide a detailed analysis of types of AE; and did not include head-to-head trials.

A meta-analysis that was published in 2004 reviews the safety, drop-out rates, global and cognitive changes and dose effects of donepezil, galantamine and rivastigmine in AD patients.[60] Twenty randomized, double-blind, placebo-controlled trials of 12-weeks duration, that were published in English, were included. Head-to-head trials were excluded. The meta-analysis was limited because trial quality was not assessed and sensitivity analyses were not performed.

When results are compared in the Trinh *et al.* meta-analysis,[55] a small but statistically significant benefit of ChEIs for IADL and a trend in benefit for ADL were found. The Lanctôt *et al.*[58] and the Ritchie *et al.*[60] meta-analyses demonstrated improvements in global impression of change. There was modest but statistically significant benefit shown for ChEIs for global improvement (NNT=12) in the study by Lanctôt *et al.*[58] AE, discontinuation rates due to AE and overall discontinuation rates were also higher with ChEIs. Ritchie *et al.*[60] demonstrated a statistically

significant benefit of ChEIs for global improvement with no dose effect. Patients on galantamine or high-dose rivastigmine were less likely to continue treatment and more patients experienced AE at higher doses of donepezil and galantamine.

6.4 Health Services Impact

Given the magnitude of the Canadian population that is aging; and the prevalence of AD and other dementias, it is expected that the health services impact of drugs used in the treatment of these diseases will continue to grow. There are three ChEIs approved for use in Canada and a few agents in clinical development. A snapshot of the Canadian utilization of the three ChEIs for the year ending June 2004 is provided in Appendix 8 Table 29. This represents a cost of C$129 million for calendar year 2004 (Appendix 8 Table 30). Decision makers will need to determine if this is money well-spent, despite small to modest statistical results in the short term and clinical benefits that are largely unknown after one year.

6.5 Knowledge Gaps

The knowledge gaps that continue with ChEIs, which have been available since 1997, include the impact of the drugs on:

- outcomes such as rate and timing of institutionalization (the impact remains unknown)
- beneficial effects on QoL (impact from both patient and caregiver perspectives need to be determined)
- functional performance (impact is still unknown and the lack of guidelines for use of scales that measure ADL is problematic)
- long-term effectiveness.

AD is a chronic neurological disorder that tends to last $\geq$10 years. Patients tend to be maintained on ChEIs for more than the 12 to 24 weeks commonly used in clinical trials. Few long-term studies have been conducted with ChEIs. Post-marketing studies to determine their long-term effectiveness for >1 year, are lacking. Despite a proven increase in AE, no available studies identify patients who are most likely to tolerate ChEIs.

7 CONCLUSION

As our population ages, it is expected that the demand for ChEIs will increase until alternative therapies are available. With the advent of new therapies, the hope is to see a shift from drugs that only act on the symptoms of AD, to drugs that prevent or cure the disease.

The objective of this report is to evaluate the evidence for efficacy and harm of the three ChEI drugs that are marketed in Canada for use in mild to moderate AD. In total, 25 unique trials were identified from a systematic review of the medical literature, not limited by date, status or language of publication. The review included head-to-head trials of ChEI drugs.

Interpretation of the results from this review is limited by the difficulty in obtaining unpublished information, the diversity of scales used to measure efficacy outcomes and the inconsistencies, such as those found in reporting trial results.

The meta-analysis revealed that ChEIs have a statistically significant, yet modest, impact on functional performance and global outcomes. These results are corroborated by other systematic reviews. Patients on ChEIs experience more AE and a greater likelihood of treatment discontinuation. The drugs did not cause an increase in the number of patients experiencing serious AE or death. Donepezil did not improve QoL or prevent institutionalization. Whether this is a class effect remains to be determined.

The few head-to-head comparisons included in the review suggest that ChEIs have comparable efficacy despite claims that the effect of galantamine on nicotinic receptors may confer neuroprotection. Nausea and vomiting may be less with donepezil compared with rivastigmine, but not galantamine. There are too few trials with methodological limitations and therefore conclusions regarding the superiority of one drug over others cannot be drawn.

Although statistical improvements were noted in the analyses, they do not necessarily translate into clinically relevant benefits for the patients receiving these drugs or for their caregivers. Accordingly, it is difficult to apply the results to individual patients. A patient may be declared improved, but the improvement may be irrelevant to the caregiver and therefore it has no impact on the care that the patient receives. Conversely, a modest treatment effect in a patient may have an enormous psychological impact on the caregiver(s).

Despite the demonstration of small benefits and higher rates of AE, the ChEI drugs continue to be extensively used in AD patients. This is to be expected in light of the fact that there are no other pharmaocologic therapies available for this condition. As a result, policy and decision makers are faced with the difficult decision of whether to make these drugs available because of pressure from families and caregivers. The functional, global and harm outcome data analyzed in this review provides additional information to be used in decision making regarding these drugs.

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APPENDIX 1: Literature Search Strategy

?	Truncation symbol, one character only
*	Truncation symbol, any number of characters
n	Near/next (i.e.,, terms are near/next to one another, any order)
" "	Phrase
l	Link (i.e.,, to subheading)
ti	Title
ab	Abstract
au	Author
de	Descriptor
dt	Publication type
tn	Trade name
rn	Registry number (i.e.,, CAS)
tw	Text word

DATABASES	**LIMITS**	**KEYWORDS/DESCRIPTORS**
DIALOG® AgeLine® BIOSIS Previews® EMBASE® MEDLINE® PASCAL PsycINFO® ToxFile	Human *(excluding PASCAL and AgeLine®)*	Clinical Search (RCTs): AgeLine: alzheimers disease/de OR presenile dementia/de OR senile dementia/de OR senility/de BIOSIS: alzheimer disease/de OR alzheimer's dementia/de OR alzheimer's disease/de OR dementia/de EMBASE: senile dementia!/de OR alzheimer disease/de OR mental deterioration/de OR multiinfarct dementia/de OR pick presenile dementia/de OR presenile dementia/de MEDLINE/ToxFile: alzheimer disease!/de PsycINFO: presenile dementia!/de OR senile dementia!/de All databases: dement*/ti,ab OR alzheimer* OR senile OR senility OR presenile OR (cognit* OR memor* OR mental*)(3n)(declin* OR impair* OR losing OR loss OR losses OR deteriorat*)/ti,ab OR confusion/ti,ab OR confused/ti,ab *AND* BIOSIS: donepezil/de OR rivastigmine/de RN=120014-06-4 OR RN=357-70-0 OR RN=120011-70-3 OR RN=142057-77-0 OR RN=1953-04-4 OR RN=123441-03-2

		EMBASE: donepezil/de OR galantamine/de OR rivastigmine/de RN=120014-06-4 OR RN=357-70-0 OR RN=120011-70-3 OR RN=142057-77-0 OR RN=1953-04-4 OR RN=123441-03-2 MEDLINE/ToxFile: galanthamine/de PsycINFO: galanthamine/de All databases: donepezil/ti,ab OR E2020/ti,ab OR aricept/ti,ab OR eranz/ti,ab OR memac/ti,ab OR rivastigmine/ti,ab OR "ENA 713"/ti,ab OR ENA713/ti,ab OR exelon/ti,ab OR prometax/ti,ab OR galant?amin/ti,ab OR galant?amine/ti,ab OR reminyl/ti,ab OR nivalin/ti,ab *AND* AgeLine: controlled clinical trials/de OR randomized controlled trials/de OR meta analysis/de OR dt=meta analysis BIOSIS: multicenter study/de OR randomized controlled trial/de OR randomized clinical trial/de OR randomized trial/de OR evidence-based medicine/de OR meta-analysis/de EMBASE: major clinical study/de OR multicenter study/de OR controlled study!/de OR randomized controlled trial/de OR drug comparison!/de OR evidence based medicine!/de MEDLINE/ToxFile: controlled clinical trials!/de OR epidemiologic research design!/de OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial PsycINFO: meta analysis/de random*/ti,ab OR "single (blind* OR dumm* OR mask*)"/ti,ab OR "double (blind* OR dumm* OR mask*)"/ti,ab OR "triple (blind* OR dumm* OR mask*)"/ti,ab OR "treble (blind* OR dumm* OR mask*)"/ti,ab OR placebo*/ti,ab OR "meta analy*"/ti,ab OR metaanaly*/ti,ab OR "quantitative* (review* OR overview*)"/ti,ab OR "systematic* (review* OR overview*)"/ti,ab OR "methodologic* (review* OR overview*)"/ti,ab OR "control* (study OR studies OR trial*)"/ti,ab OR RCT?/ti,ab OR "comparative (study OR studies)"/ti,ab OR (drug OR drugs)(3n)comparison*/ti,ab OR "crossover (design OR study OR studies OR trial*)"/ti,ab *Performed 5 May 2003* *767 unique records*

		Ageline – 1 record BIOSIS – 18 records EMBASE – 529 records Medline – 192 records Pascal – 13 records PsycINFO – 14 records ToxFile – 0 records
DIALOG® Alerts: AgeLine® BIOSIS Previews® EMBASE® MEDLINE® PASCAL PsycINFO® ToxFile	Human *(excluding PASCAL and AgeLine®)*	Clinical search (RCTs): *Same descriptors and keywords as per MEDLINE, etc.* *Updates performed biweekly from May 20, 2003 to Dec 7, 2004, inclusive*
CINAHL*direct*® CINAHL		dementia, senile!/de OR dementia, presenile!/de OR dement*/ti,ab OR alzheimer* OR senile OR senility OR presenile OR "cognit* (declin* OR impair* OR losing OR loss OR losses OR deteriorat*)"/ti,ab OR "memor* (declin* OR impair* OR losing OR loss OR losses OR deteriorat*)"/ti,ab OR "mental* (declin* OR impair* OR losing OR loss OR losses OR deteriorat*)"/ti,ab OR confusion/ti,ab OR confused/ti,ab *AND* donepezil/de OR donepezil/ti,ab OR E2020/ti,ab OR aricept/ti,ab OR eranz/ti,ab OR memac/ti,ab OR rivastigmine/ti,ab OR "ENA 713" /ti,ab OR ENA713/ti,ab OR exelon/ti,ab OR prometax/ti,ab OR galant?amin/ti,ab OR galant?amine/ti,ab OR reminyl/ti,ab OR nivalin/ti,ab *AND* clinical trials!/de OR meta analysis/de OR dt=systematic review OR random*/ti,ab OR "single (blind* OR dumm* OR mask*)"/ti,ab OR "double (blind* OR dumm* OR mask*)"/ti,ab OR "triple (blind* OR dumm* OR mask*)"/ti,ab OR "treble (blind* OR dumm* OR mask*)"/ti,ab OR placebo*/ti,ab OR "meta analy*"/ti,ab OR metaanaly*/ti,ab OR "quantitative* (review* OR overview*)"/ti,ab OR "systematic* (review* OR overview*)"/ti,ab OR "methodologic* (review* OR overview*)"/ti,ab OR "control* (study OR studies OR trial*)"/ti,ab OR RCT?/ti,ab OR "comparative (study OR studies)"/ti,ab OR drug(n)comparison*/ti,ab OR drugs(n)comparison*/ti,ab OR "crossover (design OR study OR studies OR trial*)"/ti,ab *Performed 22 May 2003* *41 records*

PubMed	Human	Clinical Search (RCTs) *Same descriptors and keywords as per DIALOG MEDLINE search* *Performed 15 May 2003* *213 records*
PubMed	Human	Clinical Search (soft study design): *Same keywords and descriptors in DIALOG RCT search, excluding RCT filter and incorporating the following:* epidemiologic studies!/de clinical trials!/de dt=clinical trial "case control (study OR studies OR trial*)"/ti,ab OR "retrospective (study OR studies OR trial*)"/ti,ab "cohort (study OR studies OR trial*)"/ti,ab OR "longitudinal (study OR studies OR trial*)"/ti,ab "prospective (study OR studies OR trial*)"/ti,ab OR "observational (study OR studies OR trial*)"/ti,ab "follow up (study OR studies OR trial*)"/ti,ab "followup (study OR studies OR trial*)"/ti,ab OR "open label (study OR studies OR trial*)"/ti,ab "clinical trial*"/ti,ab *AND* galanthamine(l)ae/de OR galanthamine(l)to/de "injurious effect*"/ti,ab OR "undesirable effect*"/ti,ab OR "side effect*"/ti,ab OR "ill effect*"/ti,ab "adverse effect*"/ti,ab OR "adverse event*"/ti,ab OR "serious event*"/ti,ab OR toxicity/ti,ab safety/ti,ab OR harm/ti,ab OR harmful/ti,ab *Performed 27 May 2003* *112 records*
The Cochrane Collaboration & Update Software Ltd.		alzheimer disease!/de OR dement*/ti,ab OR alzheimer*/ ti,ab OR senile/ti,ab OR senility/ti,ab OR presenile/ti,ab OR "cognit* (declin* OR impair* OR losing OR loss OR losses OR deteriorat*"/ti,ab OR "memor* (declin* OR impair* OR losing OR loss OR losses OR

The Cochrane Library, 2003, Issue 2		deteriorat*"/ti,ab OR mental* (declin* OR impair* OR losing OR loss OR losses OR deteriorat*"/ti,ab OR confusion/ti,ab OR confused/ti,ab *AND* Galanthamine/de OR donepezil/ti,ab OR E2020/ti,ab OR aricept/ti,ab OR eranz/ti,ab OR rivastigmine/ti,ab OR "ENA 713"/ti,ab OR ENA-713/ti,ab OR exelon/ti,ab OR prometax/ti,ab OR galant?amin/ti,ab OR galant?amine/ti,ab OR reminyl/ti,ab OR nivalin/ti,ab *282 Records* The Cochrane Database of Systematic Reviews = 4 complete reviews; The Database of Abstracts of Reviews of Effectiveness = 2 records; CENTRAL = 262 references; HTA database = 5 records; The NHS Economic Evaluation Database = 9 records *Regular updates performed to 2004, Issue 4, inclusive*
Web sites of health technology assessment (HTA) and related agencies; clinical trial registries; other databases		e.g., NZHTA; AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; etc.

APPENDIX 2: Clinical Trial Selection Form

Reviewer's initials		**Trial ID** (first author, year)	

Language of publication		**Inclusion period**	
Multicentre trial	yes / no ❑	**Industry sponsorship**	yes / no / no information ❑

Reference(s)

Intervention	
ChEI, donepezil, galantamine or rivastigmine	❑
ChEI, others	❑
Duration of treatment ≥12 weeks	❑
Duration of treatment ≤12 weeks	❑

Design	
Parallel groups	❑
Crossover	❑
Uncontrolled	❑
Others	❑

Randomization	
Yes, method described and adequate	❑
Yes, method described and inadequate	❑
Yes, method not described or unclear	❑
No	❑
Unsure	❑

Diagnostic criteria	
DSM-IV	❑
NINCDS-ADRDA	❑
Others	❑

Blinding	
Double, method described and adequate	❑
Double, method described and inadequate	❑
Double, method not described or unclear	❑
Simple	❑
No	❑
Unsure	❑

Outcome measures	
Functional	❑
Global	❑
Adverse events	❑
Others	❑

Statistical analysis	
Intention to treat	❑
Per protocol	❑

Clinical trial	**selected** ❑ **/ not selected** ❑

APPENDIX 3: Data Extraction Form

INTERVENTIONS AND PARTICIPANTS

Interventions (type, dosage, duration)	
Control group	
Treatment group(s)	

Participants		
	Treatment group(s)	Control group
Total eligible for inclusion into trial		
Total randomized into trial		
Number of withdrawals and drop-outs		
Number of participants completing the trial		

Baseline characteristics of participants		
(as given in report, specify SD, SE, range)	Treatment group(s)	Control group
Mean age, years		
Sex number of males (%) number of females (%)		
Race number of caucasians (%) number of non-caucasians (%)		
Mean weight, kg		
Mean height, cm		
Mean duration of AD, years		
Mean baseline MMSE score		
Mean baseline ADAS-cog score		

SAFETY OUTCOME MEASURES

Adverse events		
	Treatment group(s)	Control group
Total number of adverse events		
Total number of serious adverse events		
Total number of participants with adverse events		
Total number of participants with serious adverse events		
Number of participants withdrawn from trial because of adverse events		

Description of adverse events		
Type, percentage of participants	Treatment group(s)	Control group

EFFICACY OUTCOME MEASURES

Functional outcome measure		
Rating scale used to assess functional performance in the trial		
Results (as given in report, specify mean, median, SD, SE, 95% CI, p value)	Treatment group(s)	Control group
Baseline score		
Final score		
Change in score		

Global clinical impression of change		
Rating scale used to assess global functioning in the trial		
Results (as given in report, specify mean, median, SD, SE, 95% CI, p value)	Treatment group(s)	Control group
Final score		
Success rate		

Quality of life		
Rating scale used to assess the patients' quality of life in the trial		
Results (as given in report, specify mean, median, SD, SE, 95% CI, p value)	Treatment group(s)	Control group
Baseline score		
Final score		
Change in score		

Secondary outcome measures		
Results (as given in report, specify number, mean, median, SD, SE, 95% CI, p value)	Treatment group(s)	Control group
Timing of treatment discontinuation		
Deaths		
Institutionalization Time to institutionalization		

APPENDIX 4: Quality Assessment Form

STUDY QUALITY

RM # _____ Reviewer _____

Randomization Total points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "randomized" is to *receive one point.* Trials describing an appropriate method of randomization (table of random numbers, computer generated) *receive an additional point.* If the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers), *a point is deducted.*

Double-blinding Total points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "double blind", is to *receive one point.* Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to *receive an additional point.* If the report describes the trial as double blind and uses an inapropriate method (e.g., comparison of tablets versus injection with no double dummy), *a point is deducted.*

Withdrawals and drop-outs Total points: ☐ 0 ☐ 1

A trial reporting the number and reason for withdrawals is to *receive one point*. If there is no statement, *no point* is given.

Total score ☐ Lower (0 to 2 points) ☐ Higher (3 to 5 points)

Allocation concealment ☐ Adequate ☐ Inadequate ☐ Unclear

Adequate: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes.

Inadequate: Alternation; reference to case record # or date of birth.

Unclear: Allocation concealment approach is not reported or fits neither of the above categories.

APPENDIX 5: Description of Instruments Used in Selected Trials

Details are available in an earlier CCOHTA report.[45]

Instrument	Description	Administration	Interpretation	Other
Clinician's global assessments of change				
CGIC: Clinical Global Impression of Change[61]	Interviews with or without another source, reference to mental status and reference to cognition	• by clinician • takes 10 to 40 minutes	7-point scale: 1=very much improved 4=no change 7=very much worse	No instructions on how the interview should be conducted; test depends on clinician's ability to detect change; if a change is detected, it is considered clinically significant; one study used a Japanese version[16]
CIBIC and CIBIC-plus: Clinicians' Interview-Based Impression of Change[35]	A modified CGIC; CIBIC is based on patient interview only; other sources of information not allowed to minimize bias; CIBIC-plus includes interviewing patient and an informant separately; CIBIC-plus provides global rating of patient function in general, cognitive, behaviour and ADL areas	• by clinician • 10-minute interview	7-point scale: 1=very much improved 4=no change 7=very much worse	Various forms exist (e.g., Parke-Davis; NYU); when used in trials, interviews with caregivers are controversial in that they can lead to unblinding if side effects are revealed[62]
Clinician's global assessments of severity				
CDR: Clinical Dementia Rating[63]	Six domains are evaluated: memory; orientation; judgment and problem-solving; community activities; home and hobbies; personal care	• clinician conducts structured interview with patient and informant • takes 40 minutes	5-point scale: 0=no impairment 0.5=questionable 1=mild 2=moderate 3=severe dementia	CDR-SB adds scores of domains and expresses it on range of 0 to 18 points
GDS: Global Deterioration Scale[63]	Stages of dementia are evaluated; GDS assesses global progression of AD cognitively, functionally and behaviourly	• by clinician; with access to all information • not a structured interview	7-point scale: 1= normal 3=late confusion 7=late dementia	

Instrument	Description	Administration	Interpretation	Other
Comprehensive rating scales				
GBS: Gottfries-Bråne-Steen[36]	26 items that assess motor performance, intellectual impairment, emotional impairment and dementia symptoms	• by clinician • semi-structured interview of patient and caregiver	7-point scale scores range 0 to 162; high score=clinical deterioration	
ADL: Activities of Daily Living – functional assessment				
ADCS/ADL: AD Cooperative Study/ Activities of Daily Living[29]	23 items assessing daily activities in patients with AD, such as using household appliances, choosing clothes to wear, bathing and toileting		Scores 0 to 78; decrease in score shows deterioration	
ADFACS: Alzheimer's Disease Functional Assessment and Change Scale[26]	6 items to assess basic ADL and 10 items to assess instrumental activities of daily living: ability to use the telephone, performing household tasks, using household appliances, handling money, shopping, preparing food, ability to get around inside and outside of home, pursuing hobbies and leisure activities, handling personal mail and grasping situations or explanations	• based on information obtained by clinician from direct contact with patient and caregiver • takes 20 minutes	No impairment to severe impairment; basic ADL items are scored on scale of 0 to 4, total range=24; instrument ADL items scored on scale of 0 to 3, total range=54; the higher the score, the greater the impairment	
BDS: Blessed-Roth Dementia Scale[64]	Part 1 (called DS) assesses everyday activities (8 IADL items); habits (3 ADL items); personality, interests and drive (10 items); revised DS includes everyday activities and habits (11 items); part 2 assesses orientation, memory and concentration	Interview with caregiver	DS score 0 (full capacity) to 28 (extreme incapacity); score of 15= moderate dementia; revised DS score 0 (independent) to 17 (dependent)	

Instrument	Description	Administration	Interpretation	Other
BrADL: Bristol Activities of Daily Living Scale[32]	Assesses 20 daily living abilities	Caregiver-rated	Increase in score indicates functional decline	
DAD: Disability Assessment for Dementia[37]	46 questions assess basic and instrumental ADL; and leisure activities	• questionnaire answered by caregiver or structured interview • takes 20 minutes	Scores 0 to100; higher score=better functioning	
IADL: Instrumental Activities of Daily Living Scale[63]	Assesses 8 complex activities: telephoning, shopping, food preparation, housekeeping, laundry, transportation, finances and responsibility for medications	Rated by caregiver	Scores of 4 to 30; higher score means better performance	Food preparation, laundry and housekeeping are excluded when tested in men
PDS: Progressive Deterioration Scale[64]	29 items assessing IADL and ADL that affect the quality of life	Self-administered by caregiver	10 cm visual analogue scale 0=worst; 10=best; total score of 0 to 100 points	Specific to AD
Unified ADL[64]	20 items assessing self-care and mobility	Interview with caregiver	10-point rating scale	
Other functional assessment				
MENFIS: Mental Function Impairment Scale[16]	Modification of GBS scale; evaluates core symptoms of dementia including cognitive, motivational, emotional aspects	Interviews with patient and information from caregiver	Total score of 0 to 78; the higher the score, the greater the functional deficit	Used in 2 Japanese studies[16,22]
Quality of life				
QoL-P[35] and QoL-C[28]	Evaluates patient's well-being; basic domains include relationships, eating, sleeping, social and leisure activities	Patient or caregiver interview	7-item scale; items scored by marking between an analogue scale 0=worst quality 50=best quality	Not validated in AD patients

Cognition was not evaluated in this project. Cognitive tests were used as screening tools for entry into trial. Examples of cognitive tests include Alzheimer's Disease Assessment Scale-cognitive section (ADAS-cog) and Mini-Mental State Examination (MMSE).

APPENDIX 6: Excluded Reports

Duplicates or abstracts (44 reports)

Duplication/ abstract of Tariot et al, 2001[25]

Tariot P, Perdomo CA, Whalen E, Sovel MA, Schwam EM. Age is not a barrier to donepezil treatment of Alzheimer's disease in the long-term care setting [abstract]. *Int Psychogeriatr* 1999;11:134.

Tariot P, Cummings JL, Katz IR, Perdomo CA, Whalen E, Sovel MA, et al. Donepezil was well-tolerated and enhanced cognition in nursing home patients with Alzheimer's disease [abstract]. *J Am Geriatr Soc* 1999;47(9):S3 (A7).

Duplication/ abstract of Gauthier et al, 2002[27]

Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, et al. Benefits of donepezil on global function, behavior, cognition and ADLs in patients with moderate-to-severe Alzheimer's disease [abstract]. *Neurology* 2000;54(Suppl 3):A469.

Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. Donepezil provides benefits in global function in moderate to severe Alzheimer's disease [abstract]. *Neurobiol Aging* 2000;21(1 Suppl):S93.

Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. Donepezil's benefits on cognition, global function, activities of daily living and behavior in patients with moderate to severe Alzheimer's disease [abstract]. 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 Apr 5-8; Stockholm. P.174.

Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001;57(4):613-20.

Feldman H, Gauthier S, Hecker J, Vellas B, Emir B, Mastey V, et al. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc* 2003;51(6):737-44.

Gauthier S, Feldman H, Hecker J, Vellas B, Subbiah P, Whalen E. Effects of donepezil on behaviour and other domains in moderate to severe Alzheimer's disease [abstract]. *J Eur Coll Neuropsychopharmacol* 2000;10 Suppl 3:S359. Available: http://24.132.160.238/00ecnp/home.html (accessed 2003 Sep 6).

Gauthier S, Feldman H, Hecker J, Vellas B, Subbiah P, Whalen E. Benefits of donepezil on performance of basic and instrumental activities of daily living in moderate to severe Alzheimer's disease [abstract]. *Neurobiol Aging* 2000;21 Suppl 1:S161.

Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P. Exploratory analysis of the effects of donepezil in moderate and severe Alzheimer's disease patients [abstract]. 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 Jul 20-25; Stockholm. Abstract no 277.

Vellas B, Feldman H, Gauthier S, Hecker J, Subbiah P, Whalen E. Donepezil treatment in patients with moderate to severe Alzheimer's disease reduces caregiver stress [abstract]. *Neurobiol Aging* 2000;21 Suppl:S94.

Duplication/ abstract of Winblad et al, 2001[36]

Engedal K, Soininen H, Verhey F, Waldemar G, Winblad B, Wimo A, et al. Donepezil improved or stabilized cognition over one year in patients with mild and moderate Alzheimer's disease [abstract]. *J Eur Coll Neuropsychopharmacol* 2000;10 Suppl 3:S368. Available: http://24.132.160.238/00ecnp/home.html.

Mastey V, Wimo A, Winblad B, Haglund A, Jacobson L, Miceli R, et al. Donepezil reduces the time caregivers spend providing care: results of a one-year, double-blind, randomized trial in patients with mild to moderate Alzheimer's disease [abstract]. *J Am Geriatr Soc* 2001;49(4):S20.

Waldemar G, Winblad B, Engedal K, Soininen H, Verhey F, Wimo A, et al. Benefits of donepezil on cognition, function and/or neuropsychiatric symptoms in patients with Alzheimer's disease over one year [abstract]. *Neurobiol Aging* 2000;21(1 Suppl):S274.

Waldemar G, Winblad B, Engedal K, Soininen HS, Verhey FR, Wimo A, et al. Donepezil benefits patients with either mild or moderate Alzheimer's disease over one year [abstract]. *Neurology* 2000;54 Suppl 3:A470.

Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, et al. Donepezil enhances global function, cognition, and acitivities of daily living compared with placebo in a one-year, double-blind trial in patients with mild to moderate Alzheimer's disease [abstract]. *Int Psychogeriatr* 1999;11 Suppl 1. Available: http://www.ipa-online.net/pdfs/ipa1999congressposterabstracts.pdf (accessed 2003 Jun 6).

Duplication/ abstract of Mohs et al, 2001[26]

Mohs R, Doody R, Morris J, Ieni JR, Rogers SL, Perdomo CA, et al. Donepezil preserves functional status in Alzheimer's disease patients: results from a 1-year prospective placebo-controlled attrition study [abstract]. *Eur Neuropsychopharmacol* 1999;9 Suppl 5:S328.

Mohs R, Doody R, Morris J, Ieni J, Rogers S, Perdomo C, et al. Donepezil preserves functional status and improves cognition in Alzheimer's disease patients: results from a 1-year propective placebo-controlled study [abstract]. *J Am Geriatr Soc* 2000;48(8):S46.

Mohs RC, Doody RS, Morris JD, Leni JR, Rogers SL, Perdomo CA, et al. Donepezil preserves functional status in Alzheimer's disease [abstract]. 153rd Annual Meeting of the American Psychiatric Association; 2000 May 13-18; Chicago.

Mohs R, Doody R, Morris J, Ieni J, Perdomo C, Pratt R, et al. Donepezil preserves activities of daily living in Alzheimer 's disease patients: results from a one-year placebo-controlled functional survival study [abstract]. *Neurology* 2000;54(7 Suppl 3):A415.

Pratt R, Mohs R, Doody R, Morris J, Rogers S, Ieni J, et al. Donepezil preserves functional status in Alzheimer's disease patients: results from a 1-year prospective placebo controlled functional study [abstract]. 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 Apr 5-8; Stockholm.

Duplication/ abstract of Wilcock et al, 2000[38]

Lilienfeld S, Papadopoulos G. Galantamine alleviates caregiver burden in Alzheimer's disease [abstract]. 14th Annual Meeting of the American Association for Geriatric Psychiatry; 2001 Feb 23-26; San Francisco.

Parys W, Pontecorvo MJ. Treatment of Alzheimer's disease with galantamine, a compound with a dual mechanism of action [abstract]. *Neurobiol Aging* 1998;19 Suppl:S304.

Wilcock GD, Lilienfeld S. Galantamine alleviates caregiver burden in Alzheimers disease: a 6-month placebo-controlled study [abstract]. *Neurobiol Aging* 2000;21(1 Suppl):S241.

Duplication/ abstract of Tariot et al, 2000[29]

Tariot P, Parys W, Kershaw P. The efficacy and tolerability of galantamine in Alzheimer's disease: a 5-month placebo-controlled study with slow dose escalation [abstract]. *Neurology* 2000;54(7 Suppl 3):A415-A416.

Tariot PN, Kershaw P. Galantamine postpones the emergence of behavioural symptoms in Alzheimers disease: a 5-month, randomized, placebo-controlled study [abstract]. *Neurobiol Aging* 2000;21(1 Suppl):S240.

Duplication/ abstract of Raskind et al, 2000[37]

Parys W. Galantamine, a cognitive enhancer with nicotinic modulation: clinical benefits in Alzheimer' disease [abstract]. *Eur J Neurol* 1999;6 Suppl 3:186.

Raskind M, Peskind E, Prys W, Wessel T. Galantamine produces long-term cognitive and functional benefits in patients with Alzheimer's disease [abstract]. *Neurology* 2000;54 Suppl 3:A468.

Duplication/ abstract of Burns et al, 1999[34]

Bayer AJ, Rossor M, Hecker J, Gauthier S, Burns A, Petite H, et al. Donepezil improves functional activity in patients with Alzheimer's disease [abstract]. *Int J Neuropsychopharmacol* 1998;2 Suppl 1:S175.

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Gauthier S, Rosser M, Hecker J, Petite H, Rogers S, Mohr E, et al. Donepezil produces both clinical global and cognitive test improvement in patients with Alzheimer's disease [abstract]. 151st Annual Meeting of the American Psychiatric Association; 1998 May 30-Jun 4; Toronto.

Duplication/ abstract of Rosler et al, 1999[31]

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Duplication/ abstract of Rogers et al, 1996[28]

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Duplication/ abstract of Rogers et al, 1998[35]

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Duplication/ abstract of Wilkinson et al, 2001[39]

Wilcock G, Wilkinson D, Galanthamine Research Group. Galanthamine hydrobromide - interim results of a group comparative, placebo controlled, study of efficacy and safety in patients with a diagnosis of senile dementia of the Alzheimer's type [abstract]. *Neurobiol Aging* 1996;17(4 Suppl):S144-S145.

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Duplication/ abstract of Wilkinson et al, 2002[40]

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Passmore P, Wetterberg P, Adler G, Bullock R, Soininen H, Aarsland D, et al. First head to head study comparing the tolerability, ease of use, and efficacy of donepezil and galantamine in Alzheimer's disease [abstract]. 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 Jul 20-25; Stockholm. Abstract no 367.

Duplication/ abstract of Rockwood et al, 2001[30]

Rockwood K, Kershaw P. Galantamine's clinical benefits are not offset by sleep disturbance: a 3-month placebo-controlled study in patients with Alzheimer's disease [abstract]. *Neurobiol Aging* 2000;21(1 Suppl):S239.

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Duplication/ abstract of Wilcock et al, 2003[32]

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Wesnes K, Bullock R, Gold M, Mahableshwarkar AR, Members of the GAL-GBR-2 Study Group. Galantamine and donepezil in the treatment of Alzheimer's disease: effects on attention and cognition [poster]. American Psychiatric Association 156th Annual Meeting; 2003 May 17-22; San Francisco.

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Salloway S. A double blind randomized pilot study to evaluate the effects of galantamine and donepezil on sleep and attention and gastrointestinal GI tolerance in patients with mild to moderate Alzheimer's disease AD. In: *ClinicalTrials.gov* [database online]. Bethesda (MD): National Library of Medicine; 2002. NLM identifier NCT00035204. Available: http://www.clinicaltrials.gov/ct/show/NCT00035204?order=2 (accessed 2003 May 6).

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APPENDIX 7: Characteristics of Selected Trials*

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
AD 2000 Collaborative Group, 2004[24] NHS Executive R&D (West Midlands)	RCT, DB, parallel design, 48 weeks, Jadad score=4	486 participants with diagnosis of mild to moderate AD, using DSM-IV, with or without coexisting diagnosis of vascular dementia	Donepezil 5 mg or 10 mg versus placebo	D=242, P=244	Primary: entry to institution, progression of disability; secondary: BrADL, harm	Allocation concealment adequate; <20% of patients had vascular dementia; at end of 48-week treatment, patients could continue receiving DB treatment with regular wash-out periods for ≤3 years
Agid *et al.*[19] Novartis Pharma AG	RCT, DB, parallel design, 12 weeks, Jadad score=5	402 patients with mild to moderate dementia, using DSM-III-R criteria and diagnosis of probable AD, according to NINCDS-ADRDA criteria	Rivastigmine 1.0 to 1.5 mg BID week 1, then 2 mg BID for 12 weeks; or 1.0 to 2.5 mg BID weeks 1 to 3, then 3 mg BID for 10 weeks versus placebo	R4mg=136, R6mg=133, P=133	Primary: CGIC; secondary: IADL, harm	Allocation concealment is adequate; 4 mg is not a therapeutic dose; exclusion criteria not reported; few baseline characteristics reported; placebo group older by 2 years (p value not reported)
Burns *et al.*[34] Eisai Inc.	RCT, DB, parallel design, 24 weeks, Jadad score=3	818 patients with DAT defined by DSM-III-R and probable AD, according to NINCDS-ADRDA criteria, MMSE of 10 to 26, CDR scores of 1 or 2	Donepezil 5 mg HS or 5 mg HS for 7 days then 10 mg HS versus placebo 1 tablet HS	D5mg=271, D10mg=273, P=274	Primary: CIBIC-plus; secondary: modified IDDD, CDR-SB, QoL-P, harm	Allocation concealment is unclear; comorbidities and concomitant drug therapy not reported
Corey-Bloom *et al.*[21] Novartis Pharmaceuticals Corporation	RCT, DB, parallel design, 26 weeks, Jadad score=5	699 patients with DAT defined by DSM-IV and probable AD according to NINCDS-ADRDA criteria; MMSE of 10 to 26; patients with Hachinski ≥5 were excluded†	Rivastigmine low dose (1 mg to 4 mg daily in 2 divided doses) or high dose (6 mg to 12 mg daily in two divided doses) versus placebo	R-low=233, R-high=231, P=235	Primary: CIBIC-plus; secondary: PDS,† harm	Allocation concealment is adequate; 1 mg to 4 mg daily doses are not therapeutic; 1 exclusion criterion reported

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Forette *et al.*[17] Novartis Pharmaceuticals Corporation	RCT, DB, parallel design, 18 weeks, Jadad score=3	114 patients with mild to moderate dementia defined by DSM-III-R and diagnosis of probable DAT defined by NINCDS-ADRDA criteria; MMSE of 12 to 26	Rivastigmine BID or TID: 2 mg daily to 12 mg daily with dose increments of 1 mg at day 4; 0.5 mg every 4th day until day 28; and 1 mg weekly thereafter, patients were titrated to tolerable doses and maintained for 8 weeks versus placebo	R-BID=45, R-TID=45, P=24	Primary: CIBIC-plus; NOSGER; secondary: harm	Allocation concealment is unclear; patients who did not tolerate 6 mg daily discontinued from study; few baseline characteristics reported
Gauthier *et al.*[27] Pfizer Inc.	RCT, DB, parallel design, 24 weeks, Jadad score=5	207 patients with clinically probable or clinically possible AD according to NINCDS-ADRDA criteria; sMMSE of 10 to 17	Donepezil 5 mg HS x 28 days, may increase dose to 10 mg HS, according to clinician's judgement, for 20 weeks versus placebo equivalent	D=102, P=105	Primary: CIBIC-plus; secondary: DAD, PSMS+, IADL+, harm	Allocation concealment is unclear; dose adjustment permitted; data on withdrawals was reported in another publication[65]
Homma *et al.*[22] Sponsorship not stated	RCT, DB, parallel design, 12 weeks, Jadad score=2	190 patients with mild to moderate DAT according to DSM-III-R and NINCDS-ADRDA criteria	Donepezil 3 mg OD or 5 mg OD versus placebo	D3mg=66, D5mg=64, P=60	MENFIS, CDR-SB, FGIR, GUR, harm	Original article is in Japanese; allocation concealment is unclear; 3 mg is not a therapeutic dose
Homma *et al.*[16] Sponsorship not stated	RCT, DB, parallel design, 24 weeks, Jadad score=3	268 outpatients with AD according to DSM-IV, CDR scores of 1 or 2; MMSE 10 to 26, ADAS-J cog score of $\geq$15	Donepezil 3 mg OD for week 1, then 5 mg OD versus placebo OD	D5=136, P=132	Primary: CGIC-J; secondary: CDR-SB, MENFIS, harm	Allocation concealment is unclear; statistical difference in baseline MMSE (p=0.035) and ADAS-cog (p=0.001); with ANCOVA, significance is p<0.15

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Jones *et al.*[33] Eisai Inc. and Pfizer Inc.	RCT, open-label, rater-blinded, 12 weeks, Jaded score=3	120 patients with probable or possible, mild or moderate AD consistent with NINCDS-ADRDA and DSM-IV criteria; MMSE 10 to 24	Galantamine 4 mg BID for 4 weeks then 8 mg BID for 4 weeks then 12 mg BID versus donepezil 5 mg OD for 4 weeks then 10 mg OD; for both drugs, dose could be decrease if not tolerated.	G24=56, D10=64	Secondary: DAD (not rater-blinded), harm	Allocation concealment is unclear; galantamine group older by 1.3 years (p value not reported); more females in galantamine group (p=0.03)
Mohs *et al.*[26] Eisai Inc. and Pfizer Inc.	RCT, DB, survival design, 54 weeks, Jadad score=3	431 patients with probable AD according to DSM-IV and NINCDS criteria; MMSE of 12 to 21, CDR of 1 or 2, modified Hachinski ischemia score ≤4, able to perform 8 of 10 instrumental ADL and able to perform 5 of 6 basic ADL on ADFACS	Donepezil 5 mg HS x 28 days then dose increased to 10 mg versus placebo at HS	D10=214, P=217	Primary: time to reach clinically evident functional decline; secondary: CDR-SB, ADFACS, harm	Allocation concealment is adequate; more non-caucasians in placebo group (p=0.04)
Peng *et al.*[23] Sponsorship not stated	RCT, single-blind, parallel design, 12 weeks, Jaded score=2	89 patients with mild to moderate AD; diagnosed by DSM-IV and NINCDS-ARDRDA criteria; MMSE 10 to 24	Donepezil 5 mg OD versus placebo OD	D5=46, P=43	CDR, ADL, harm	Original article in Chinese; allocation concealment is unclear

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Raskind *et al.*[37] Janssen Research Foundation	RCT, DB, parallel design, 24 weeks, Jadad score=5	636 with probable AD, according to NINCDS-ADRDA criteria; MMSE of 11 to 24, ADAS-cog ≥12	Galantamine 8 mg daily week 1; 16 mg daily week 2; and 24 mg daily week 3; at week 4, one group maintained on 24 mg daily and another group increased to 32 mg daily for 5 months; all doses taken in 2 divided doses and compared with placebo 1 tablet BID	G24mg=212, G32mg=211, P=213	Primary: CIBIC-plus; secondary: DAD, harm	Allocation concealment is unclear; significant difference (p=0.02) in time since diagnosis of probable AD in 32 mg group (1.4 years versus 1 year in other groups); protocol deviations occurred in 10% of patients (comparable across treatment groups)
Rockwood *et al.*[30] Janssen Research Foundation	RCT, DB, parallel design, 12 weeks, Jadad score=5	386 patients with probable AD according to NINCDS-ADRDA criteria; MMSE of 11 to 24, ADAS-cog >2	Galantamine 8 mg daily week 1; 16 mg daily week 2; and 24 mg daily week 3; could increase to 32 mg daily week 4; at end of week 4 could decrease to 24 mg daily; all doses taken in 2 divided doses and compared with placebo BID	G=261, P=125	Primary: CIBIC-plus; secondary: DAD, harm	Allocation concealment is adequate; protocol deviations occurred in 9.8% of patients; more patients withdrew or dropped out of galantamine group (33% versus 10%)
Rogers *et al.*[28] Eisai Inc.	RCT, DB, parallel design, 12 weeks, Jadad score=4	161 patients with diagnosis of AD based on DSM-III-R and NINDCS criteria; MMSE 10 to 26 and CDR of 1 or 2	Donepezil 1 mg, 3 mg or 5 mg HS versus placebo HS	D1mg=42, D3mg=40, D5mg=39, P=40	Primary: CGIC; secondary: CDR-SB, Unified ADL, QoL-P, QoL-C, harm	Allocation concealment is unclear; 1 mg and 3 mg daily doses are not therapeutic; ratio of males to female is different between groups; patients with MMSE of >26 and <10 included despite inclusion criteria

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Rogers *et al.*[18] Eisai Inc.	RCT, DB, parallel design, 12 weeks, Jadad score=4	468 patients with probable AD according to NINCDS-ADRDA and DSM-III-R criteria; MMSE of 10 to 26, CDR scores of 1 or 2	Donepezil 5 mg HS or 5 mg for 7 days then increased to 10 mg HS versus placebo 2 tablets HS	D5mg=157, D10mg=158, P=153	Primary: CIBIC-plus; secondary: CDR-SB, QoL-P, harm	Allocation concealment is unclear; ratio of males to female is different in 5 mg group; patients with MMSE of 27 to 28 and 8 to 9 included in treatment groups
Rogers *et al.*[35] Eisai Inc.	RCT, DB, parallel design, 24 weeks, Jaded score=4	473 patients with probable AD according to NINCDS-ADRDA and DSM-III-R criteria; MMSE of 10 to 26, CDR scores of 1 or 2	Donepezil 5 mg HS or 5 mg for week 1 and increased to 10 mg HS versus placebo	D5mg=154, D10mg=157, P=162	Primary: CIBIC-plus; secondary: CDR-SB, QoL-P, harm	Allocation concealment is unclear; dose adjustments not permitted; no data on withdrawals; 10 mg group was older (p=0.03 versus placebo)
Rosler *et al.*[31] Novartis Pharma AG	RCT, DB, parallel design, 26 weeks, Jadad score=5	725 patients with DAT as described in DSM-IV and probable AD according to NINCDS-ADRDA criteria; MMSE of 10 to 26; patients with Hachinski ≥5 were excluded†	Rivastigmine low dose (1 mg to 4 mg daily) or high dose (6 mg to 12 mg daily) versus placebo	R-low=243, R-high=243, P=239	Primary: CIBIC-plus; secondary: PDS†, harm	Allocation concealment is adequate; patients with MMSE>26 included; baseline characteristics not reported by group; 1 mg to 4 mg daily doses are not therapeutic
Tariot *et al.*[29] Janssen Research Foundation	RCT, DB, parallel design, 20 weeks, Jadad score=5	978 with probable AD according to NINCDS-ADRDA criteria; MMSE of 10 to 22, ADAS-cog ≥18	Galantamine 8 mg daily for 5 months or 8 mg daily for 4 weeks then 16 mg daily for 17 weeks or 8 mg daily for 4 weeks, then 16 mg daily for 4 weeks; then 24 mg daily for weeks 9 to 21. All doses taken in 2 divided doses compared with placebo 1 tablet BID	G8mg=140, G16mg=279, G24mg=273, P=286	Primary: CIBIC-plus; secondary: ADCS/ADL, harm	Allocation concealment is unclear; 8 mg daily dose is not used clinically but group was studied to test for dose-response effect

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Tariot *et al.*[25] Eisai Inc. and Pfizer Inc.	RCT, DB, parallel design, 24 weeks, Jaded score=5	208 patients with probable or possible AD or AD with cerebrovascular disease according to NINCDS-ADRDA criteria; MMSE of 5 to 26, 1 symptom from NIP-NH, patients residing in nursing home	Donepezil one 5 mg tablet and one placebo tablet OD days 1 to 28; then dose increased to 10 mg (2x5 mg tablets) OD versus 2 placebo tablets OD	D10=103, P=105	Secondary: CDR-SB (nursing home version), PSMS, harm	Allocation concealment is adequate; approximately 25% of patients had severe AD (MMSE<10); donepezil patients had less heart or vascular diseases yet use of beta-blockers and CCB higher; subgroup analysis done for MMSE 10 to 26
Wang *et al.*[20] Sponsorship not stated	RCT, open-label, parallel design, 16 weeks, Jaded score=2	124 patients with mild to moderate AD diagnosed by DSM-IV and NINCDS-ARDRDA criteria; MMSE 10 to 26, Hachinski scale used to distinguish AD from vascular dementia	Rivastigmine 1.5 mg BID weeks 1 to 4, then 3 mg BID weeks 5 to 16 if initial dose tolerated versus donepezil 5 mg OD weeks 1 to 4, then 10 mg OD weeks 5 to 16, if no serious AE	R=62, D=62	GDS, BDS, harm	Original article is in Chinese; allocation concealment is unclear; baseline characteristics not reported
Wilcock *et al.*[38] Janssen Research Foundation	RCT, DB, parallel design, 24 weeks, Jadad score=5	653 patients with probable AD according to NINCDS-ADRDA criteria; MMSE of 11 to 24, ADAS-cog ≥12	Galantamine 8 mg daily week 1, 16 mg daily week 2 and 24 mg daily week 3; at week 4 one group maintained on 24 mg daily and another group increased to 32 mg daily for 5 months; all doses taken in 2 divided doses and compared with placebo 1 tablet BID	G24mg=220, G32mg=218, P=215	Primary: CIBIC-plus; secondary: DAD, harm	Allocation concealment is adequate; patients who did not complete study were older (74.1 versus 71.7 years)

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Wilcock *et al.*[32] Janssen-Cilal UK, Janssen Pharmaceutical L.P.; and Shire Pharmaceuticals Ltd.	RCT, rater-blinded, parallel design, 52 weeks, Jadad score=3	188 patients with probable AD according to NINCDS-ADRDA criteria; MMSE of 9 to 18	Galantamine 4 mg BID weeks 1 to 4 and 8 mg BID weeks 5 to 13; at week 13 investigator could increase to 12 mg BID versus donepezil 5 mg OD for 4 weeks; investigator could increase dosage to 10 mg OD based on patient's tolerance	G=97, D=91	Primary: BrADL; secondary: harm	Allocation concealment is adequate; stratified randomization based on DAD score; not rater-blinded for harm evaluation; more females in donepezil group
Wilkinson *et al.*[39] Shire Pharmaceuticals	RCT, DB, parallel design, 12 weeks, Jadad score=5	285 outpatients with probable AD according to NINCDS-ADRDA and DSM-III-R criteria; MMSE of 13 to 24	Galantamine 4 mg BID, dose increased every 2 to 3 days until reached 6 mg, 8 mg or 12 mg TID versus placebo	G18mg=88, G24mg=56, G36mg=54, P=87	Secondary: CGIC, PDS-1, harm	Allocation concealment is adequate; high withdrawals due to side effects (44% in 36 mg group); study not powered to detect differences in secondary outcomes
Wilkinson *et al.*[40] Eisai Inc., and Pfizer Inc.	RCT, open-label, parallel design, 12 weeks, Jaded score=2	112 patients with probable or possible AD according to DSM-IV and NINCDS-ARDRDA criteria; MMSE of 10 to 26	Rivastigmine 1.5 mg BID for 14 days, then 3 mg BID for 14 days, then 4.5 mg BID for 14 days, then 6 mg BID for 6 weeks versus donepezil 5 mg OD for 28 days, then 10 mg OD for 8 weeks	R12=55, D10=57	Secondary: harm	Allocation concealment is unclear; patients outside MMSE range criteria (<10 and >26) were included; patients who did not tolerate 6 mg daily of rivastigmine or 5 mg daily of donepezil discontinued from study; dose adjustment was permitted

Study and Funding Source	Method	Participants	Interventions	N	Outcomes of Interest	Notes
Winblad *et al.*[36] Pfizer Inc.	RCT, DB, parallel design, 52 weeks, Jadad score=4	286 patients with probable or possible AD according to DSM-IV and NINCDS-ARDRDA criteria; MMSE of 10 to 26	Donepezil 5 mg OD x 28 days, dose increased to 10 mg OD as per clinician's judgement versus placebo	D=142, P=144 (90.1% were on 10 mg donepezil)	Primary: GBS; secondary: PDS, GDS, harm	Allocation concealment is unclear.

*For details on acronyms, please refer to the list of abbreviations; RCT=randomized controlled trial; DB=double-blind; BID=twice daily; TID=three times a day; OD=once daily; HS=evening or at bedtime. †Data obtained from FDA report

APPENDIX 8: Tables

Table 1: Cholinesterase inhibitor drugs available in Canada[7,66]

Generic Name	Brand Name (Manufacturer)	Dosage Form	Notice of Compliance	Cost per Unit	Approved Dosage
donepezil	Aricept® (Pfizer)	5 mg and 10 mg tablets	August 12, 1997	$4.777/tablet	5 to 10 mg daily
galantamine	Reminyl® (Janssen-Ortho)	4 mg, 8 mg and 12 mg tablets	July 31, 2001	$2.4672/tablet	16 to 24 mg daily, administered in two divided doses
rivastigmine	Exelon® (Novartis)	1.5 mg, 3 mg, 4.5 mg and 6 mg capsules	April 13, 2000	$2.387/capsule	6 to 12 mg daily, administered in two divided doses

Table 2: Selected trials with more than one publication

Comparators	Main Publication	Total Number of Publications	Number of Different First Authors
donepezil versus placebo	Burns A *et al.*[34]	4	3
	Gauthier S *et al.*[27]	10	3
	Mohs RC *et al.*[26]	6	2
	Rogers SL *et al.*[28]	2	1
	Rogers SL *et al.*[35]	3	1
	Tariot PN *et al.*[25]	3	1
	Winblad B *et al.*[36]	6	4
galantamine versus placebo	Raskind MA *et al.*[37]	3	2
	Rockwood K *et al.*[30]	3	2
	Tariot PN *et al.*[29]	3	1
	Wilcock G *et al.*[38]	4	3
	Wilkinson D *et al.*[39]	3	1
rivastigmine versus placebo	Rosler M *et al.*[31]	2	1
galantamine versus donepezil	Jones *et al.*[33]	2	2
	Wilcock G *et al.*[32]	3	3
rivastigmine versus donepezil	Wilkinson D *et al.*[40]	3	2

Table 3: Summary of quality assessment for selected trials

Comparators	Number of Studies	Mean Jadad Score (range)	Allocation Concealment	
			Adequate	Unclear
donepezil versus placebo	12	3.6 (2 to 5)	3	9
galantamine versus placebo	5	5.0	3	2
rivastigmine versus placebo	4	4.5 (3 to 5)	3	1
galantamine versus donepezil	2	3.0	1	1
rivastigmine versus donepezil	2	2.0	0	2

Table 4: ADFACS scores for donepezil 10 mg at 12 weeks and at 54 weeks

ADFACS	Groups	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	donepezil 10 mg versus placebo	1	214/217	0.40 (3.80)	1.31 (3.80)	−0.91 (−1.63; −0.19)
54 weeks	donepezil 10 mg versus placebo	1	214/217	2.38 (4.40)	3.90 (5.00)	−1.52 (−2.41; −0.63)

Table 5: DAD scores for donepezil 5 mg to 10 mg at 12 weeks and at 24 weeks

DAD	Groups	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	donepezil 5 mg to 10 mg versus placebo	1	102/105	2.20 (13.90)	−3.80 (14.70)	6.00 (2.10; 9.90)
24 weeks	donepezil 5 mg to 10 mg versus placebo	1	102/105	0.00 (14.40)	−9.25 (15.10)	9.25 (5.23; 13.27)

Table 6: Unified ADL scores for donepezil 5 mg at 12 weeks

Unified ADL	Group	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	donepezil 5 mg versus placebo	1	39/40	−3.10 (10.40)	1.50 (15.10)	−4.60 (−10.31; 1.11)

Table 7: ADCS/ADL scores for galantamine 16 mg and 24 mg at 20 weeks

ADCS/ ADL	Groups	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
20 weeks	galantamine 16 mg versus placebo	1	279/286	−0.70 (8.00)	−3.80 (14.60)	3.10 (1.16, 5.04)
	galantamine 24 mg versus placebo	1	273/286	−1.50 (9.50)	−3.80 (14.60)	2.30 (0.27, 4.33)

Table 8: DAD scores for galantamine 24 mg to 32 mg at 12 weeks

DAD	Group	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	galantamine 24 mg to 32 mg versus placebo	1	261/125	−1.20 (13.40)	−5.30 (13.10)	4.10 (1.29; 6.91)

Table 9: BrADL scores for galantamine 24 mg compared with donepezil 10 mg at 52 weeks

BrADL	Group	Studies	Patients (galantamine/ donepezil)	Change in Score: Galantamine (SD)	Change in Score: Donepezil (SD)	Treatment Difference (95% CI)
52 weeks	galantamine 24 mg versus donepezil 10 mg	1	97/91	2.46 (6.90)	2.67 (6.90)	−0.21 (−2.18; 1.76)

Table 10: DAD scores for galantamine 24 mg compared with donepezil 10 mg at 12 weeks

DAD	Group	Studies	Patients (galantamine/ donepezil)	Change in Score: Galantamine (SD)	Change in Score: Donepezil (SD)	Treatment Difference (95% CI)
12 weeks	galantamine 24 mg versus donepezil 10 mg	1	55/64	−0.40 (4.40)	1.50 (4.00)	−1.90 (−3.42; −0.38)

Table 11: BDS scores for rivastigmine 6 mg compared with donepezil 10 mg at 16 weeks

BDS	Group	Studies	Patients (rivastigmine/ donepezil)	Change in Score: Rivastigmine (SD)	Change in Score: Donepezil (SD)	Treatment Difference (95% CI)
16 weeks	rivastigmine 6 mg versus donepezil 10 mg	1	62/ 62	−1.80 (2.60)	−1.40 (3.20)	−0.40 (−1.43; 0.63)

Table 12: Patients' improvement (success rate <4) with donepezil 5 mg and 10 mg at 12 weeks

Success Rate <4	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
12 weeks	donepezil 5 mg versus placebo	1	49/157	27/153	1.77 (1.17; 2.67)	7 (4; 23)
12 weeks	donepezil 10 mg versus placebo	1	58/158	27/153	2.08 (1.40; 3.10)	5 (3; 10)

Table 13: Patients' improvement (success rate <5) with donepezil 5 mg at 12 weeks and donepezil 5 mg to 10 mg at 24 weeks

Success Rate <5	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
12 weeks	donepezil 5 mg versus placebo	1	34/39	32/40	1.09 (0.90; 1.33)	NS
24 weeks	donepezil 5 mg to 10 mg versus placebo	1	69/102	49/105	1.45 (1.14; 1.85)	5 (3; 12)

Table 14: GBS scores for donepezil 5 mg to 10 mg at 12 weeks and at 52 weeks

GBS	Group	Studies	Patients (treatment/ control	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	donepezil 5 mg to 10 mg versus placebo	1	142/144	1.50 (11.40)	3.00 (14.80)	−1.50 (−4.56; 1.56)
52 weeks	donepezil 5 mg to 10 mg versus placebo	1	142/144	8.00 (17.60)	11.70 (18.00)	−3.70 (−7.83; 0.43)

Table 15: Patients improved or no change from baseline for galantamine 16 mg and 24 mg at 20 weeks

Success Rate <5	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
5 months (endpoint)	galantamine 16 mg versus placebo	1	169/279	128/286	1.30 (1.15; 1.59)	6 (4; 13)
	galantamine 24 mg versus placebo	1	162/273	128/286	1.33 (1.13; 1.56)	7 (4; 15)

Table 16: CIBIC-plus/CGIC final scores for rivastigmine 6 mg to 12 mg at 12 weeks and at 26 weeks

CIBIC-plus/CGIC	Group	Studies	Patients (treatment/ control)	Final Score: Treatment (SD)	Final Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	rivastigmine 6 mg to 12 mg versus placebo	1	242/239	3.88 (1.30)	3.96 (1.30)	−0.06 (−0.24; 0.12)
26 weeks	rivastigmine 6 mg to 12 mg versus placebo	1	242/239	3.91 (1.40)	4.38 (1.40)	−0.34 (−0.52; −0.16)

Table 17: Patients' improvement (success rate <4) for rivastigmine 10 mg at 18 weeks

Success Rate <4	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
18 weeks	rivastigmine 10 mg versus placebo	1	10/45	3/24	1.78 (0.54; 5.85)	NS

Table 18: QoL-C for donepezil 5 mg at 12 weeks

QoL-C	Group	Studies	Patients (treatment/ control	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
12 weeks	donepezil 5 mg versus placebo	1	39/40	0.30 (48.80)	3.70 (38.00)	−3.40 (−22.72; 15.92)

Table 19: QoL-P for donepezil 10 mg at 24 weeks

QoL-P	Group	Studies	Patients (treatment/ control)	Change in Score: Treatment (SD)	Change in Score: Control (SD)	Treatment Difference (95% CI)
24 weeks	donepezil 10 mg versus placebo	1	157/162	7.95 (54.10)	−1.59 (49.10)	9.54 (−1.81; 20.89)

Table 20: Discontinuation rate for donepezil 5 mg at 54 weeks

Discontinuation	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
54 weeks	donepezil 5 mg versus placebo	1	60/214	56/217	1.09 (0.80; 1.48)	NS

Table 21: Discontinuation rate for donepezil 10 mg at 12 weeks

Discontinuation	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNT (95% CI)
12 weeks	donepezil 10 mg versus placebo	1	29/158	11/153	2.55 (1.92; 4.93)	9 (5; 27)

Table 22: Discontinuation rates for galantamine 24 mg at 12 weeks

Discontinuation	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNH (95% CI)
12 weeks	galantamine 24 mg versus placebo	1	14/56	14/87	1.55 (0.80; 3.01)	NS

Table 23: Discontinuation rates for galantamine 24 mg to 32 mg at 12 weeks

Discontinuation	Group	Studies	n/N Treatment	n/N Control	RR (95% CI)	NNH (95% CI)
12 weeks	galantamine 24 mg to 32 mg versus placebo	1	86/261	12/125	3.43 (1.95; 6.04)	4 (3; 6)

Table 24: Selected AE for galantamine compared with donepezil

Type of AE	Studies	n/N Galantamine	n/N Donepezil	RR (95% CI)	NNH (95% CI)
diarrhea	1	8/56	6/64	1.52 (0.56; 4.13)	NS
dizziness	1	3/56	1/64	3.43 (0.37; 32.02)	NS
agitation	1	18/97	11/91	1.54 (0.77; 3.07)	NS
deaths	1	2/97	3/91	0.63 (0.11; 3.66)	NS

Table 25: Select AE for rivastigmine compared with donepezil

Type of AE	Studies	n/N Rivastigmine	n/N Donepezil	RR (95% CI)	NNH (95% CI)
anorexia	1	5/55	1 /56	5.09 (0.61; 42.18)	NS
nausea	1	23/55	6/56	3.90 (1.72; 8.84)	3 (2; 6)
headache	1	10/55	4/56	2.55 (0.85; 7.63)	NS
deaths	1	1/55	0/56	3.05 (0.13; 73.38)	NS

Table 26: Summary of results for placebo controlled trials

	Donepezil			Galantamine				Rivastigmine	
	5 mg	**10 mg**	**5 mg to 10 mg**	**16 mg**	**24 mg**	**32 mg**	**24 mg to 32 mg**	**6 mg to 10 mg**	**6 mg to 12 mg**
Functional (based on one or two trials)									
ADCS/ADL	x	x	x	++[c]	++[c]	x	x	x	x
ADFACS	x	++[a,k]	x	x	x	x	x	x	x
DAD	x	x	++[a,d]	x	x	x	++[a,h]	x	x
IADL	x	x	x	x	x	x	x	●[f]	x
MENFIS	+[a,h]	x	x	x	x	x	x	x	x
PDS	x	x	x	x	x	x	x	x	++[e]
unifiedADL	+[a]	x	x	x	x	x	x	x	x
Global (based on one to six trials)									
CDR-SB	++[a,d,h]	++[a,d,h]	x	x	x	x	x	x	x
CIBIC-final	++[a,d,h]	++[a,d,h]	x	x	++[i]	++[d]	x	x	++[e]
CIBIC-success <4	++[a,d,h]	++[a,d,h]	x	x	+[d]	+[d]	+[a,h]	x	++[e,j]
CIBIC-success <5	+[a]	x	++[d]	++[c]	++[c]	x	x	x	x
GBS	x	x	+[a,k]	x	x	x	x	x	x
QoL (based on one to three trials)									
patient	++[a]	+[d]	x	x	x	x	x	x	x
caregiver	●[a]	x	x	x	x	x	x	x	x
Harm (based on two to eleven trials)									
nausea	x	x	++	x	x	x	++	x	++
vomiting	x	x	++§	x	x	x	++	x	++
diarrhea	x	x	++	x	x	x	++	x	+
anorexia	x	x	++	x	x	x	++	x	++
weight loss	x	x	++	x	x	x	+	x	x
dizziness	x	x	++	x	x	x	++	x	++
headache	x	x	++§	x	x	x	++	x	++
agitation	x	x	+	x	x	x	+	x	x
serious AE	x	x	+	x	x	x	+	x	+
D/C AE	x	x	+	x	x	x	++	x	++
death	x	x	●	x	x	x	●	x	+
Other (based on one to seven trials)									
Institution	x	x	●[m]	x	x	x	x	x	x
Drop-outs	+[a,k,m] ●[d]	++[a] +[d,h]	●[k]	x	++[i,h]	++[d,h]	++[a]	++[f]	++[e,m]

[a]=12 weeks;[b]=18 weeks;[c]=20 weeks, [d]=24 weeks; [e]=26 weeks; [f]=12 and 18 weeks combined; [g]=12 and 20 weeks combined,
[h]=12 weeks and 24 weeks combined; [i]=20 weeks and 24 weeks combined; [j]=18 weeks and 26 weeks combined; [k]=≥48 weeks;
[m]=other duration; D/C=discontinued
++=statistically significant for treatment
+=non-significant for treatment
●=non-significant for placebo
x=not reported
§=results non-significant when excluding trials of low quality

Table 27: Results for head-to-head trials

	Galantamine versus Donepezil	**Rivastigmine versus Donepezil**
Functional		
BDS	x	ns for rivastigmine 6 mg versus donepezil 10 mg (one trial of 16 weeks)
BrADL	ns for galantamine 24 mg versus donepezil 10 mg (one trial of 52 weeks)	x
DAD	ss, favours donepezil (one trial of 12 weeks: galantamine 24 mg versus donepezil 10 mg)	x
Harm (based on one or two trials only)		
nausea	ns	ss; less with donepezil
vomiting	ns	ss; less with donepezil
diarrhea	ns	x
anorexia	x	ns
dizziness	ns	x
headache	ns	ns
agitation	ns	x
serious AE	ns	ns
discontinued due to AE	ns	ns
death	ns	ns
Other		
discontinuation rates	ns for galantamine 24 mg versus donepezil 10 mg (12 weeks and 52 weeks combined)	ss; less with donepezil (rivastigmine 6 mg to 12 mg versus donepezil 10 mg at 12 weeks and 16 weeks combined)

ns=results are non-significant
ss=results are statistically significant
x=not reported

Table 28: Recently published systematic reviews

Author/Year	Design of Included Studies	Patient Population	Outcomes Measured
Trinh *et al.*[55]	29 parallel groups or crossover RCTs, DB, placebo versus all ChEIs (including agents such as physostigmine), trial duration >1 month, English and non-English	Outpatients diagnosed with mild to moderate, probable AD, according to NINCDS-ADRDA and MMSE of 10 to 26	Neuropsychiatric and functional outcomes (NPI, ADAS-cog, ADL, IADL)
Lanctôt *et al.*[58]	16 parallel group RCTs, DB, placebo versus all three marketed ChEIs; trial duration ≥12 weeks; English only	Adults with AD, according to DSM-IV or NINCDS-ADRDA	Cognitive and global outcomes (CGIC/CIBIC-plus, ADAS-cog); safety; discontinuation rates
Ritchie *et al.*[60]	20 RCT, DB; placebo versus all three marketed ChEIs; trial duration not stated; English only	Mild to moderate AD according to explicit operationalized criteria (one trial included severe AD; one trial included vascular AD)	Cognitive and global outcomes (ADAS-cog, CGIC/CIBIC-plus); safety; drop-out rates; dose-effects
Perras *et al.* (current report)	21 parallel groups, RCT, DB, placebo versus all three marketed ChEIs; 4 parallel groups, RCT head-to-head trials; trial duration ≥12 weeks; English and non-English	Participants with diagnostic evidence of mild to moderate, possible or probable AD, according to DSM-IV or NINCDS-ADRDA	9 functional and 5 global outcomes; safety; discontinuation rates; institutionalization; QoL-P; QoL-C; mortality

ADAS-cog=Alzheimer's disease Assessment Scale-cognitive; DB=double-blind; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; RCT=randomized controlled trial.

Table 29: Drug utilization in Canada

Estimated Total Number of Prescriptions Dispensed from Canadian Retail Pharmacies (12 months ending June 2004)	
Product	**Number of Prescriptions**
Aricept®	620,547
Reminyl®	155,413
Exelon®	133,448
Total	909,408

IMS Health, Canada, Compuscript. 2004

Table 30: Drug costs in Canada

Retail Cost of Prescriptions Dispensed in Canada			
Alzheimer Type Dementia	**2004**	**12 Months Ending June 2004**	**12 Months Ending June 2005**
Aricept®	$85,833,927	$81,551,130	$88,751,380
Exelon®	$18,824,313	$16,522,631	$19,961,392
Reminyl®	$24,559,861	$20,847,800	$27,674,627
Total	$129,220,105	$118,921,561	$136,387,399

IMS Health, Canada, Compuscript. 2004 and 2005

APPENDIX 9: Figures

Figure 1: Selected reports

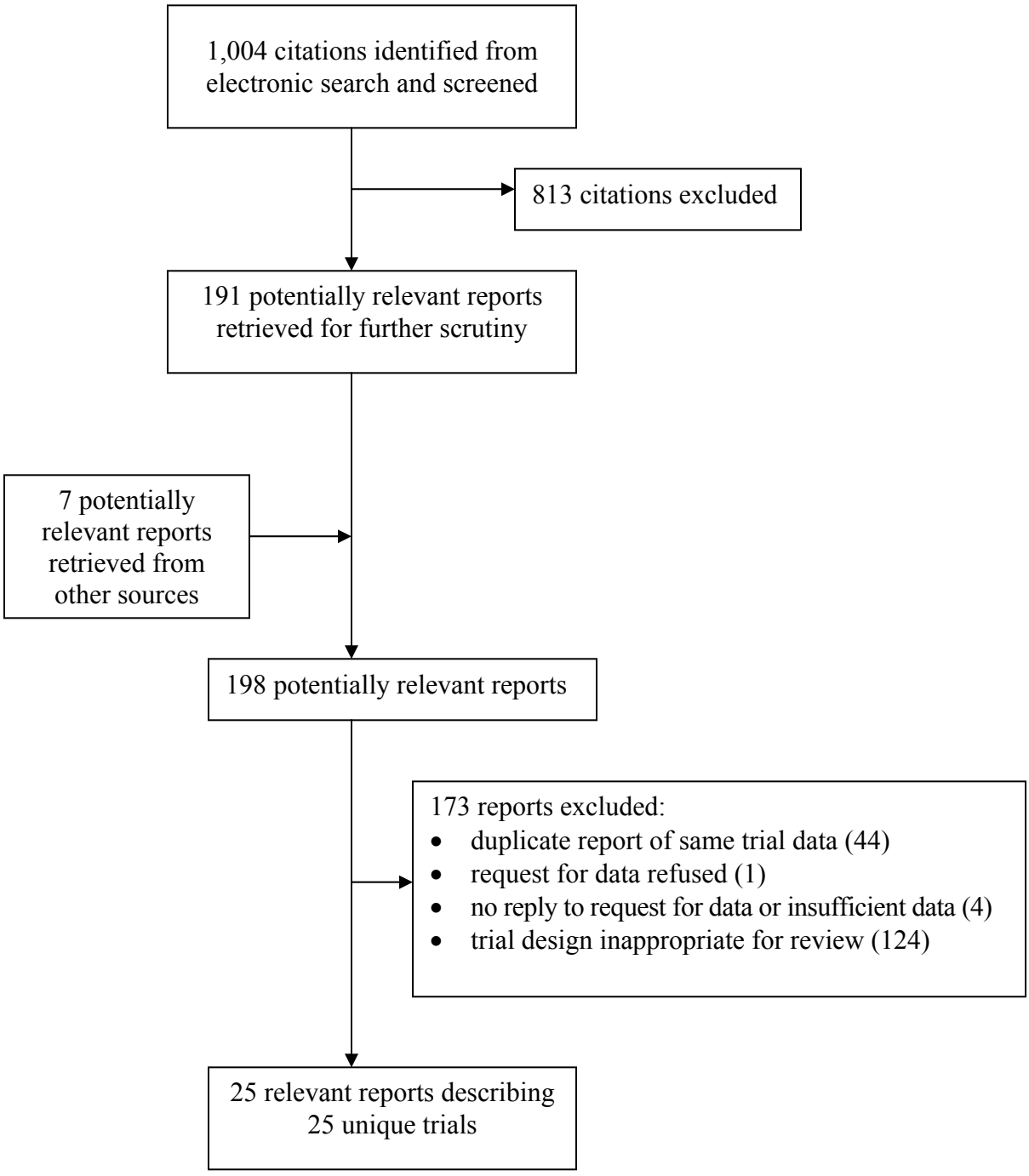


Figure 2: Pooled data for MENFIS scores; donepezil 5 mg at 12 weeks

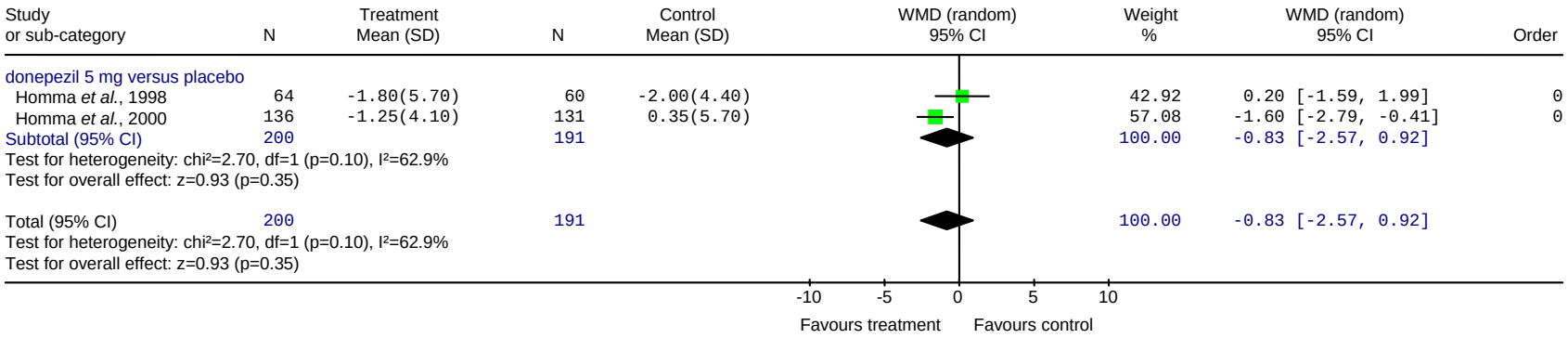


Figure 3: Pooled data for MENFIS scores; donepezil 5 mg at endpoint at 12 weeks and 24 weeks combined

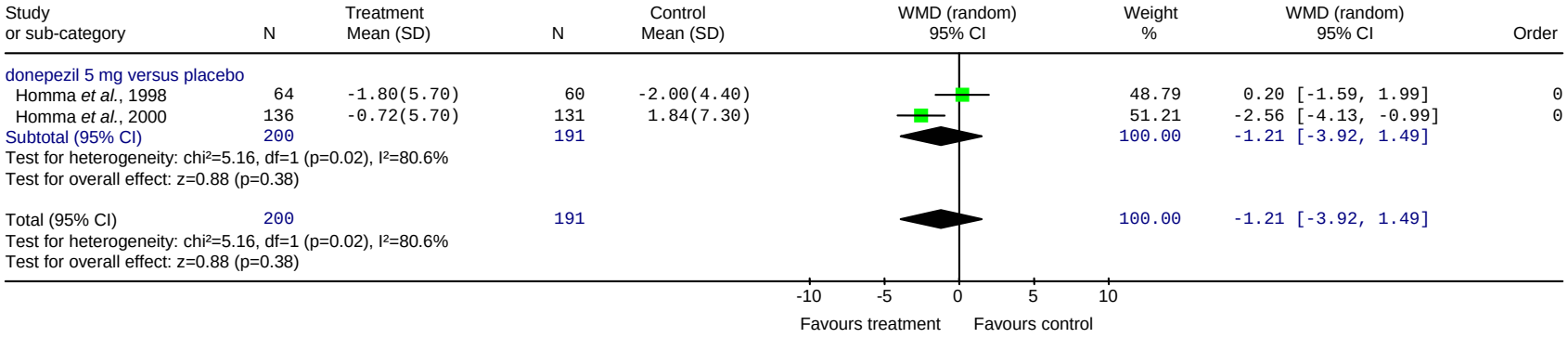


Figure 4: Pooled data for DAD scores; galantamine 24 mg to 32 mg at endpoint at 12 weeks and 24 weeks combined

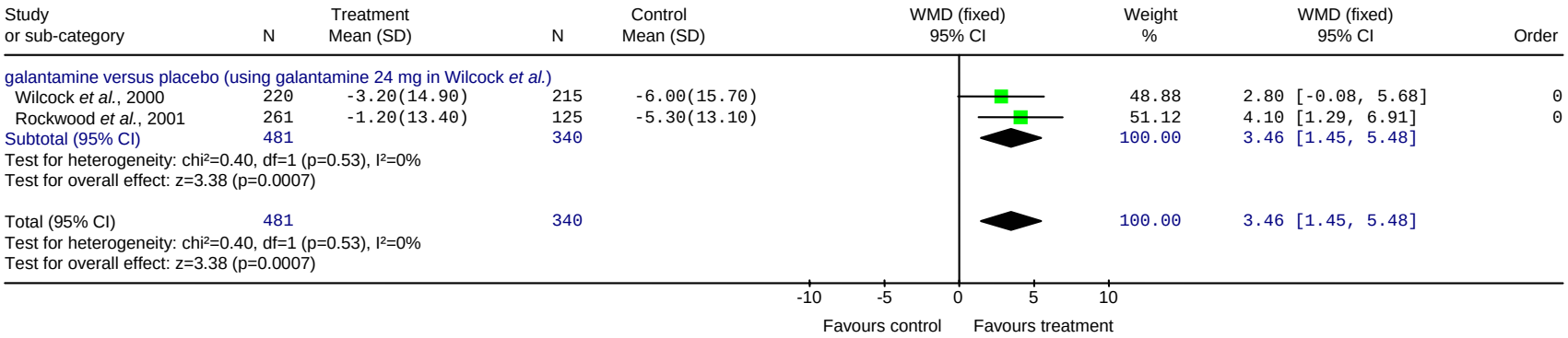


Figure 5: Pooled data for IADL scores; rivastigmine 6 mg to 10 mg at endpoint at 12 weeks and 18 weeks combined

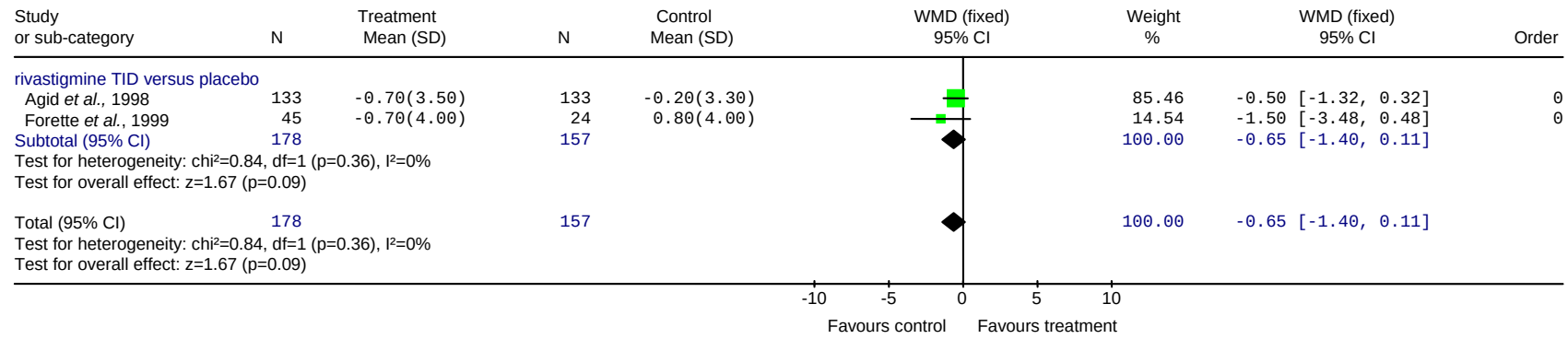


Figure 6: Pooled data for PDS scores; rivastigmine 6 mg to 12 mg at 26 weeks

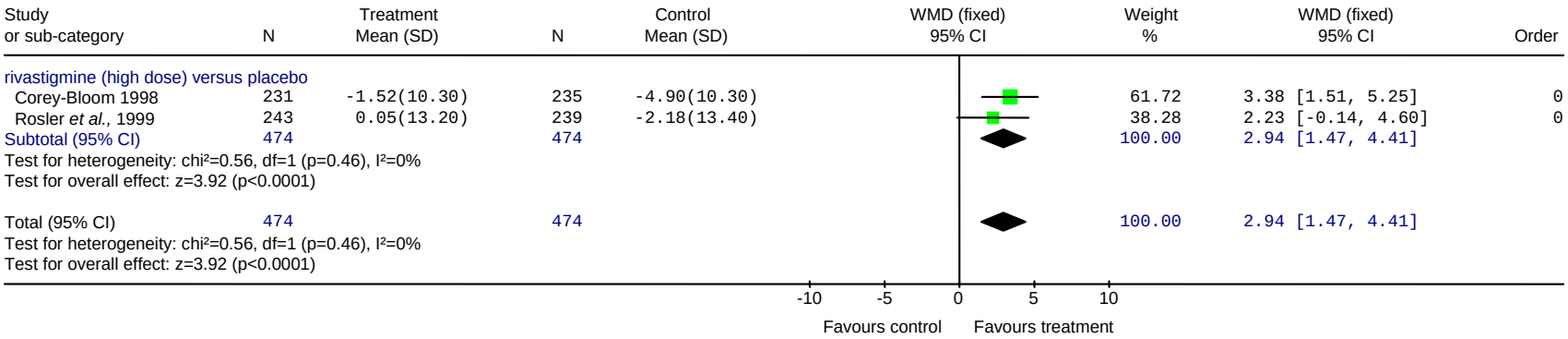


Figure 7: Pooled data for CDR-SB scores; donepezil 5 mg at 12 weeks

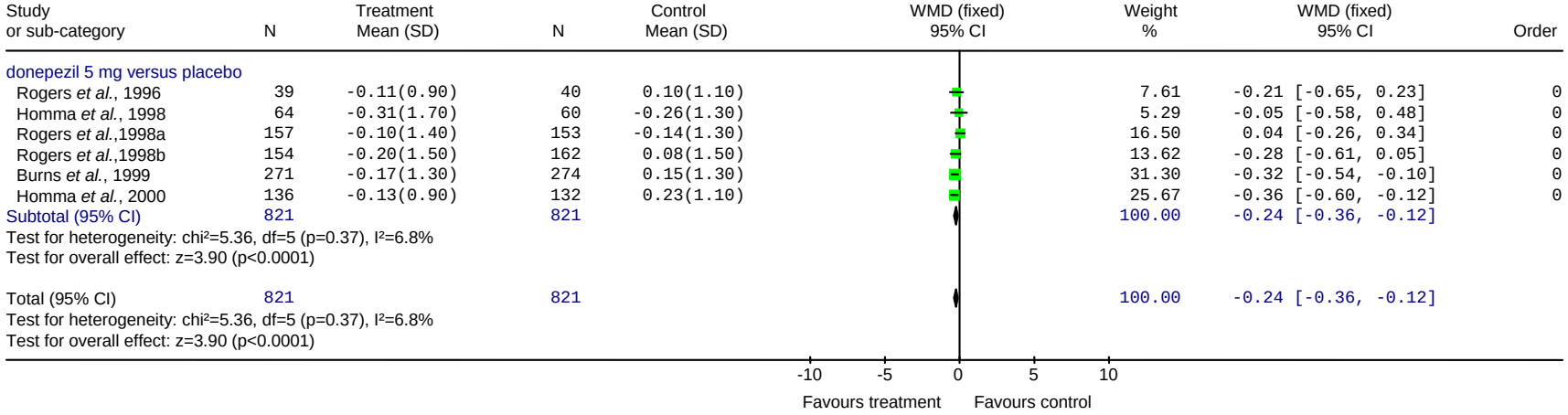


Figure 8: Pooled data for CDR-SB scores; donepezil 10 mg at 12 weeks

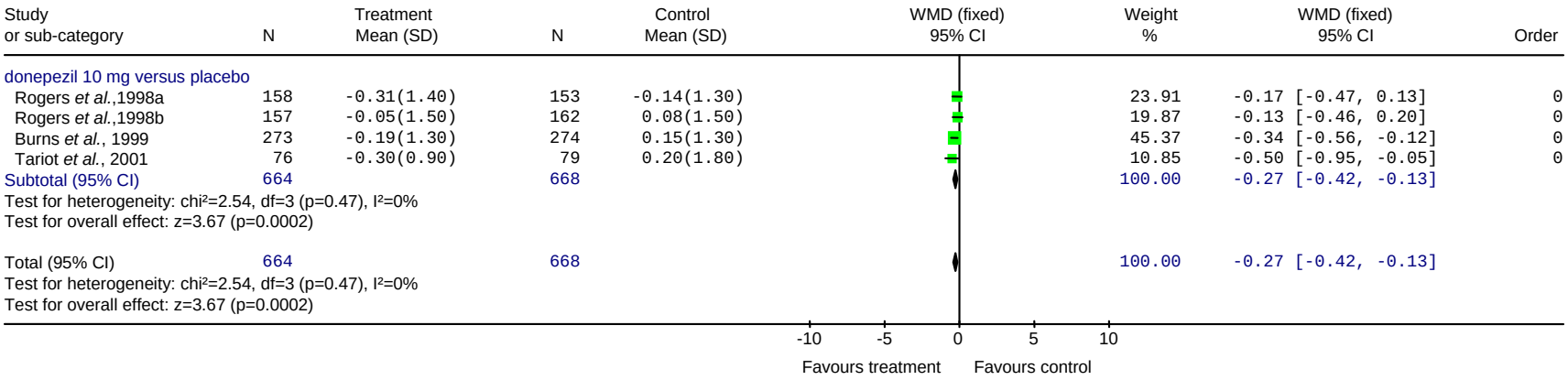


Figure 9: Pooled data for CDR-SB scores; donepezil 5 mg at 24 weeks

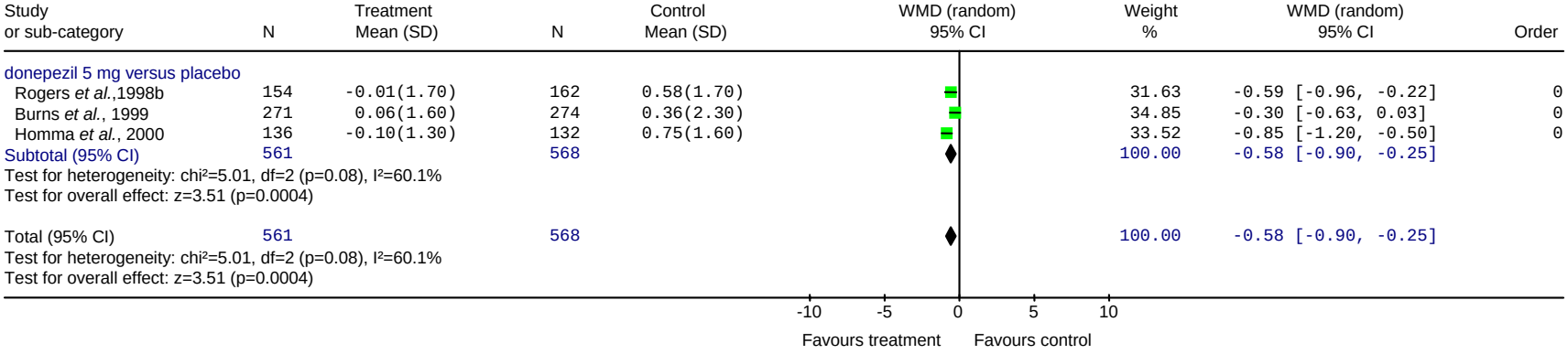


Figure 10: Pooled data for CDR-SB scores; donepezil 10 mg at 24 weeks

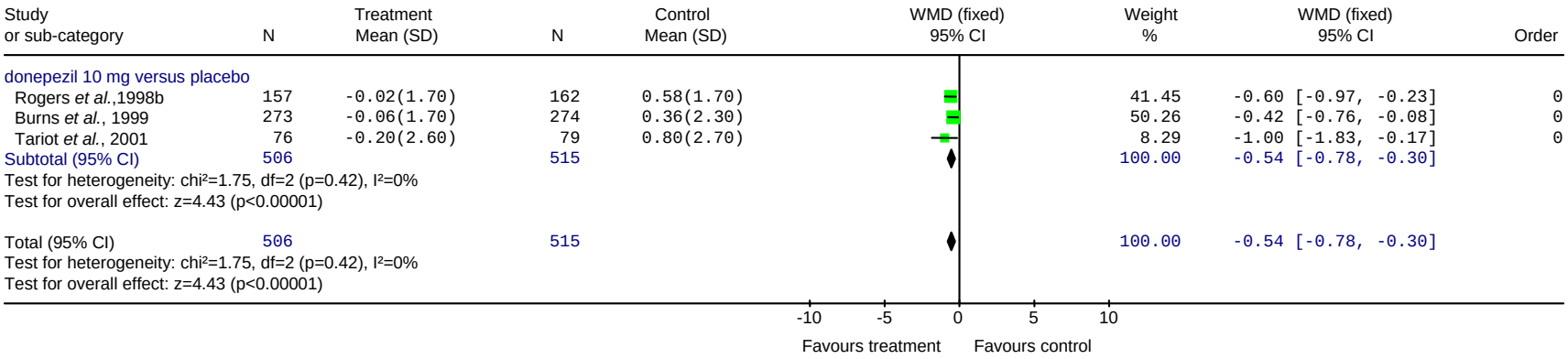


Figure 11: Pooled data for CDR-SB scores; donepezil 5 mg at endpoint at 12 weeks and 24 weeks combined

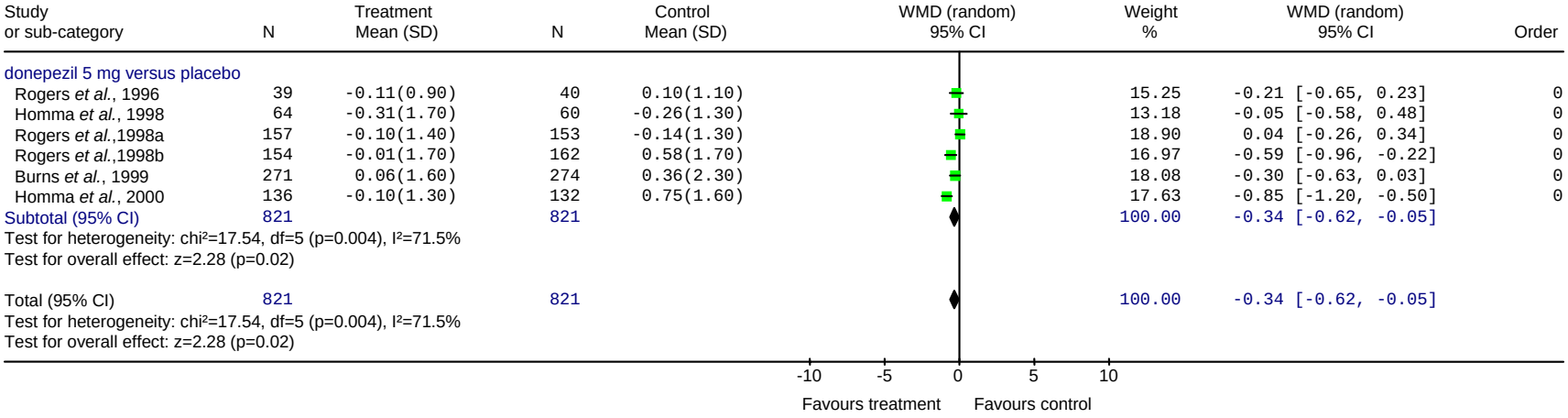


Figure 12: Pooled data for CDR-SB scores; donepezil 10 mg at endpoint at 12 weeks and 24 weeks combined

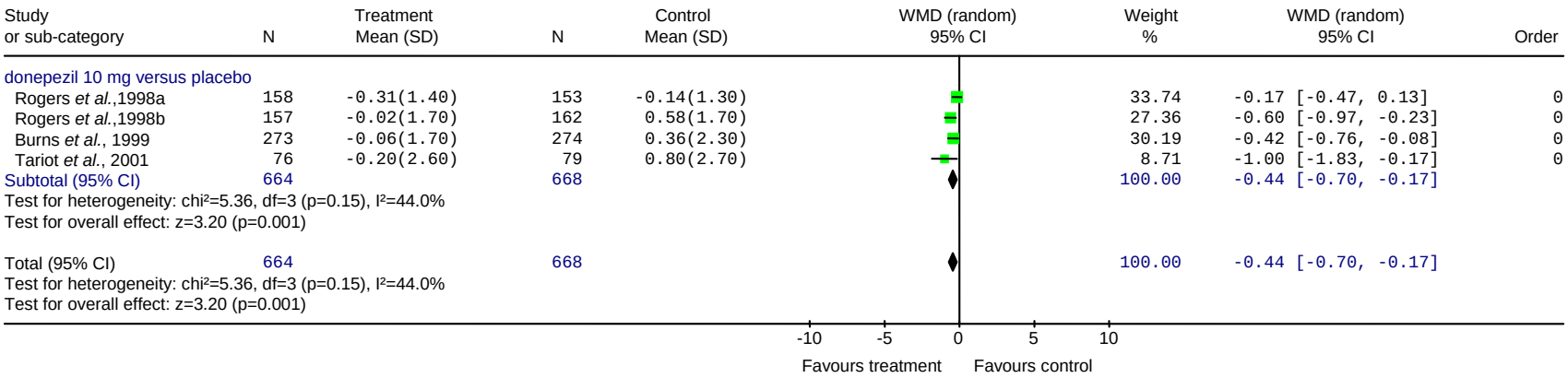


Figure 13: Pooled data for CDR-SB scores; donepezil 5 mg at 12 weeks, with removal of low quality studies (Jadad <3)

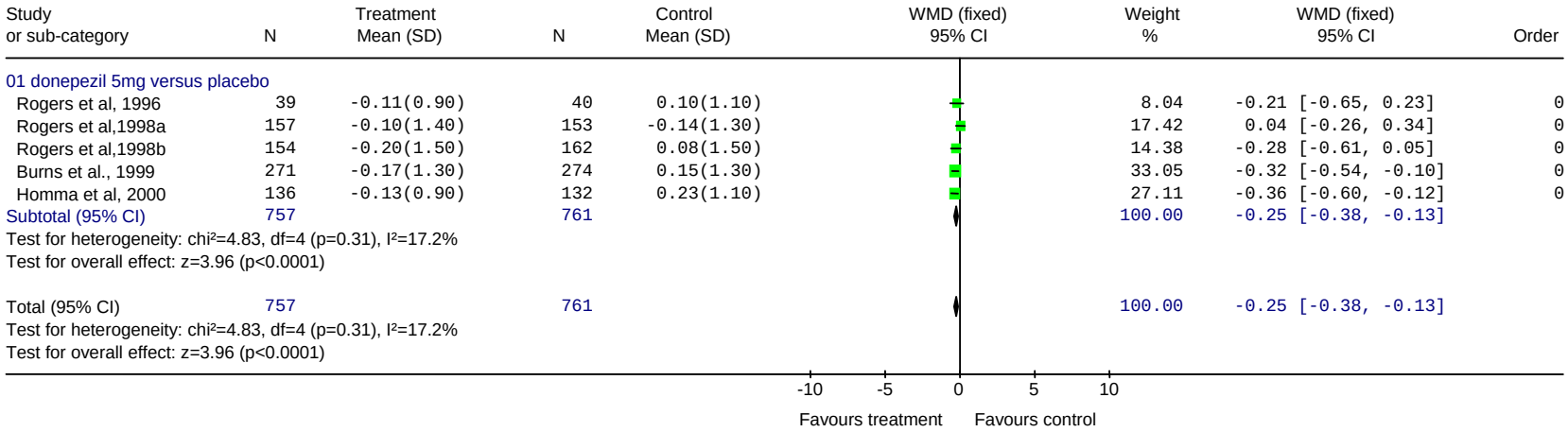


Figure 14: Pooled data for CIBC-plus/CGIC final scores; donepezil 5 mg at 12 weeks

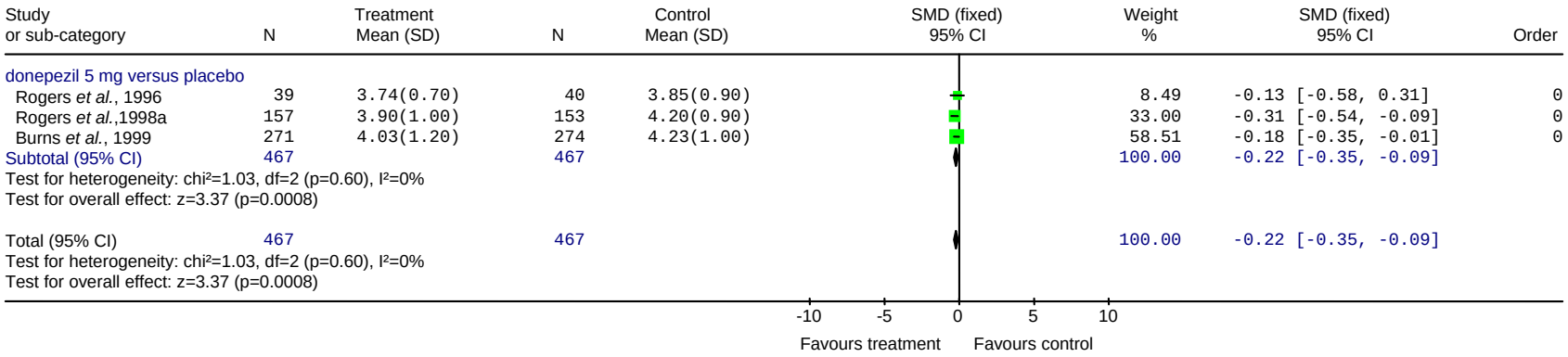


Figure 15: Pooled data for CIBC-plus/CGIC final scores; donepezil 10 mg at 12 weeks

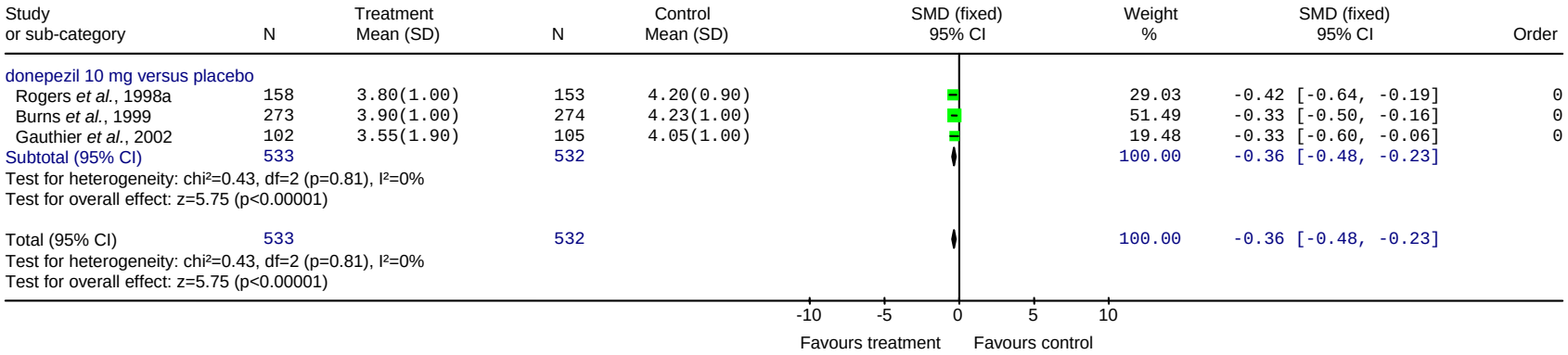


Figure 16: Pooled data for CIBC-plus/CGIC final scores; donepezil 5 mg at 24 weeks

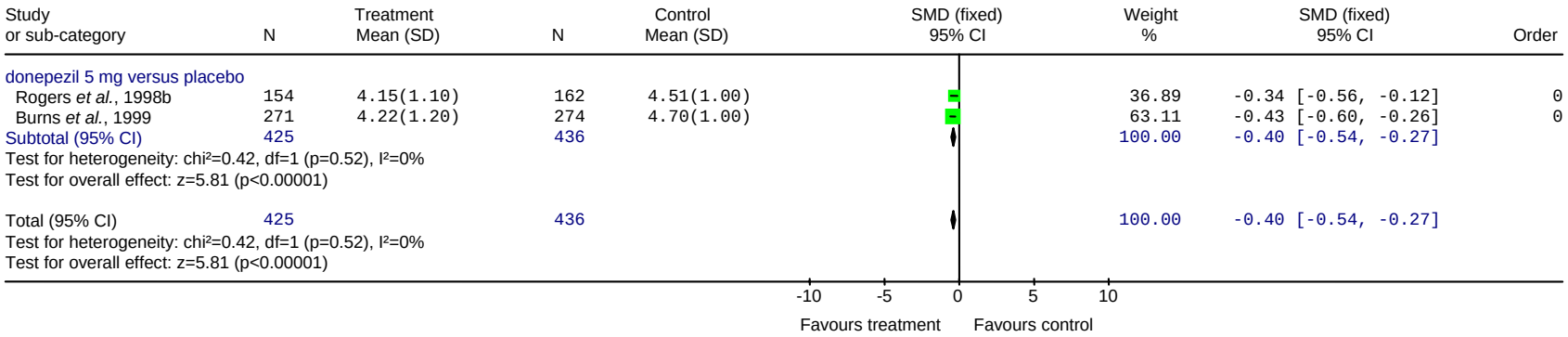


Figure 17: Pooled data for CIBC-plus/CGIC final scores; donepezil 10 mg at 24 weeks

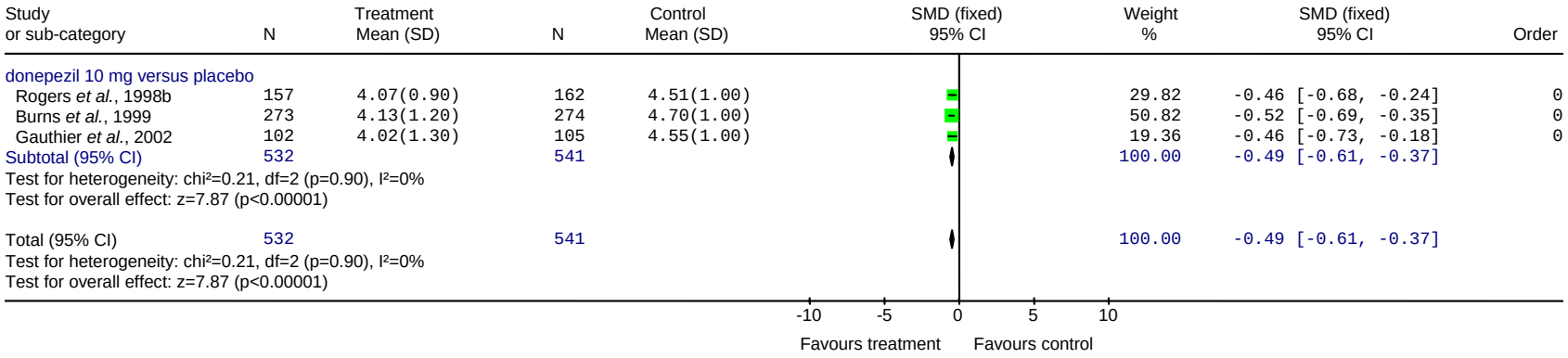


Figure 18: Pooled data for CIBC-plus/CGIC final scores; donepezil 5 mg at endpoint at 12 weeks and 24 weeks combined

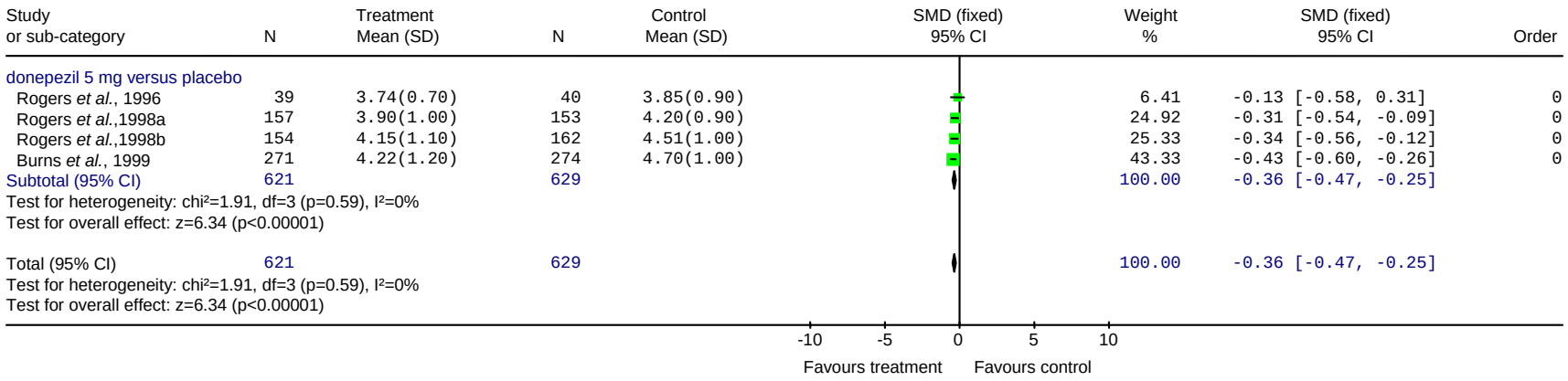


Figure 19: Pooled data for CIBC-plus/CGIC final scores; donepezil 10 mg at endpoint at 12 weeks and 24 weeks combined

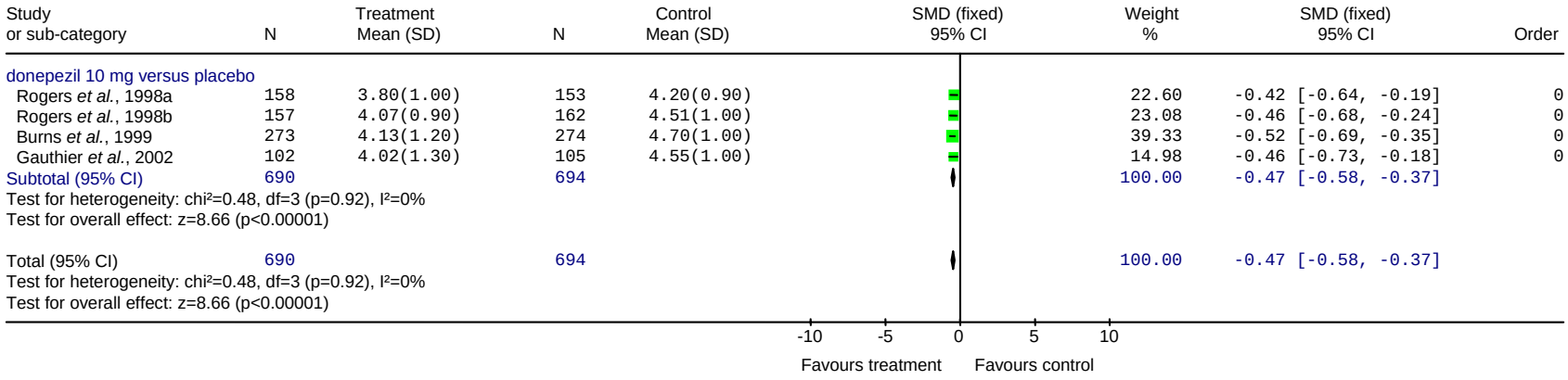
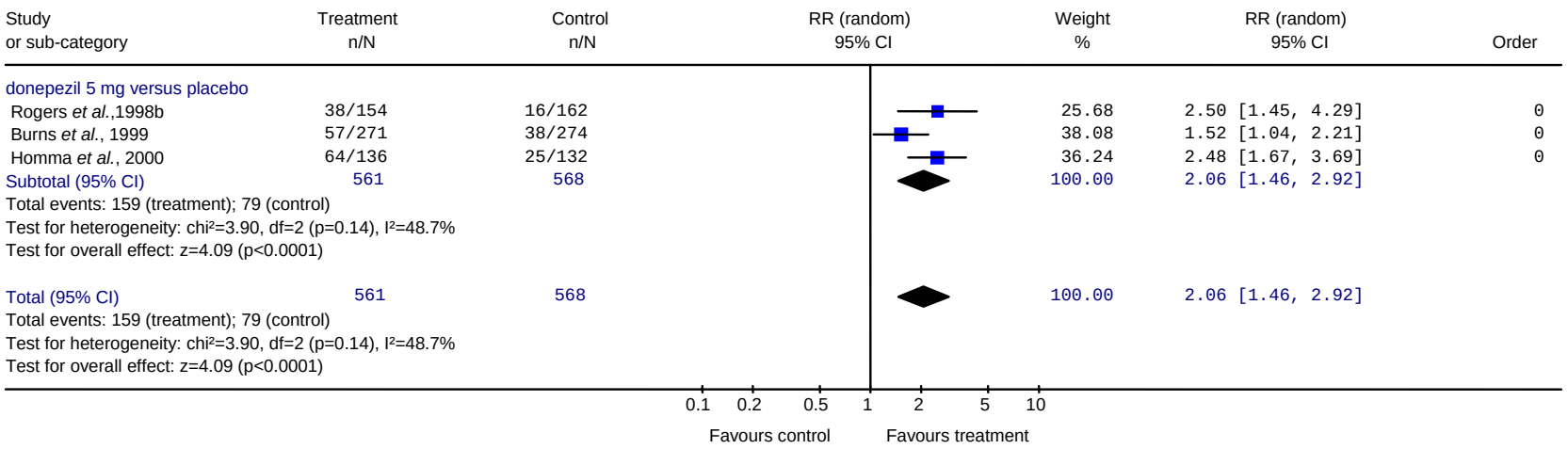
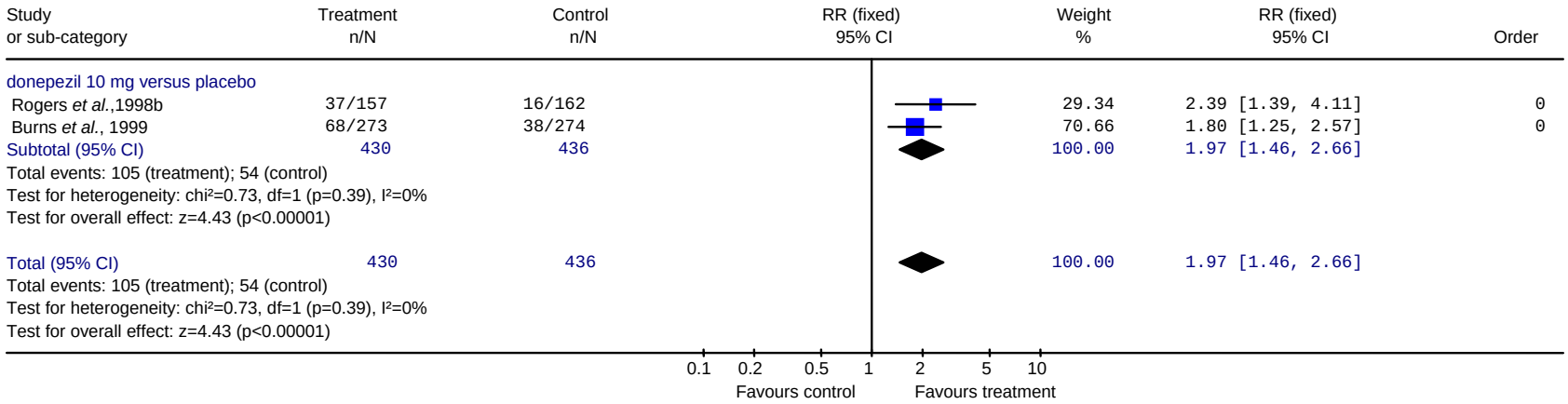


Figure 20: Pooled data for patients improvement (success rate <4); donepezil 5 mg at 24 weeks



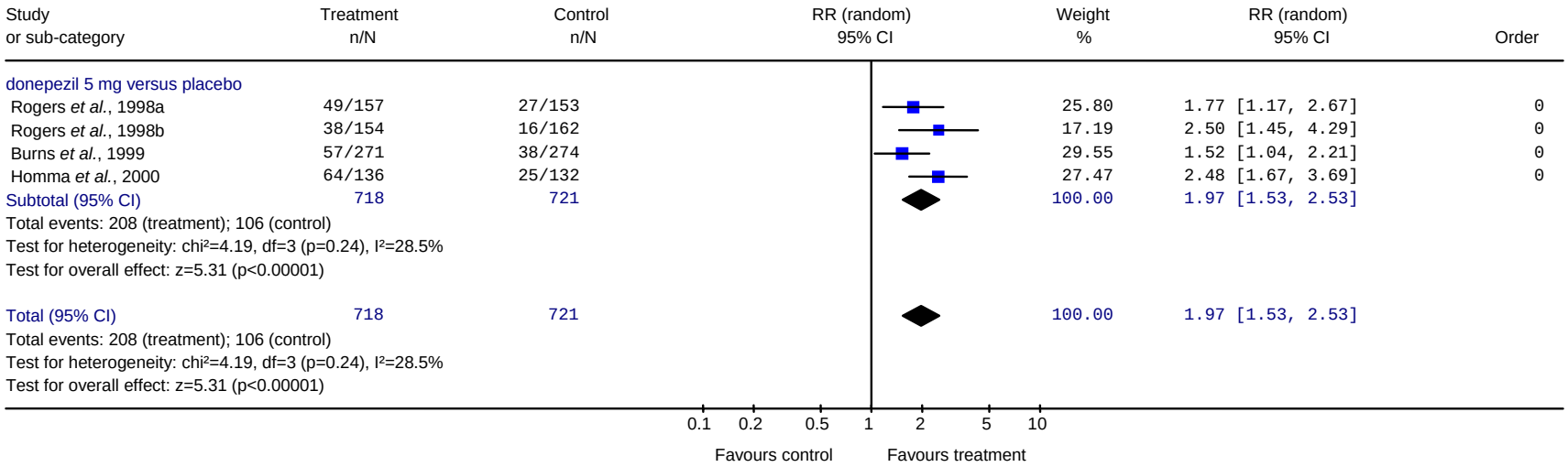
NNT=7 (95% CI: 5; 10)

Figure 21: Pooled data for patients improvement (success rate <4); donepezil 10 mg at 24 weeks



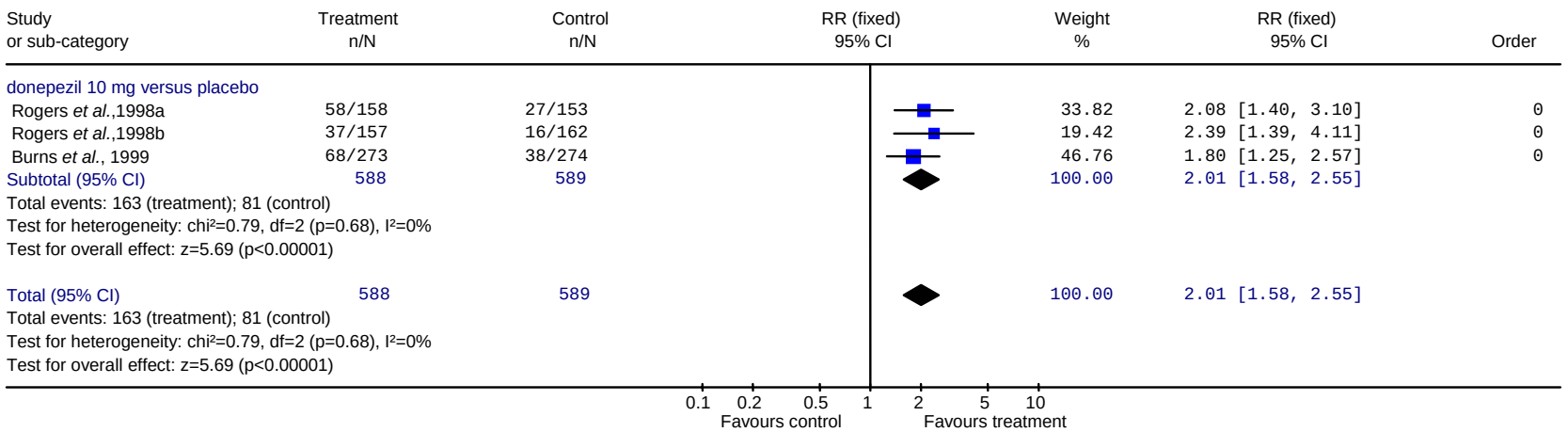
NNT=8 (95% CI: 6; 14)

Figure 22: Pooled data for patients improvement (success rate <4); donepezil 5 mg at endpoint at 12 weeks and 24 weeks combined



NNT=7 (95% CI: 5; 10)

Figure 23: Pooled data for patients improvement (success rate <4); donepezil 10 mg at endpoint at 12 weeks and 24 weeks combined



NNT=7 (95% CI: 5; 11)

Figure 24: Pooled data for patients improvement (success rate <5) with donepezil 5 mg to 10 mg at endpoint at 12 weeks and 24 weeks combined

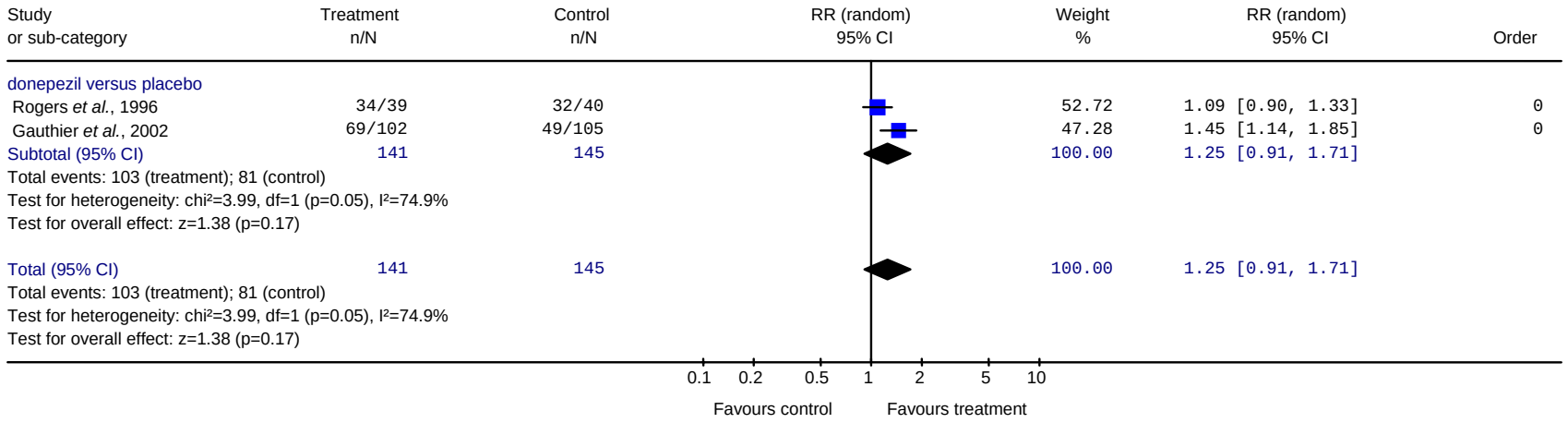


Figure 25: Pooled data for CIBC-plus/CGIC final scores; galantamine 24 mg at endpoint at 20 weeks to 24 weeks combined

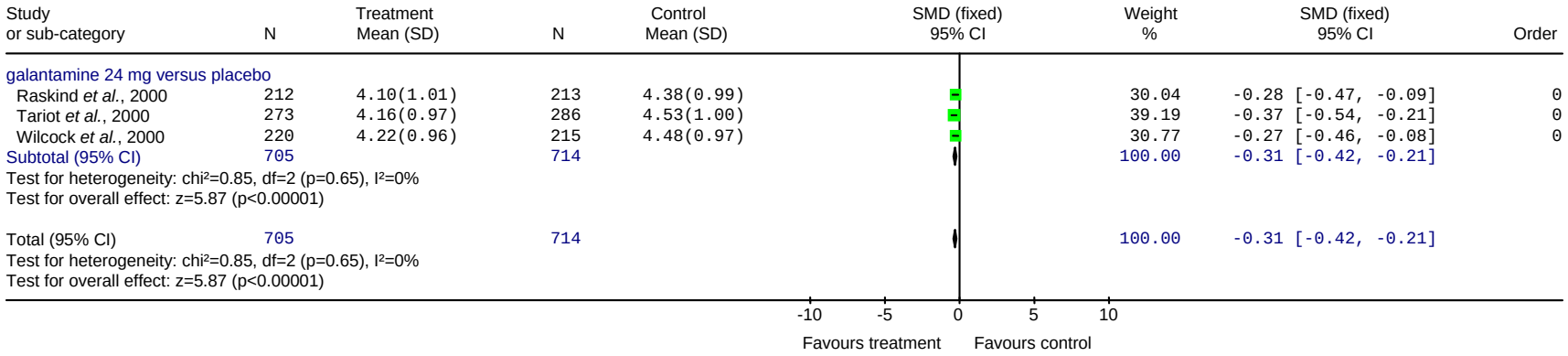


Figure 26: Pooled data for CIBC-plus/CGIC final scores; galantamine 32 mg at 24 weeks

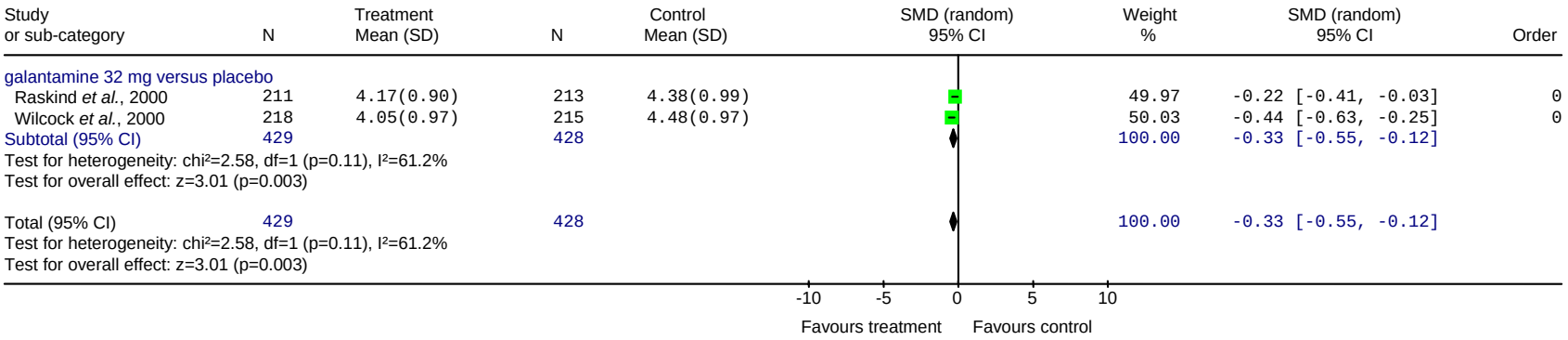


Figure 27: Pooled data for patients' improvement (success rate <4); galantamine 24 mg to 32 mg at 12 weeks

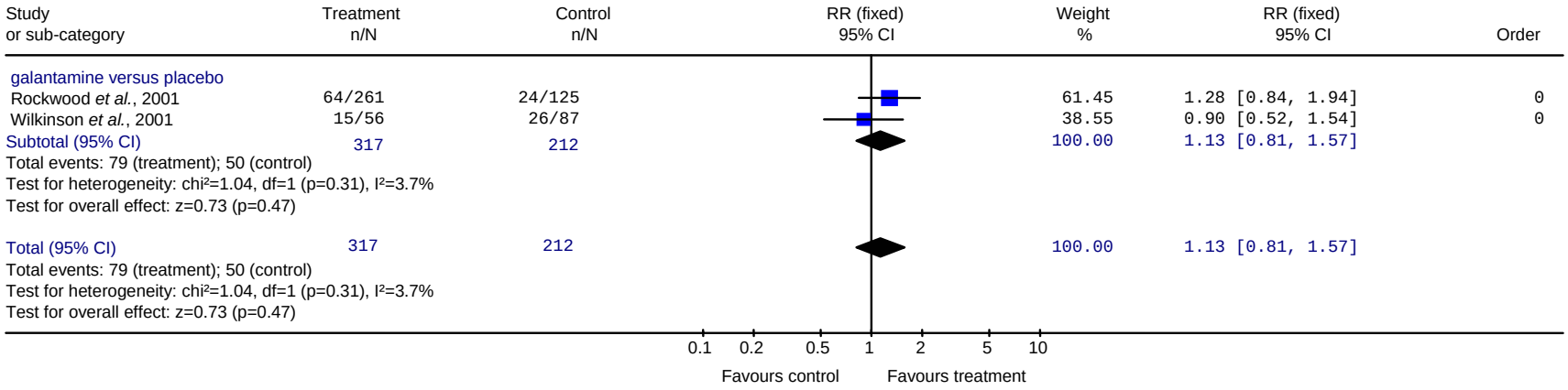


Figure 28: Pooled data for patients' improvement (success rate <4); galantamine 24 mg at 24 weeks

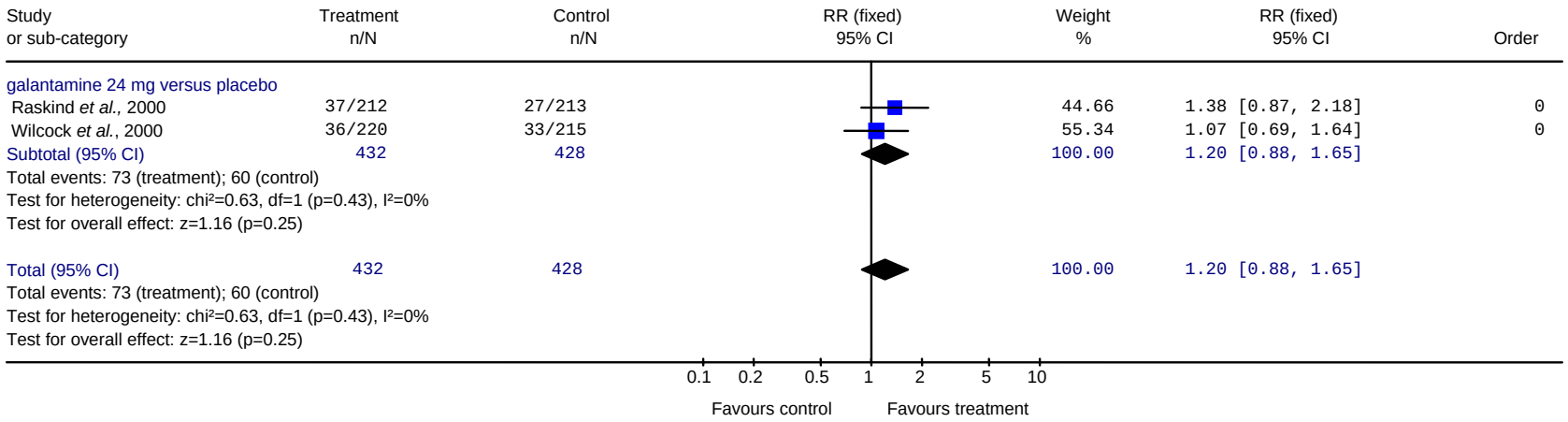


Figure 29: Pooled data for patients' improvement (success rate <4); galantamine 32 mg at 24 weeks

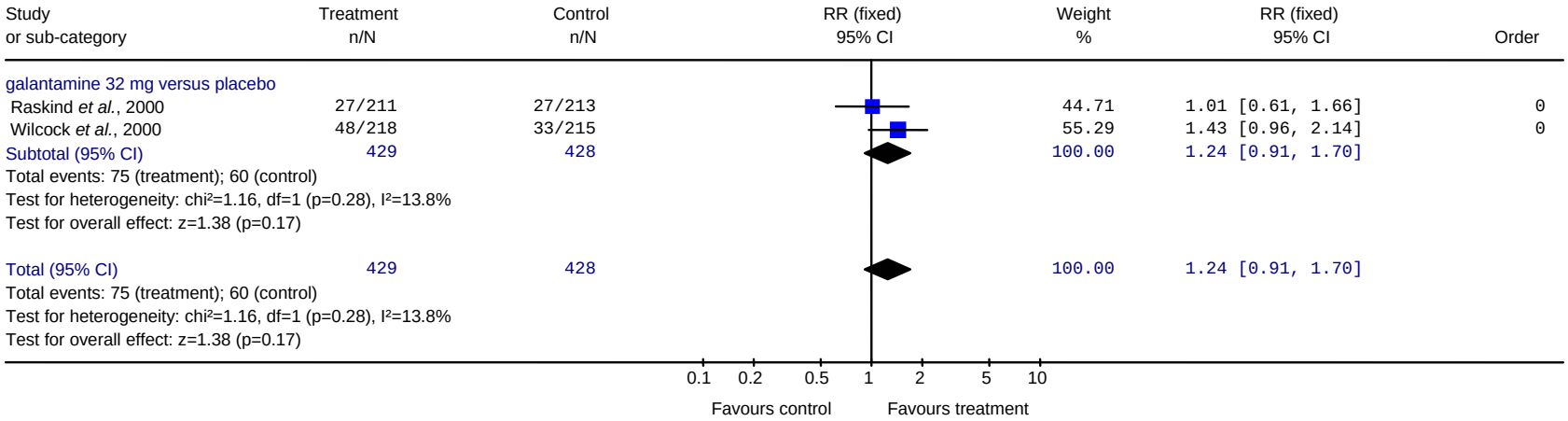


Figure 30: Pooled data for patients' improvement (success rate <4); galantamine 24 mg to 32 mg at endpoint at 12 weeks and 24 weeks combined

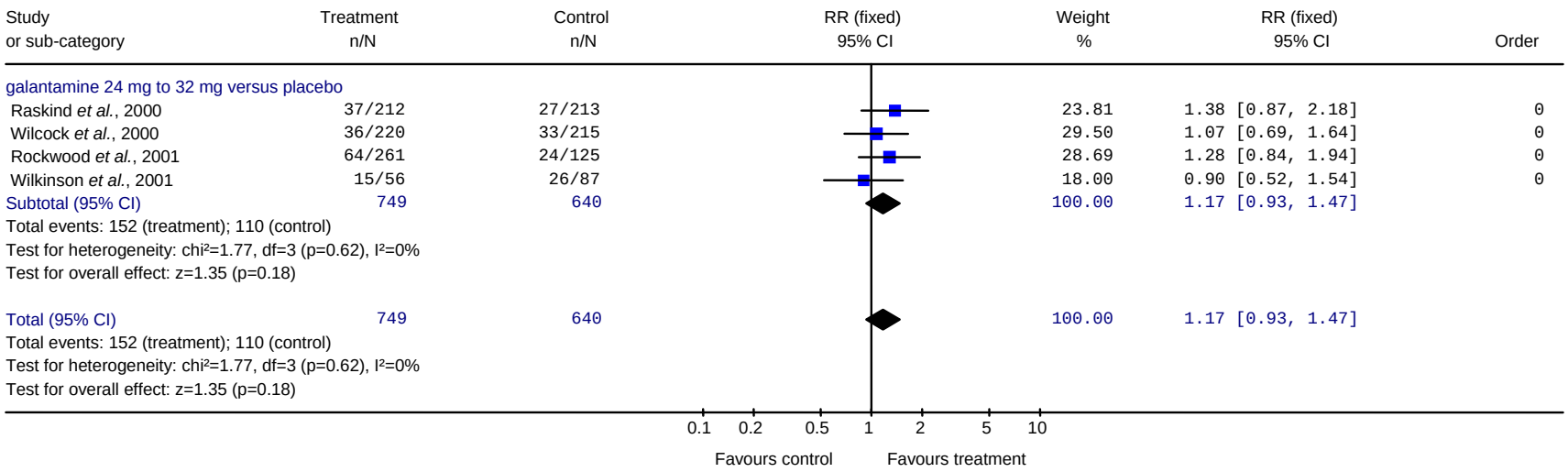
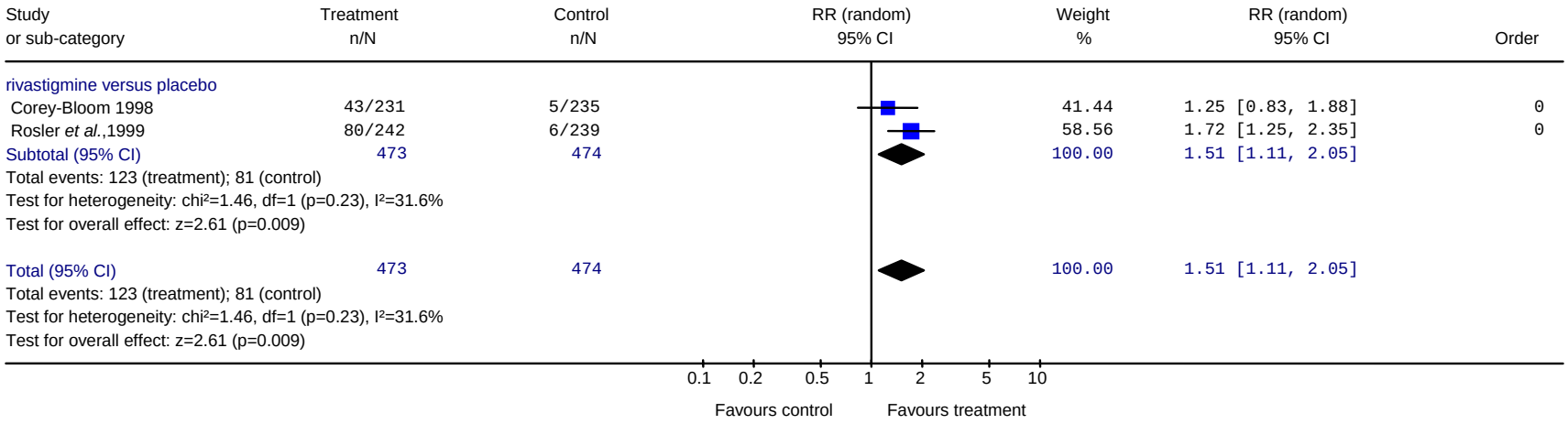
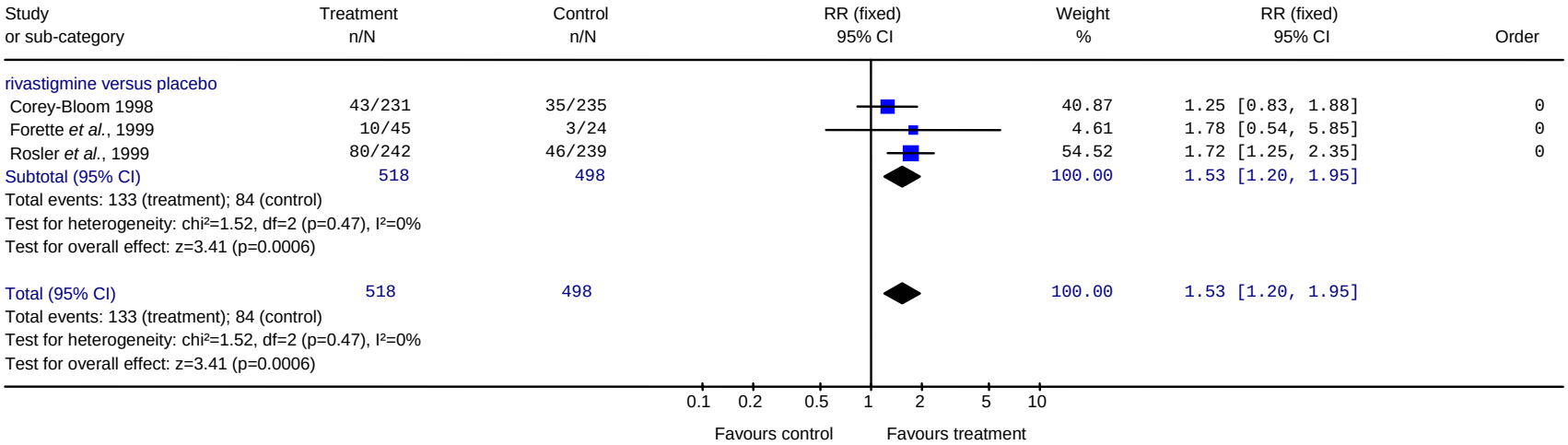


Figure 31: Pooled data for patients' improvement (success rate <4); rivastigmine 6 mg to 12 mg at 26 weeks



NNT=11 (95% CI: 7; 27)

Figure 32: Pooled data for patients' improvement (success rate <4); rivastigmine 6 mg to 12 mg at endpoint at 18 weeks and 26 weeks combined



NNT=11 (95% CI: 7; 26)

Figure 33: Pooled data for QoL-P; donepezil 5 mg at 12 weeks

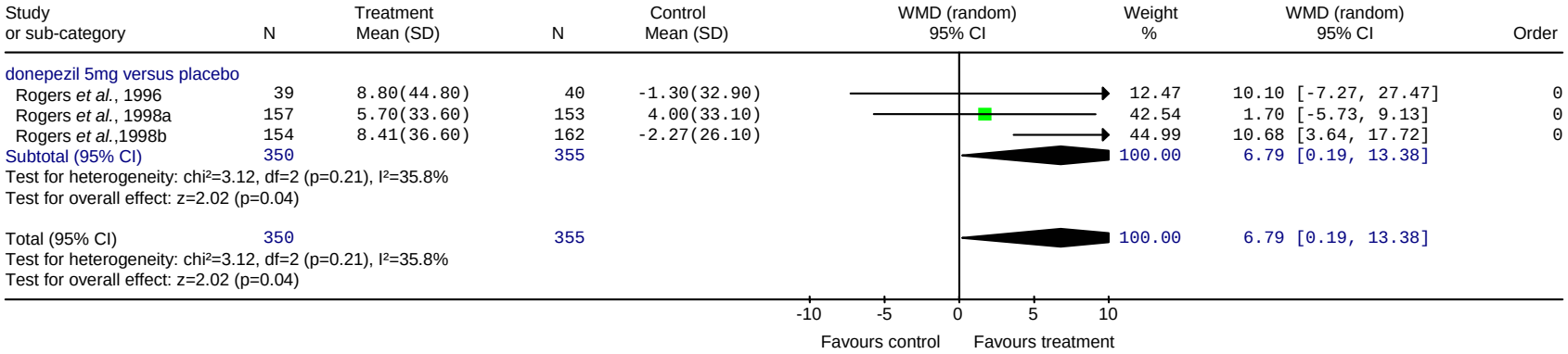


Figure 34: Pooled data for QoL-P; donepezil 10 mg at 12 weeks

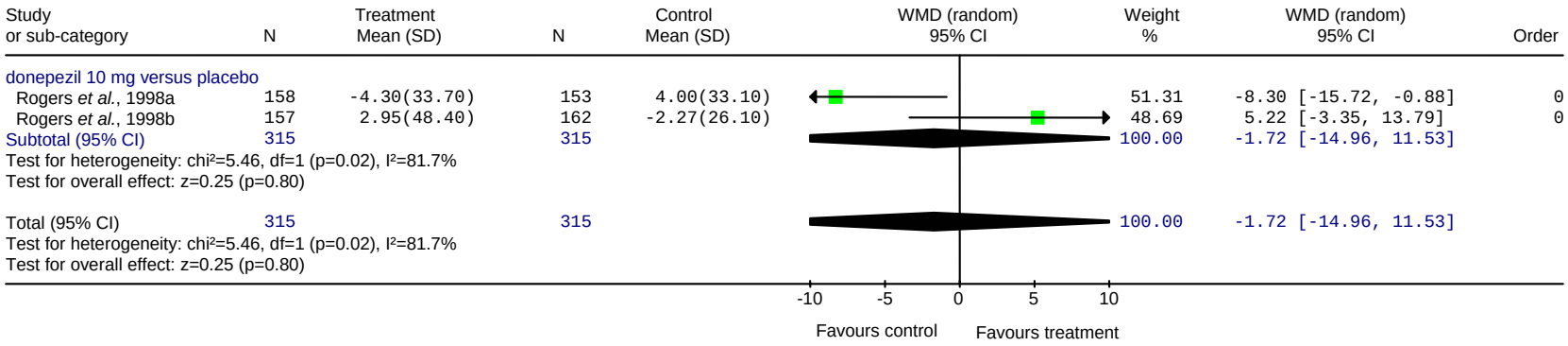


Figure 35: Pooled data for institutionalization; donepezil 5 mg to 10 mg versus placebo at 12 weeks, 48 weeks and 54 weeks combined

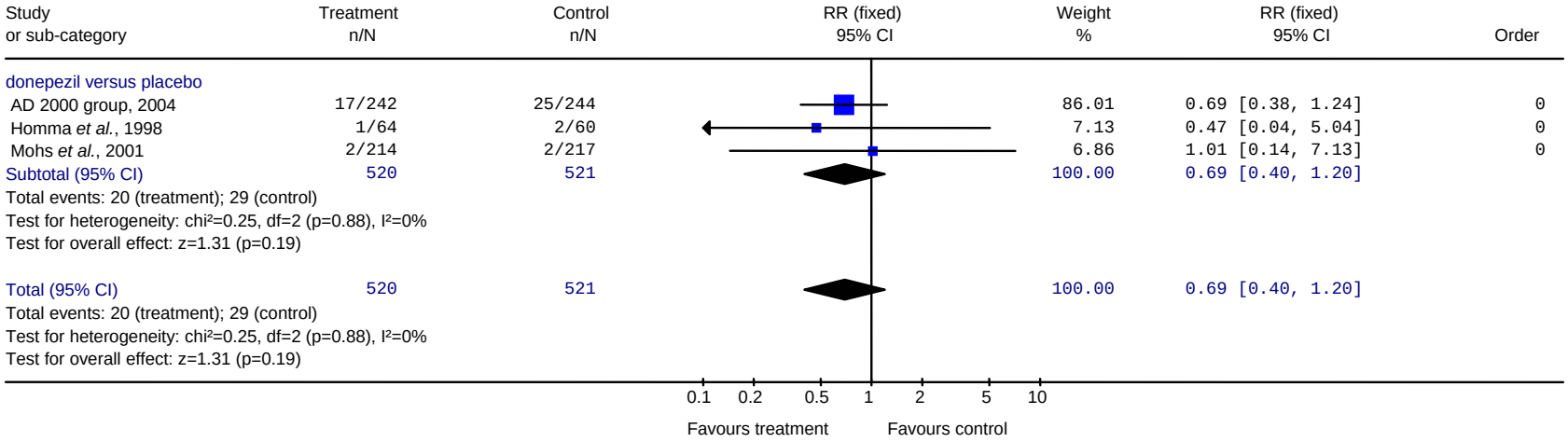


Figure 36: Pooled data for institutionalization; donepezil 5 mg to 10 mg versus placebo at 48 weeks and 52 weeks combined

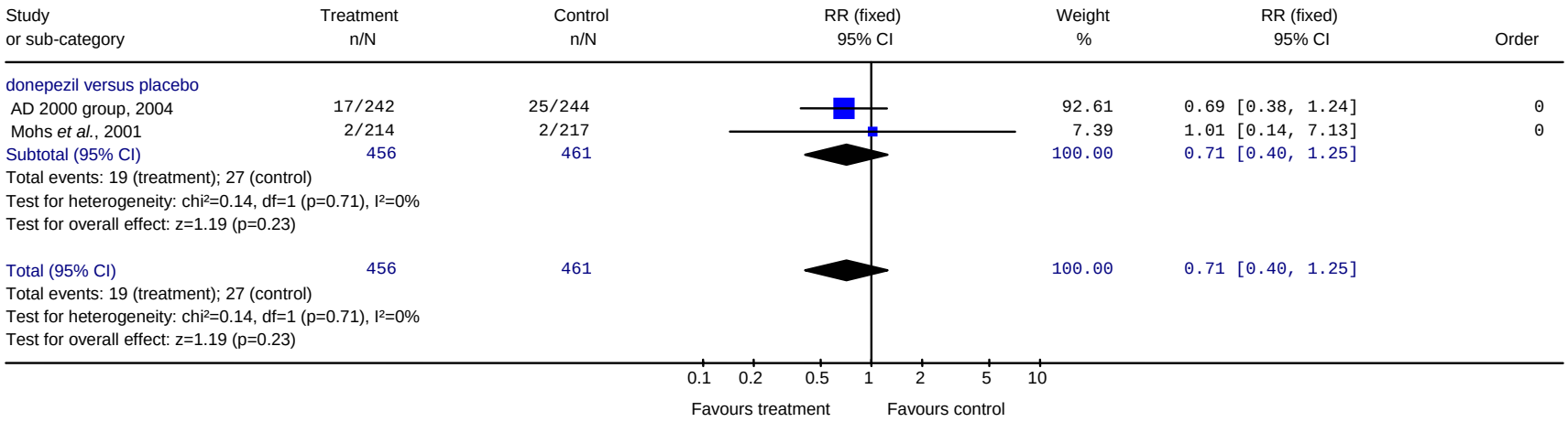


Figure 37: Pooled data for discontinuation rates; donepezil 5 mg at 12 weeks

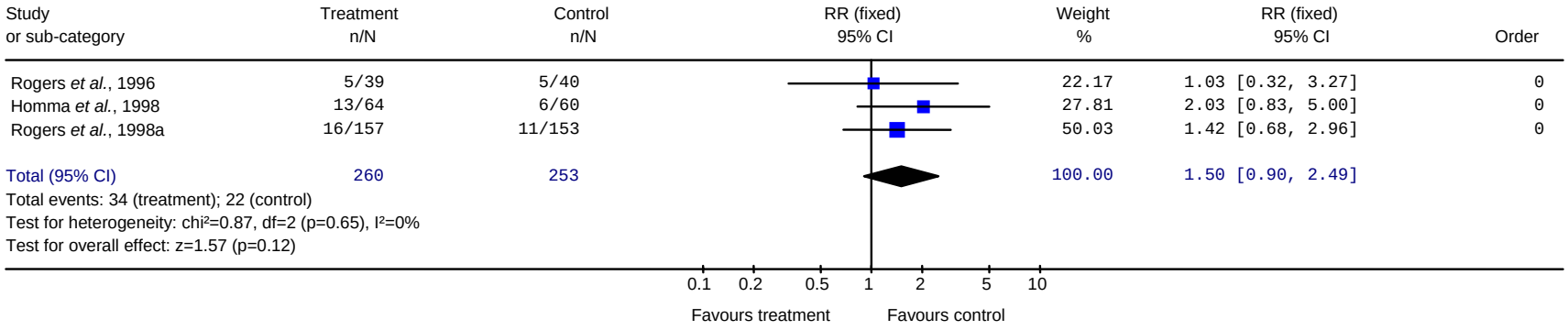


Figure 38: Pooled data for discontinuation rates; donepezil 5 mg at 24 weeks

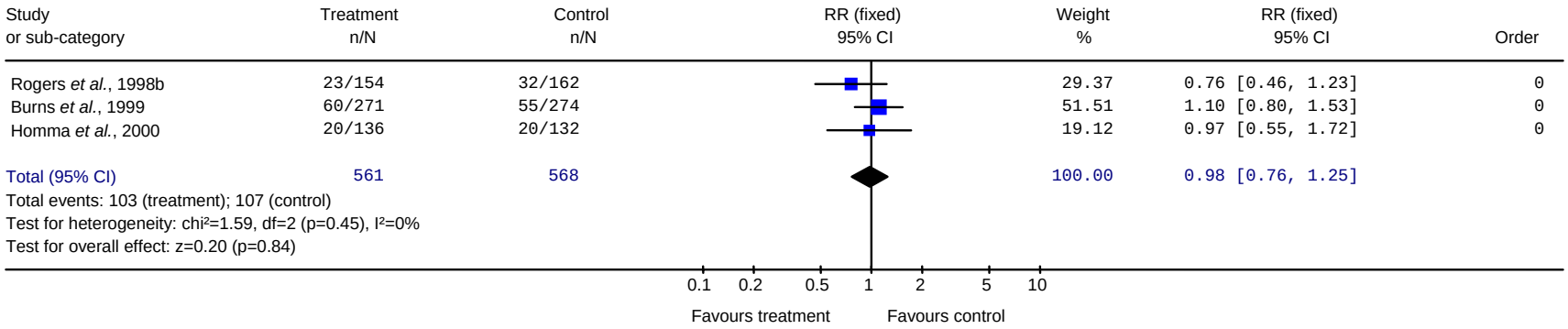


Figure 39: Pooled data for discontinuation rates; donepezil 5 mg at endpoint at 12 weeks, 24 weeks and 54 weeks combined

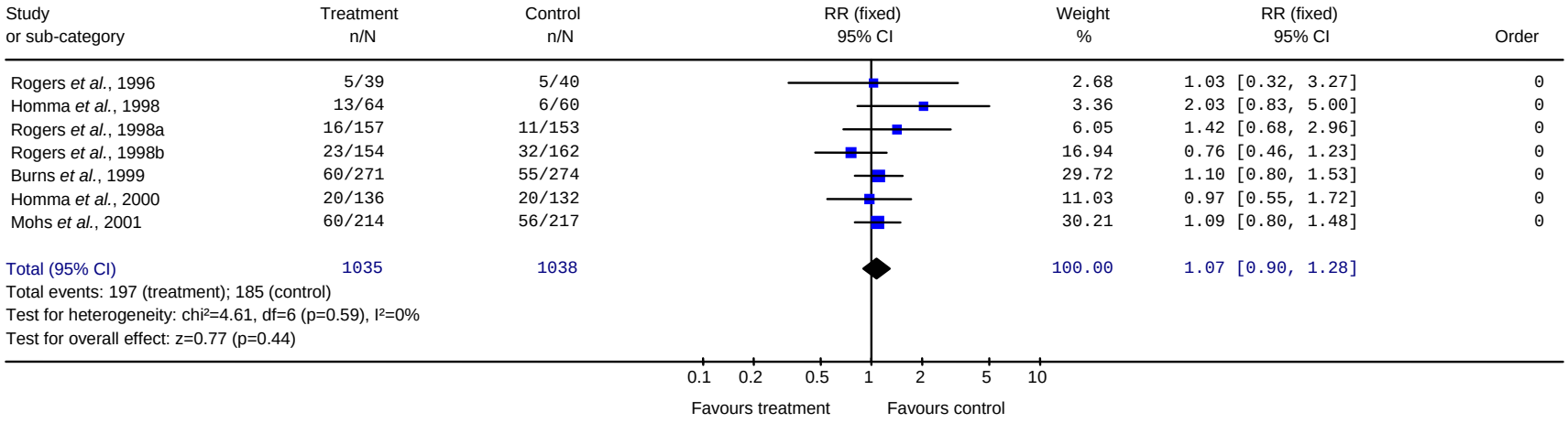


Figure 40: Pooled data for discontinuation rates; donepezil 10 mg at 24 weeks

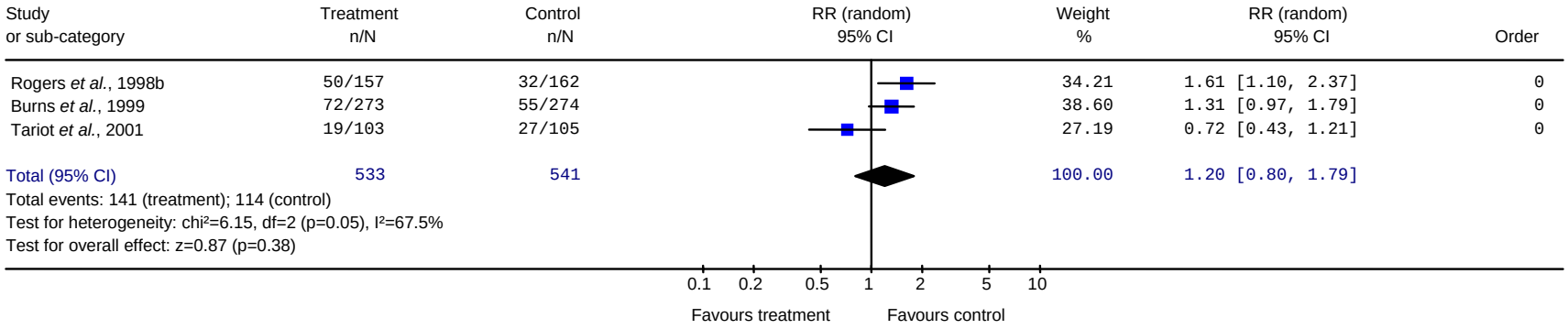


Figure 41: Pooled data for discontinuation rates; donepezil 10 mg at endpoint at 12 weeks and 24 weeks combined

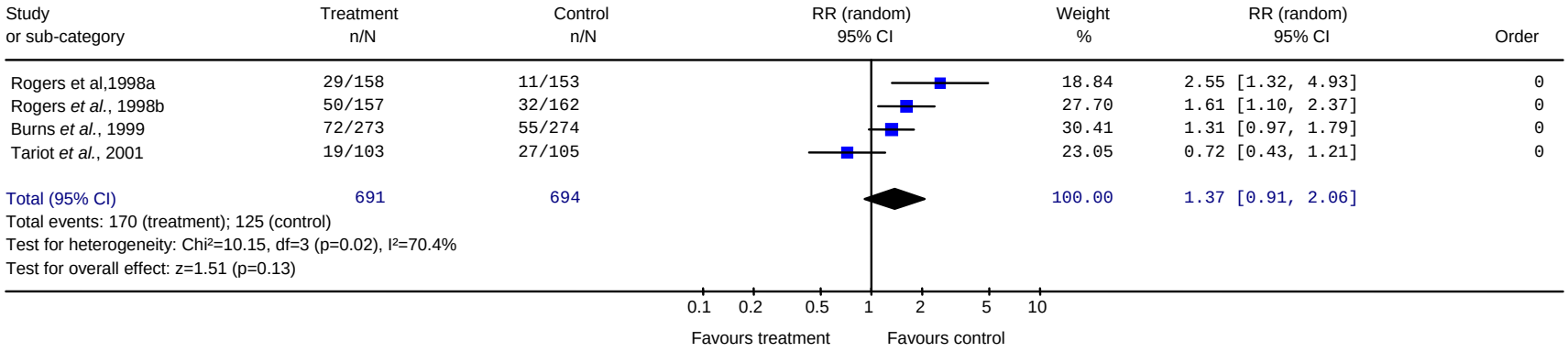


Figure 42: Pooled data for discontinuation rates; donepezil 5 mg to 10 mg versus placebo at endpoint at 48 weeks to 54 weeks

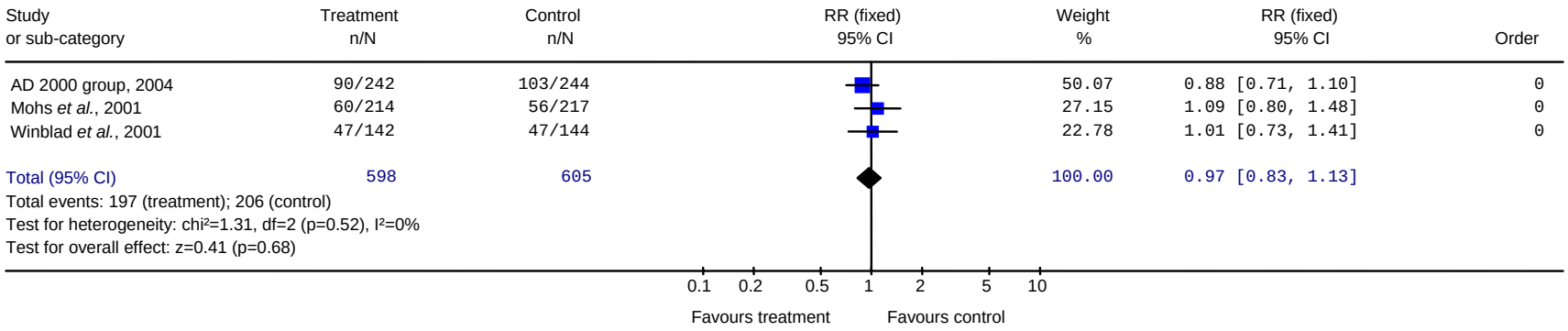
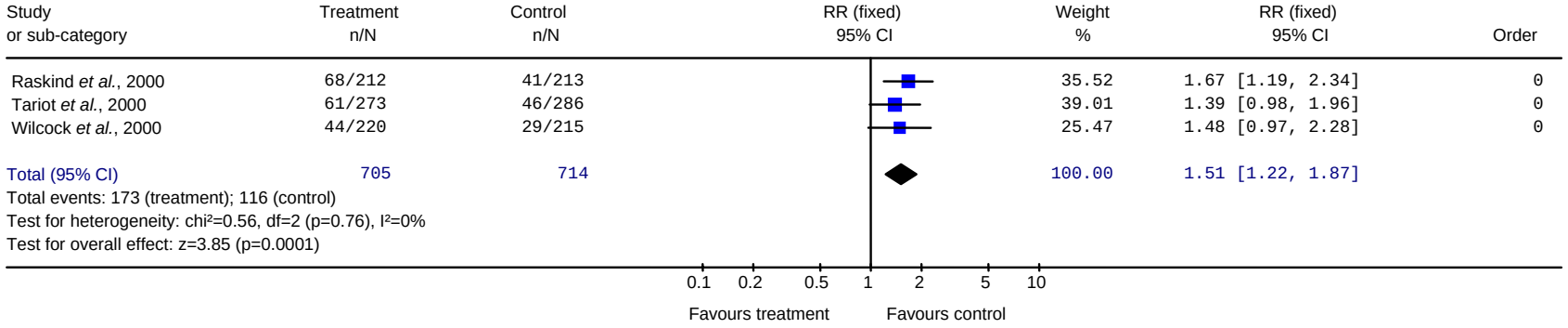
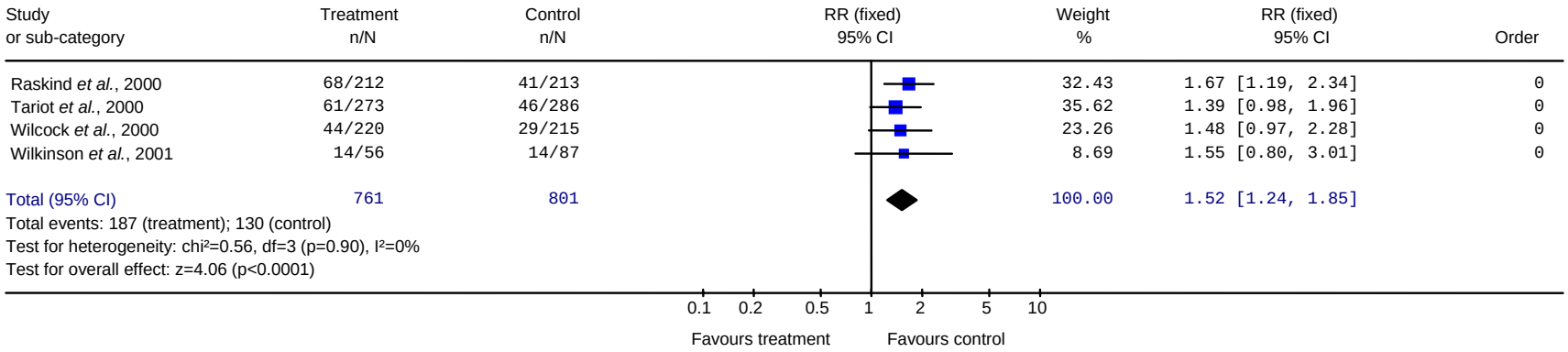


Figure 43: Pooled data for discontinuation rates; galantamine 24 mg at 20 weeks to 24 weeks



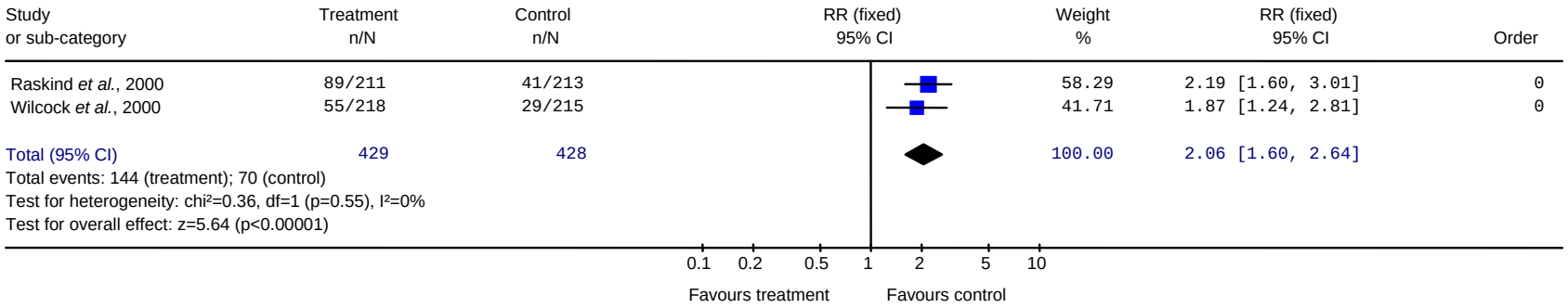
NNH=12 (95% CI: 8; 24)

Figure 44: Pooled data for discontinuation rates; galantamine 24 mg at endpoint at 12 weeks to 24 weeks combined



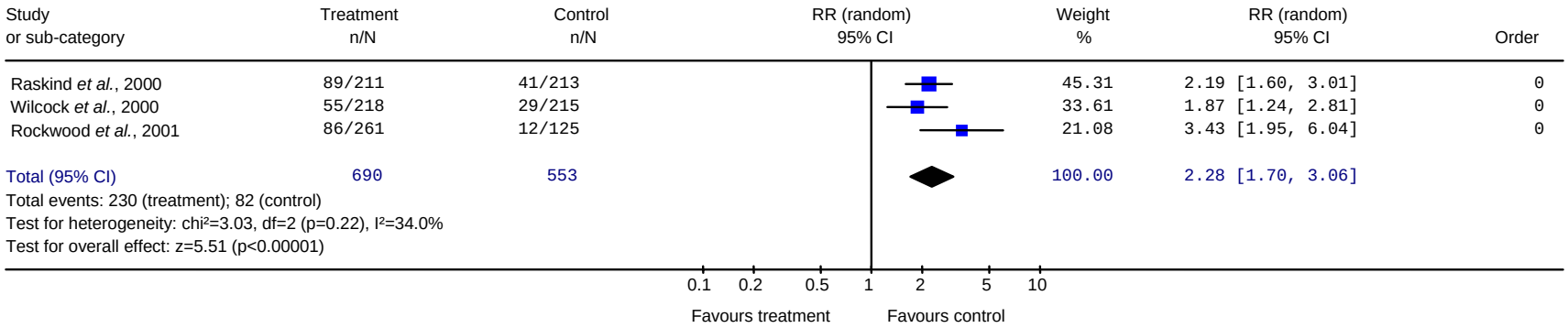
NNH=12 (95% CI: 8; 23)

Figure 45: Pooled data for discontinuation rates; galantamine 32 mg at 24 weeks



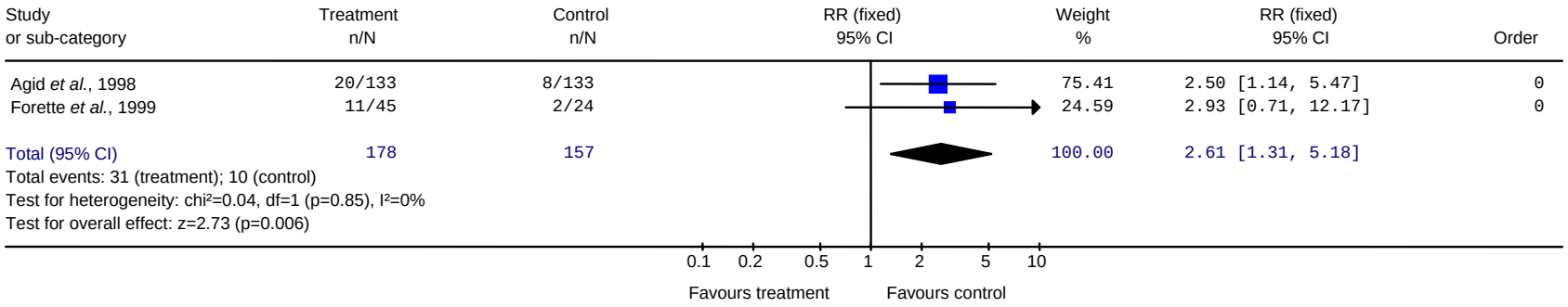
NNH=6 (95% CI: 4; 9)

Figure 46: Pooled data for discontinuation rates; galantamine 32 mg at endpoint at 12 weeks and 24 weeks combined



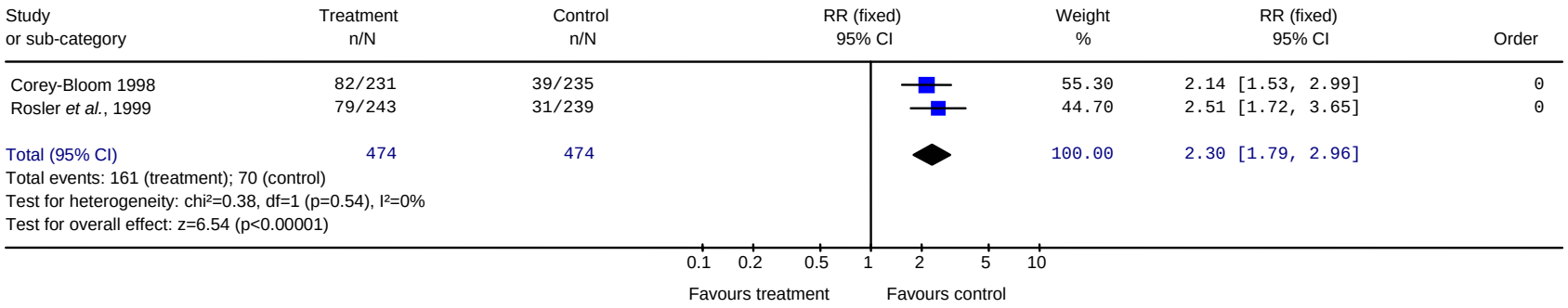
NNH=5 (95% CI: 4; 7)

Figure 47: Pooled data for discontinuation rates; rivastigmine 6 mg to 10 mg at endpoint at 12 weeks to 18 weeks combined



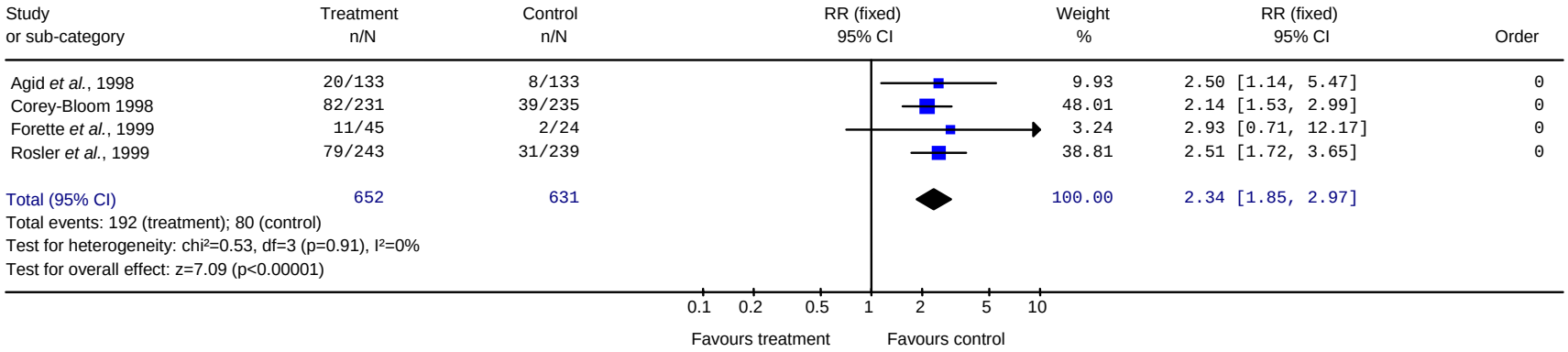
NNH=9 (95% CI: 6; 24)

Figure 48: Pooled data for discontinuation rates; rivastigmine 6 mg to 12 mg at 26 weeks



NNH=4 (95% CI: 3; 4)

Figure 49: Pooled data for discontinuation rates; rivastigmine 6 mg to 12 mg at endpoint at 12 weeks to 26 weeks combined



NNH=6 (95% CI: 5; 8)

Figure 50: Pooled data for discontinuation rates; galantamine 24 mg compared with donepezil 10 mg at endpoint at 12 weeks and 52 weeks combined

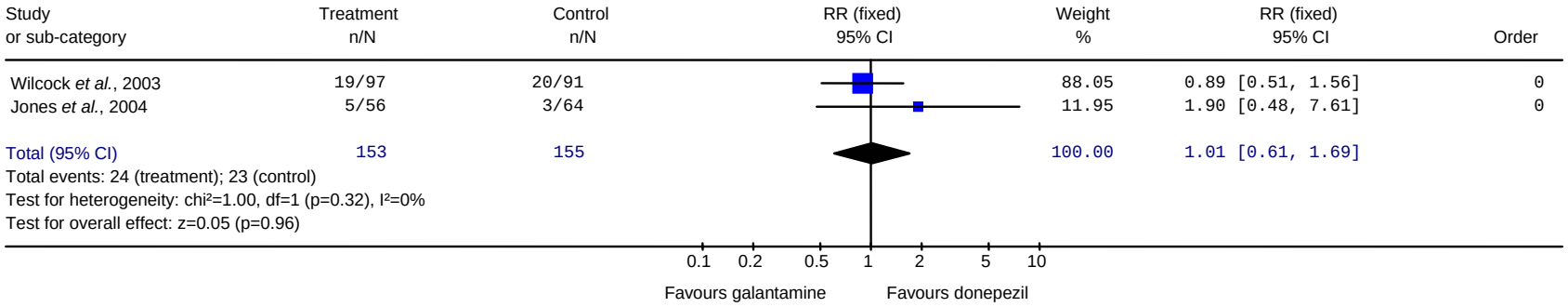


Figure 51: Pooled data for discontinuation rates; rivastigmine 6 mg to 12 mg compared with donepezil 10 mg at endpoint (12 weeks and 16 weeks combined)

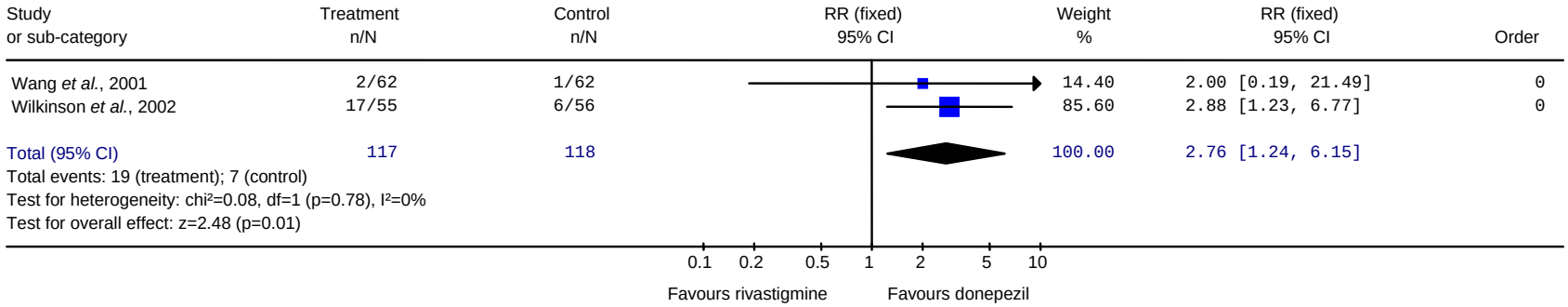


Figure 52: Pooled data for agitation; donepezil versus placebo

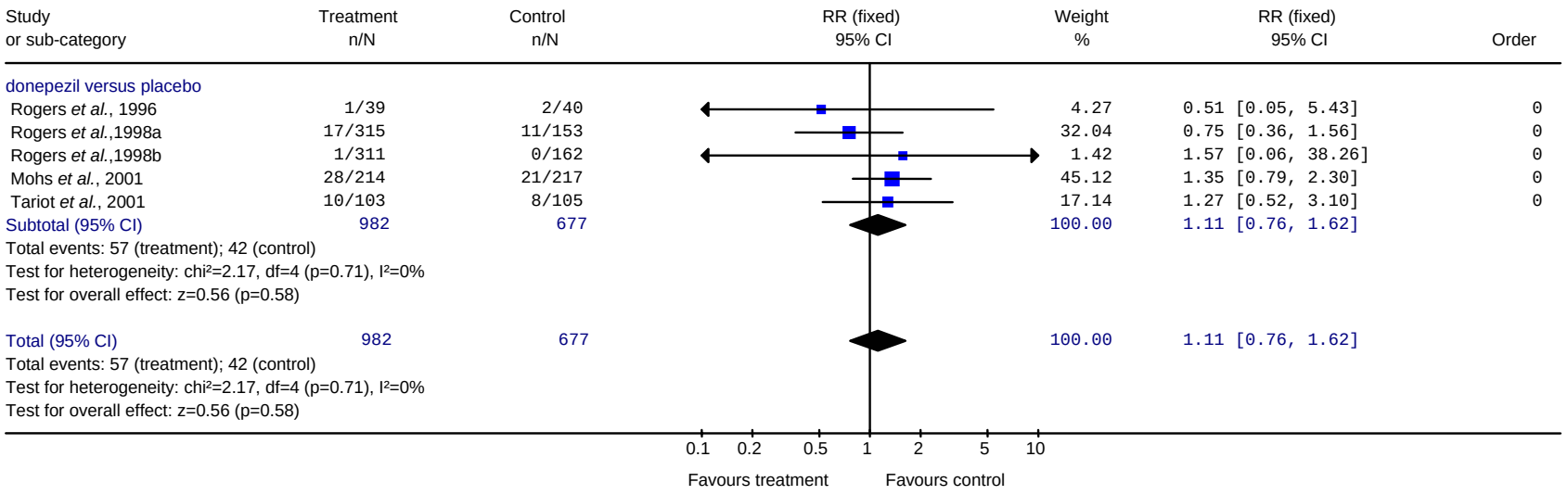


Figure 53: Pooled data for anorexia; donepezil versus placebo

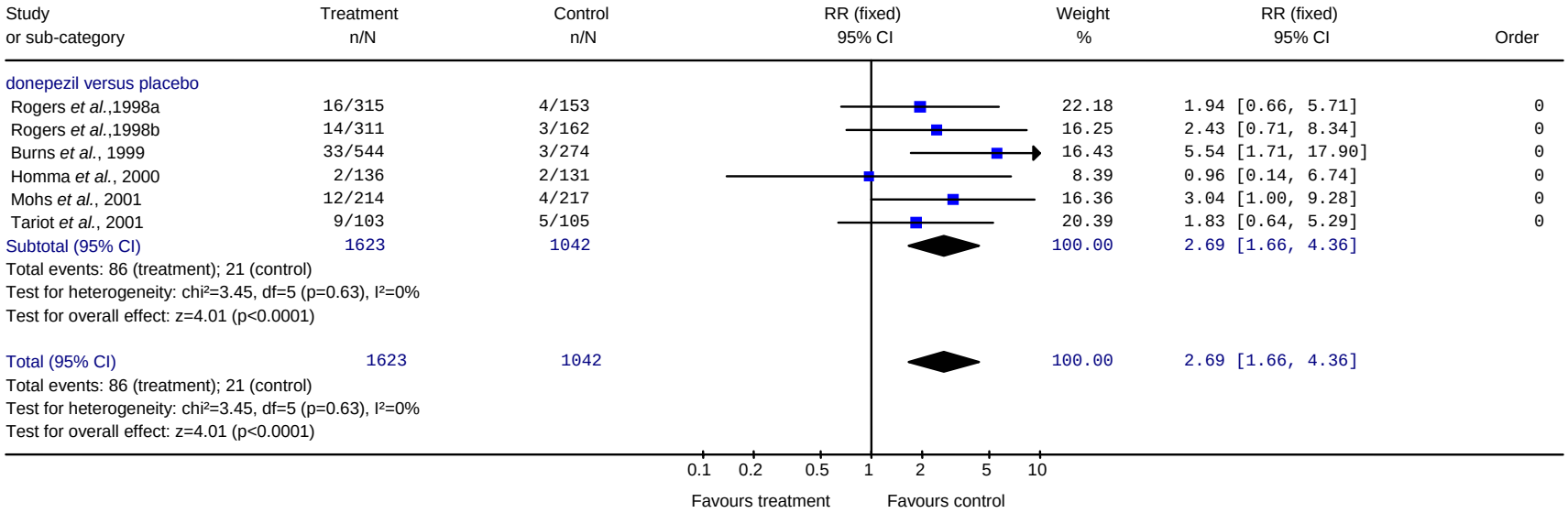


Figure 54: Pooled data for diarrhea; donepezil versus placebo

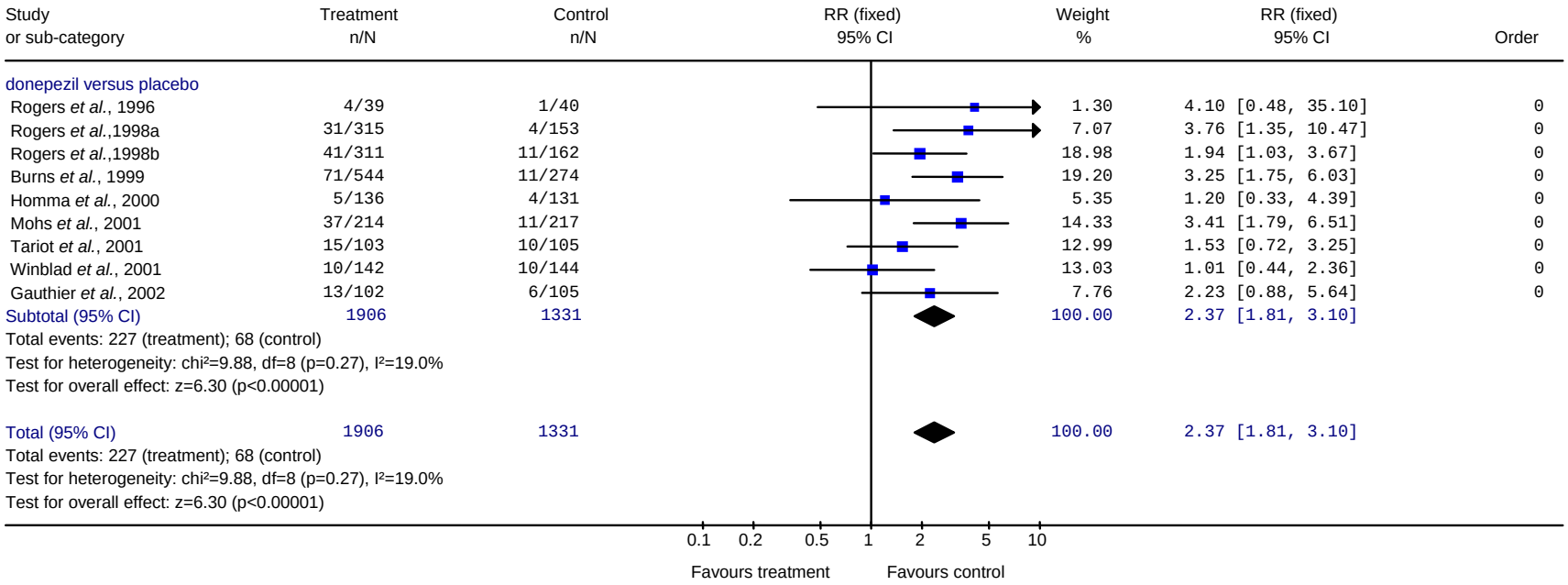


Figure 55: Pooled data for dizziness; donepezil versus placebo

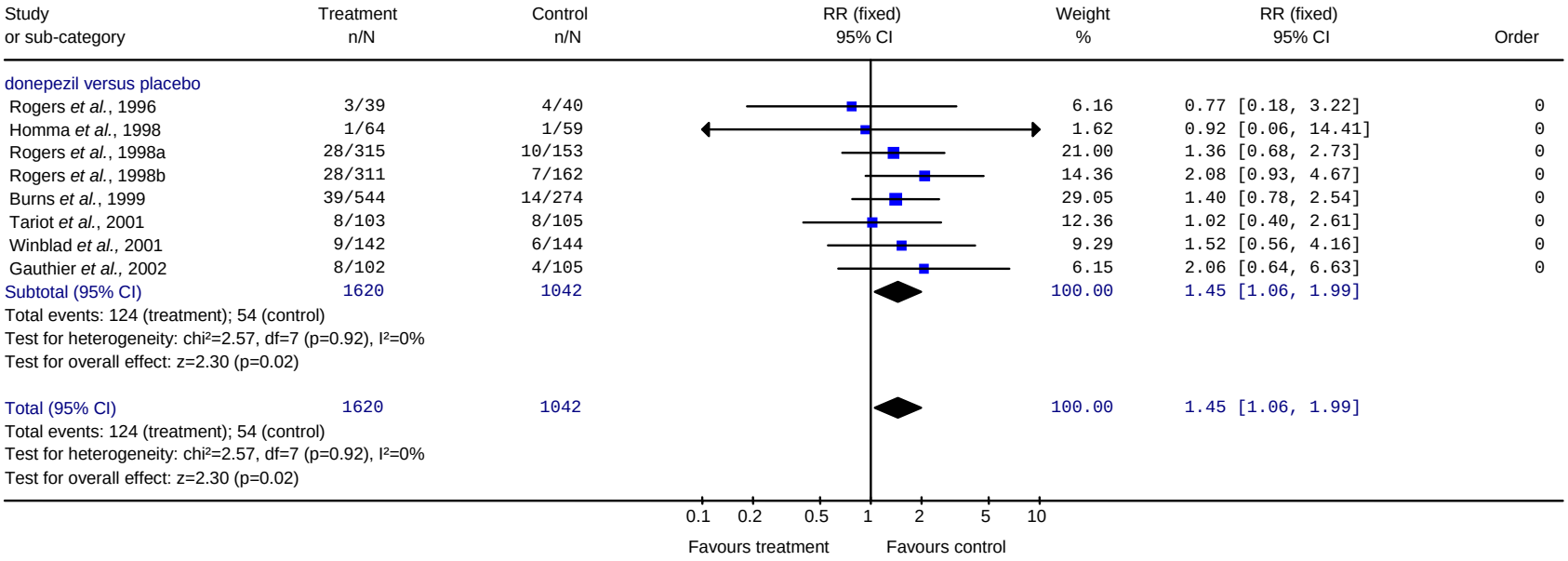


Figure 56: Pooled data for headache; donepezil versus placebo

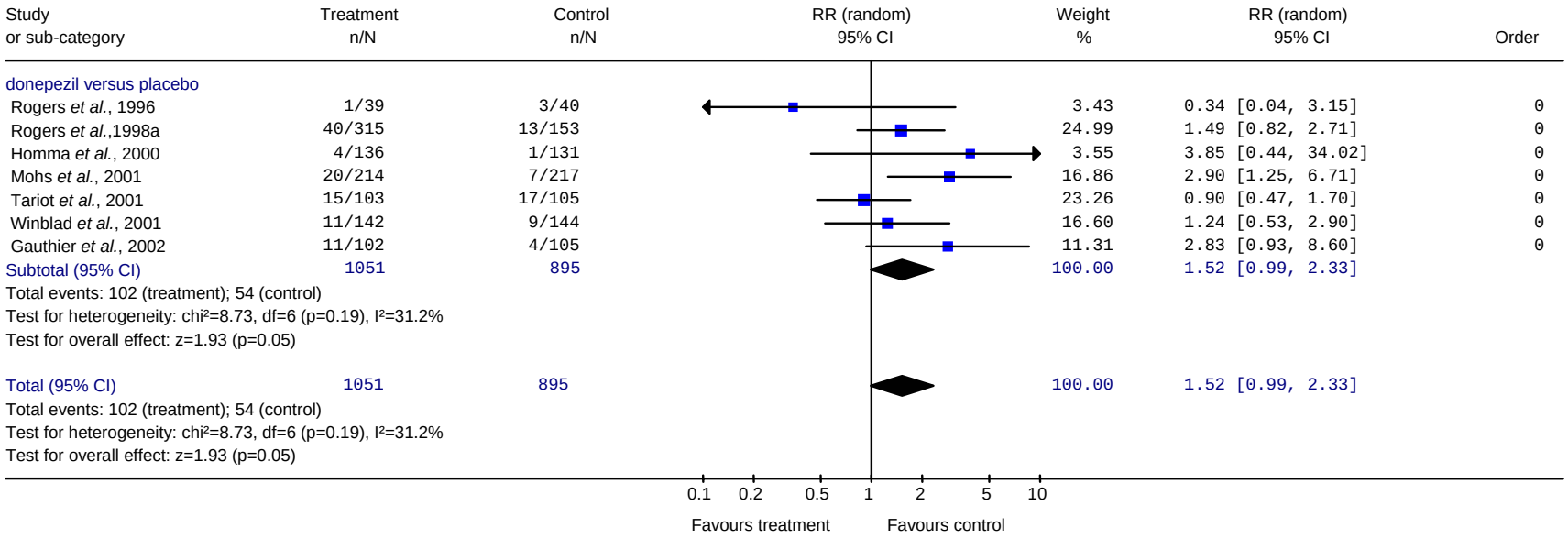


Figure 57: Pooled data for nausea; donepezil versus placebo

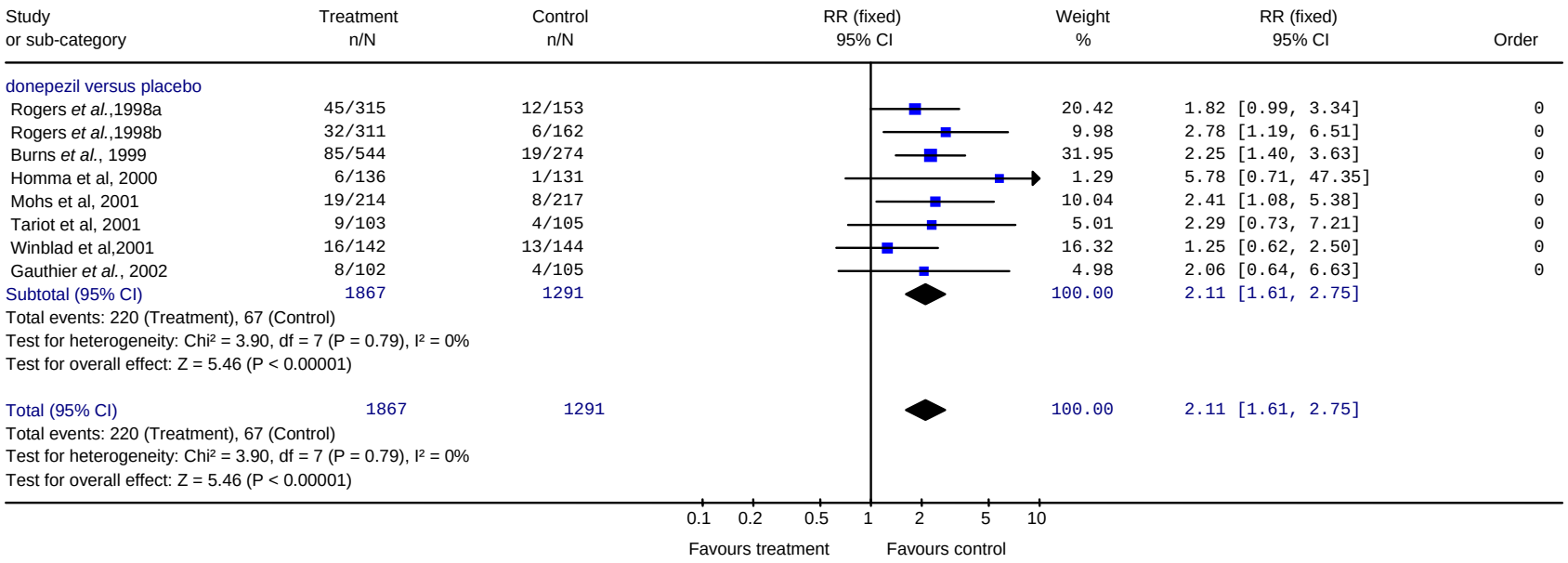


Figure 58: Pooled data for vomiting; donepezil versus placebo

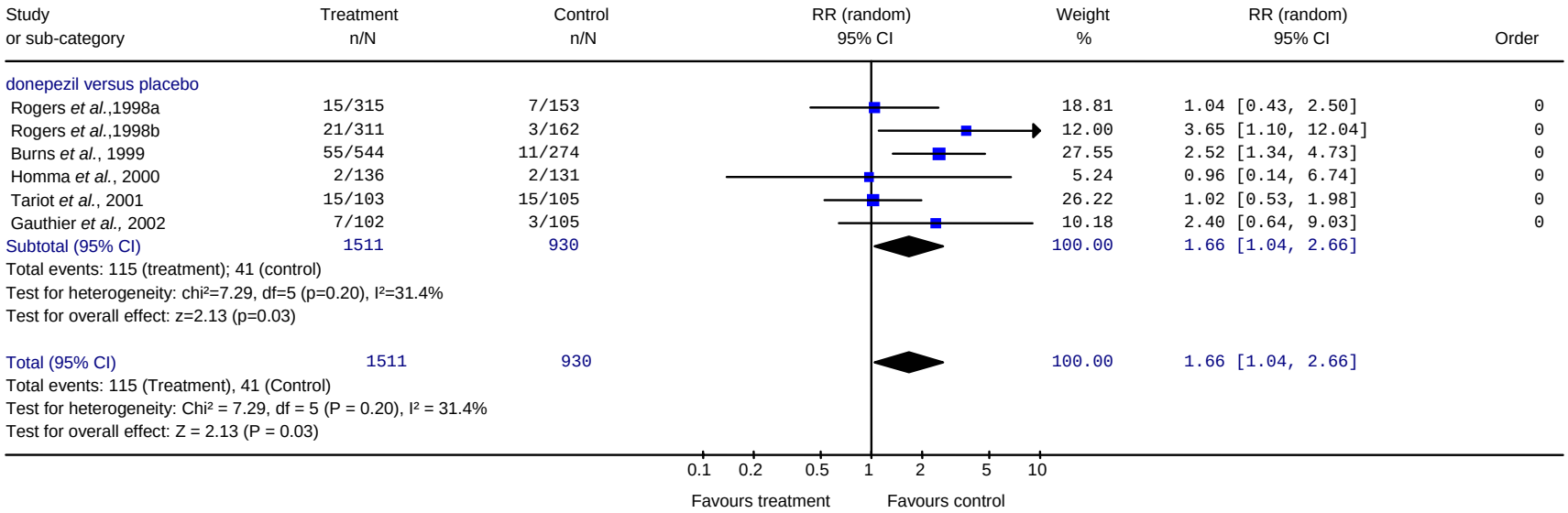


Figure 59: Pooled data for weight loss; donepezil versus placebo

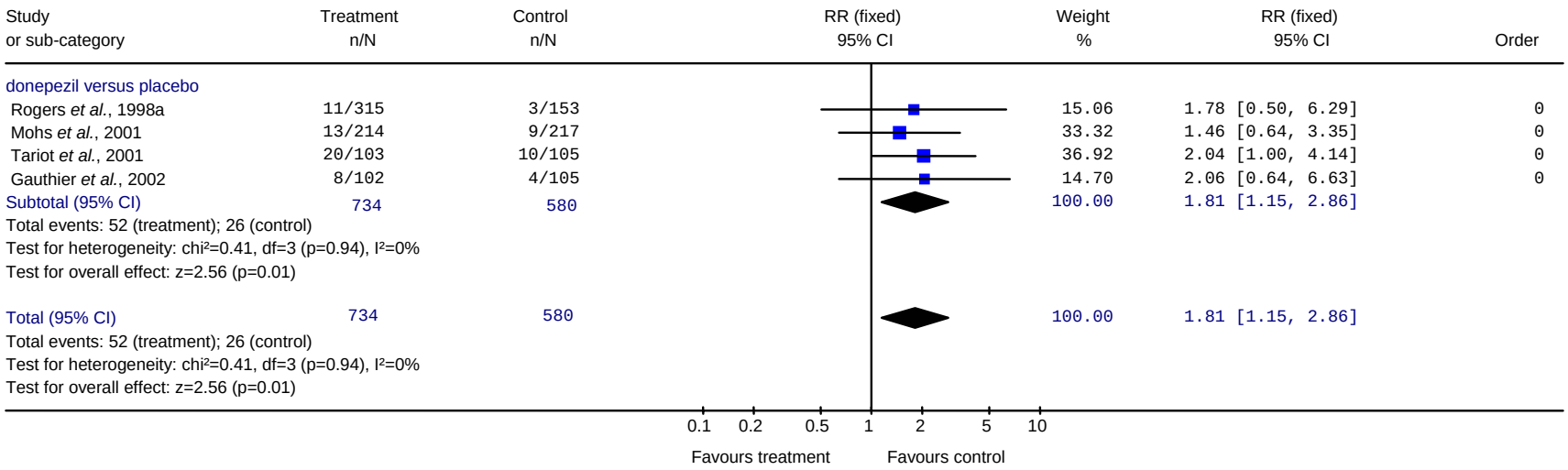


Figure 60: Pooled data for participants with serious AE; donepezil versus placebo

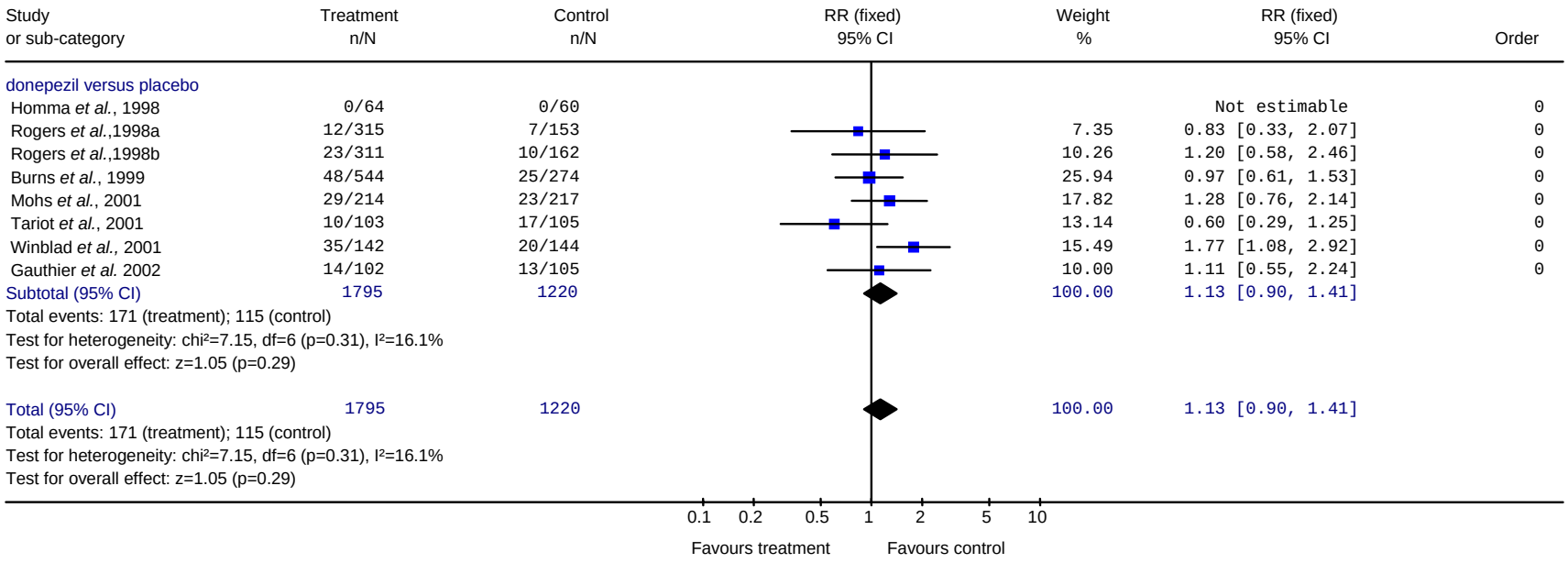


Figure 61: Pooled data for participants withdrawn due to AE; donepezil versus placebo

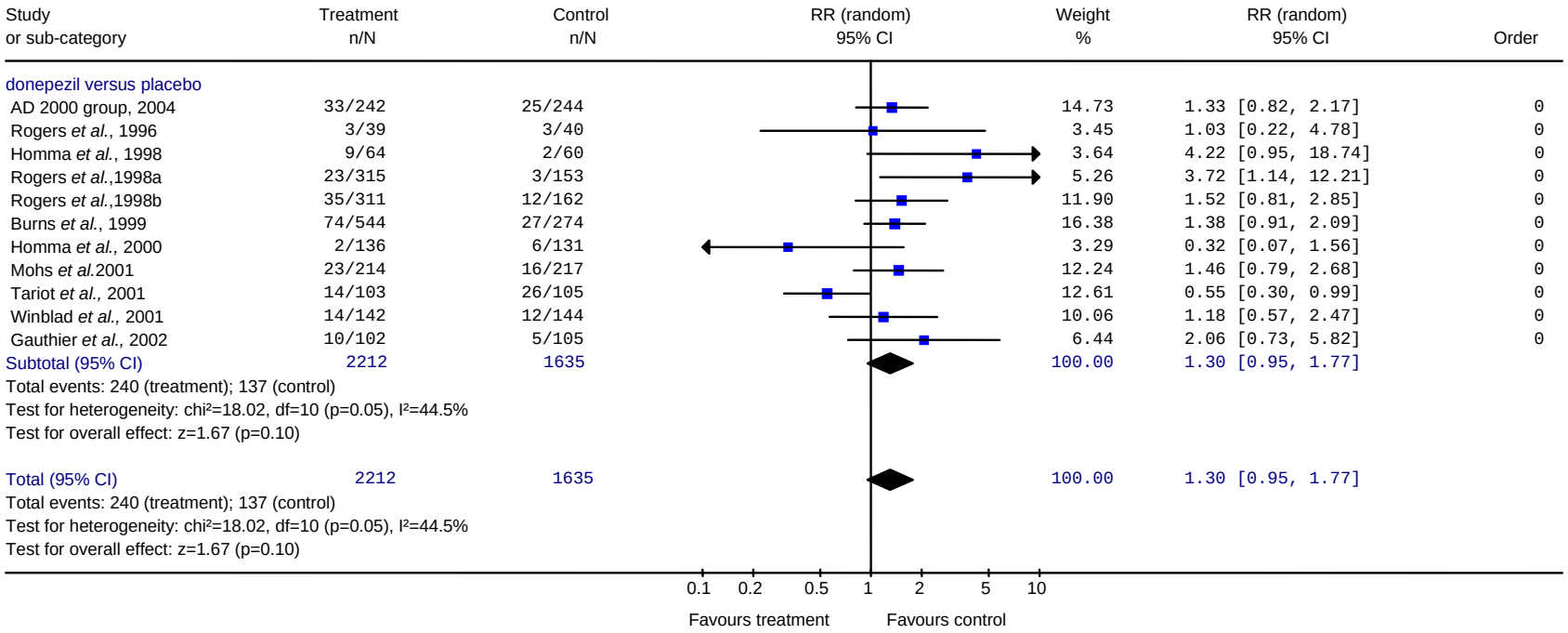


Figure 62: Pooled data for deaths; donepezil versus placebo

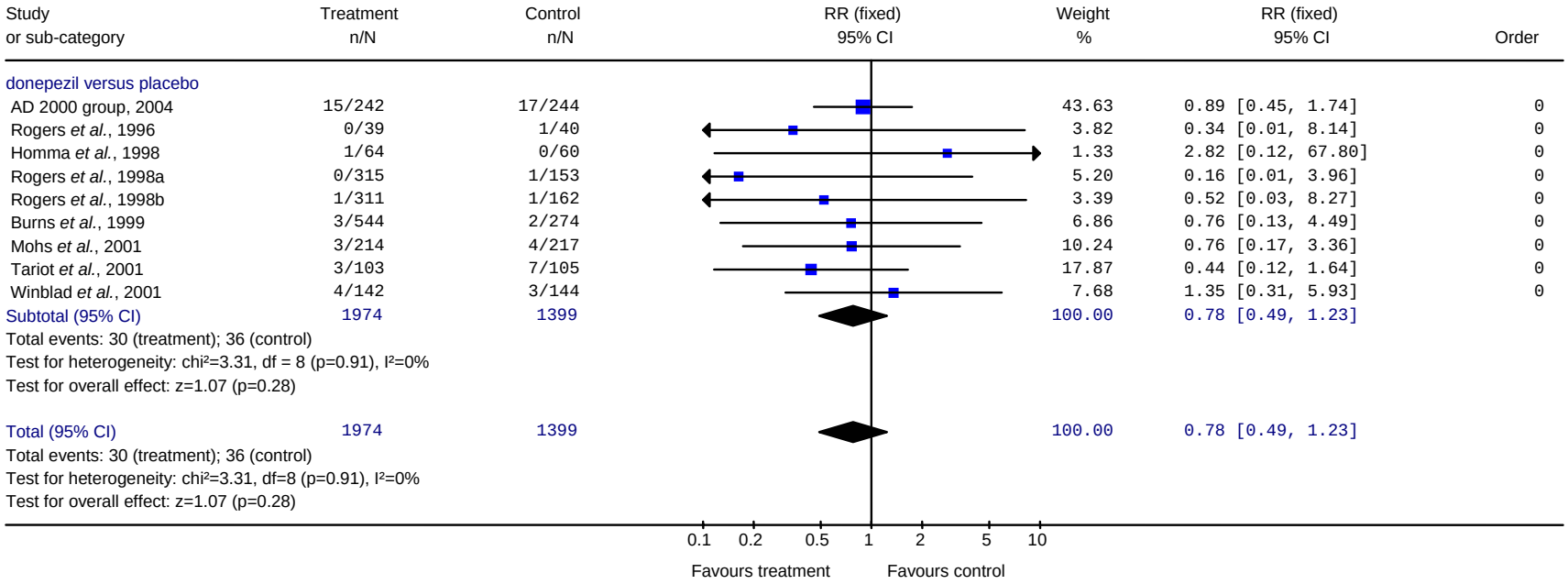


Figure 63: Pooled data for agitation; galantamine versus placebo

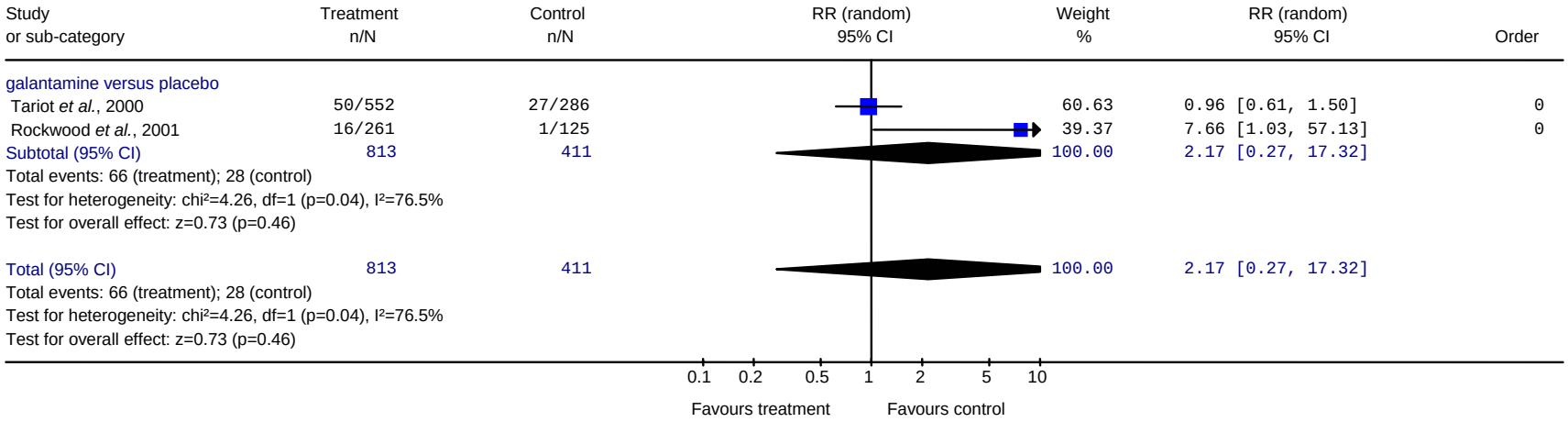


Figure 64: Pooled data for anorexia; galantamine versus placebo

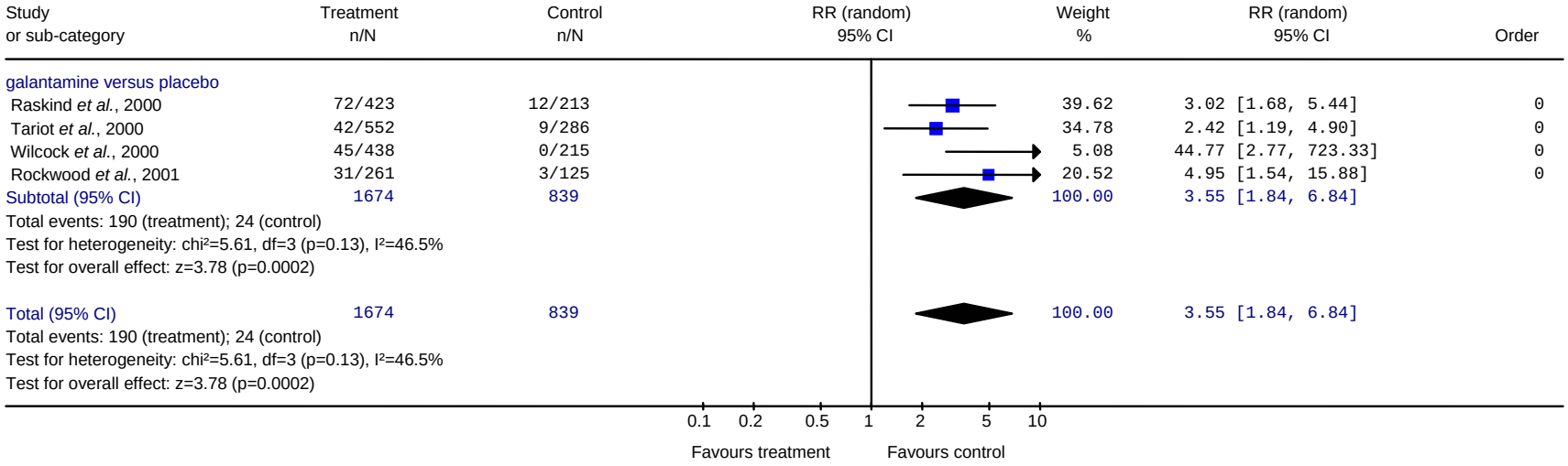


Figure 65: Pooled data for diarrhea; galantamine versus placebo

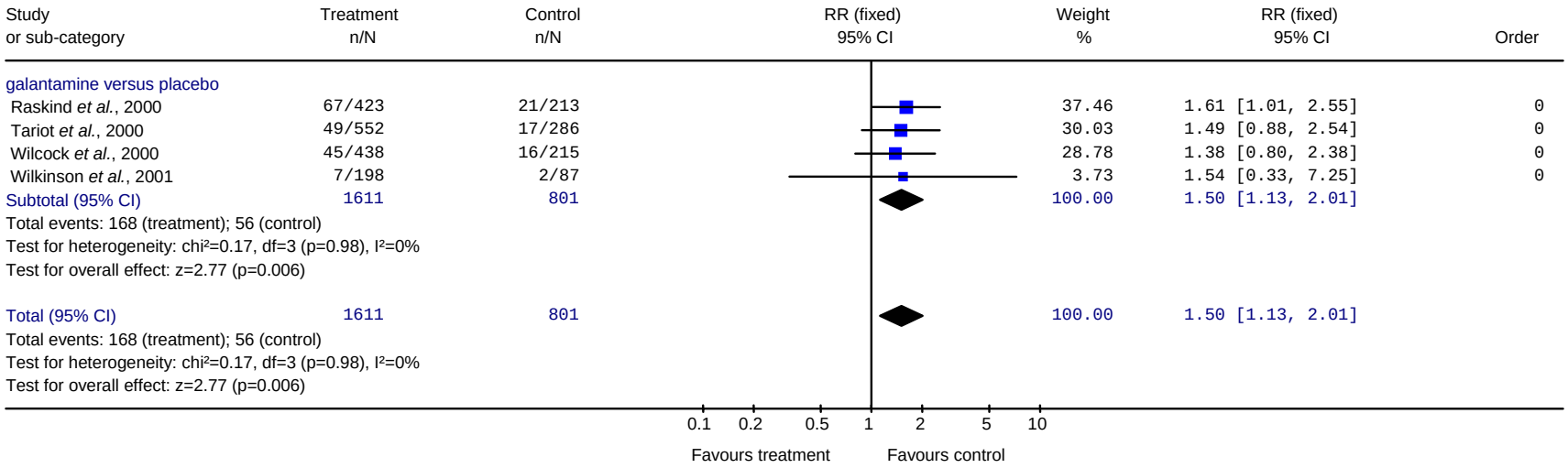


Figure 66: Pooled data for dizziness; galantamine versus placebo

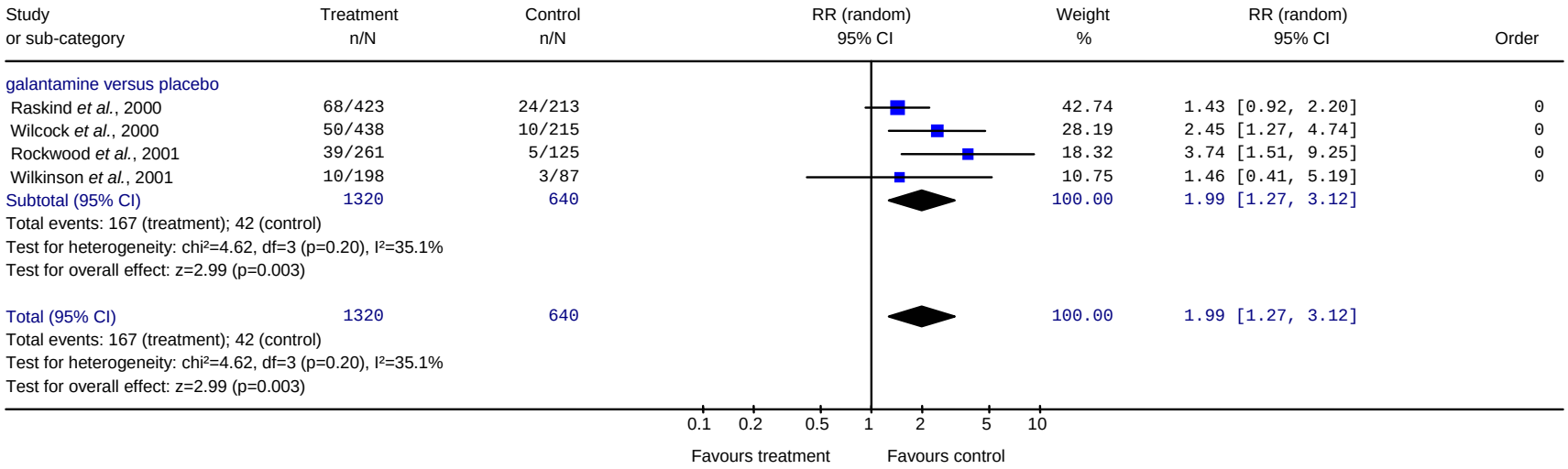


Figure 67: Pooled data for headache; galantamine versus placebo

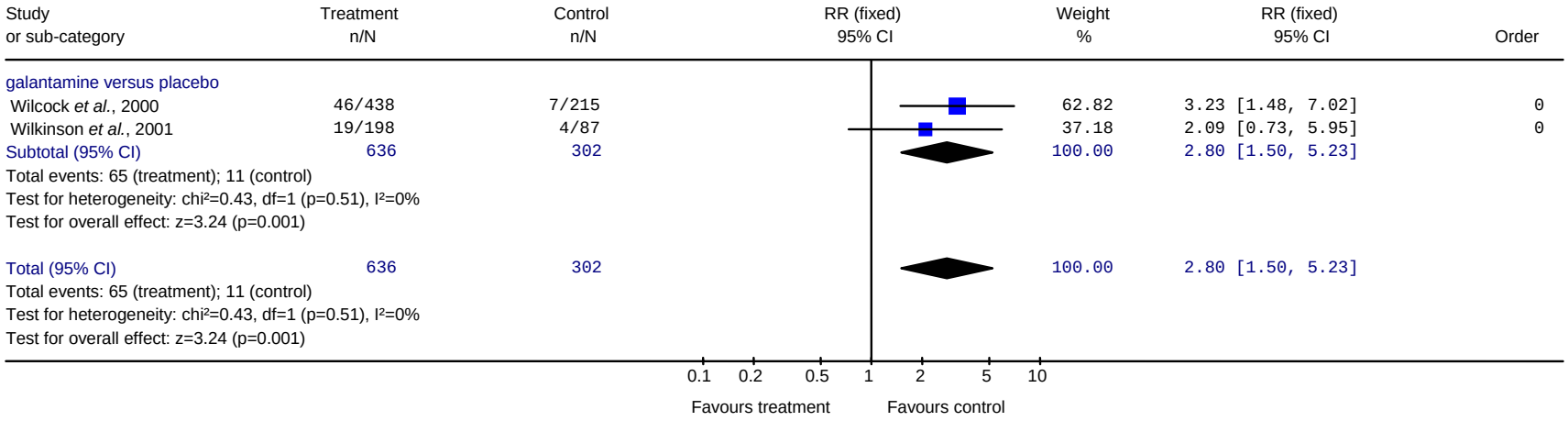


Figure 68: Pooled data for nausea; galantamine versus placebo

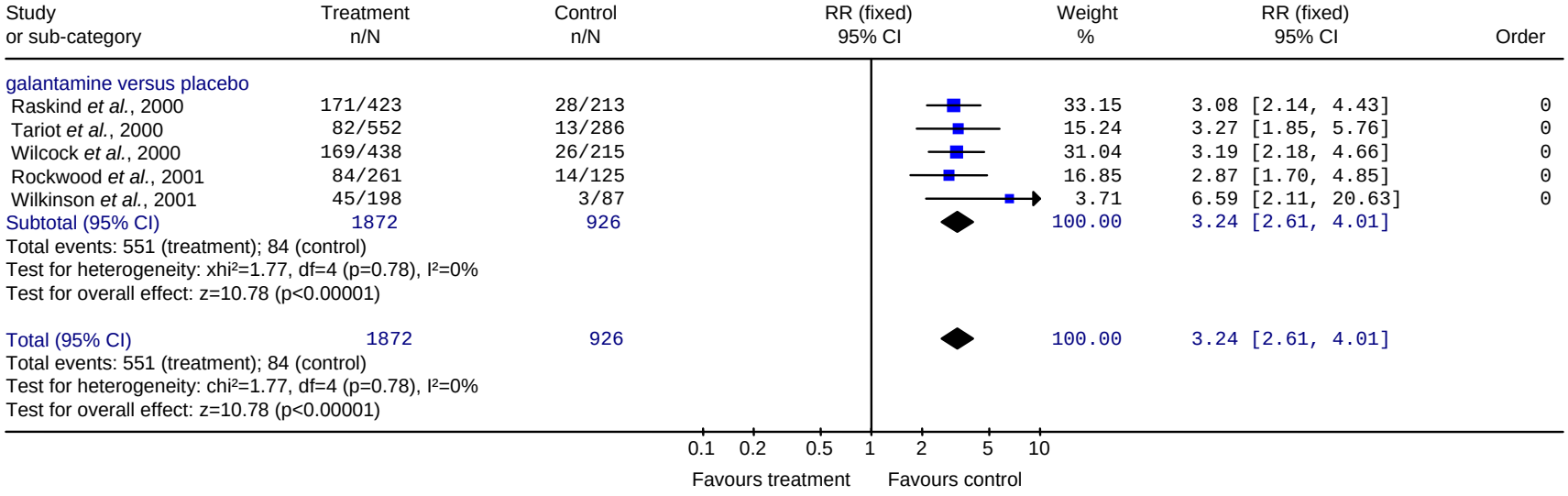


Figure 69: Pooled data for vomiting; galantamine versus placebo

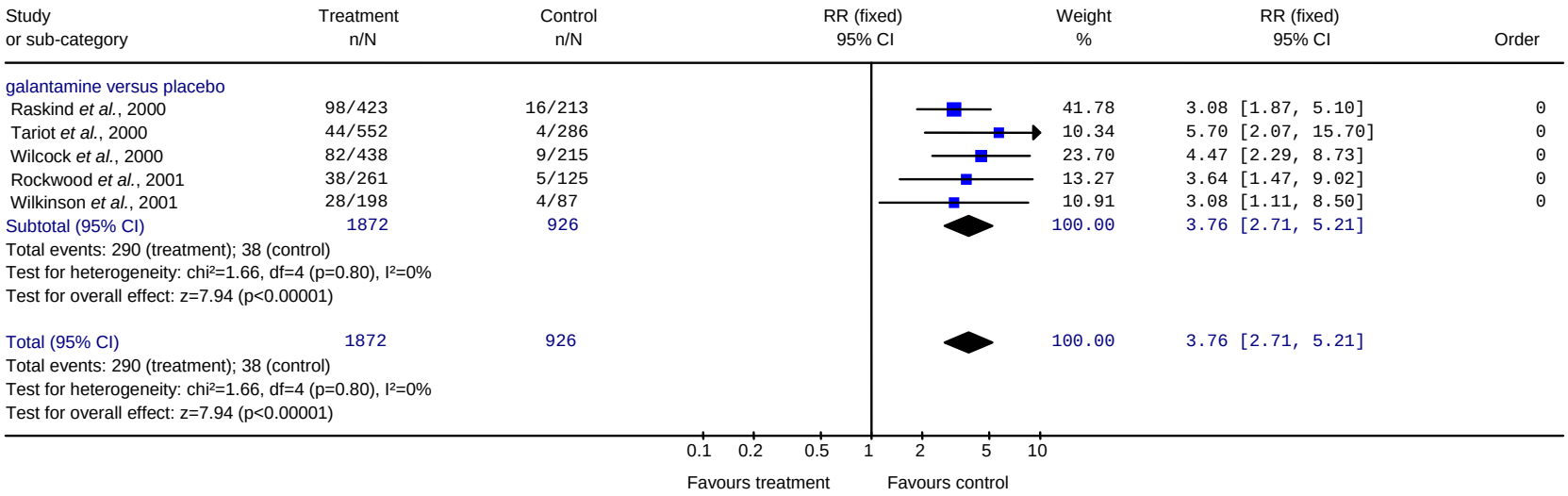


Figure 70: Pooled data for weight loss; galantamine versus placebo

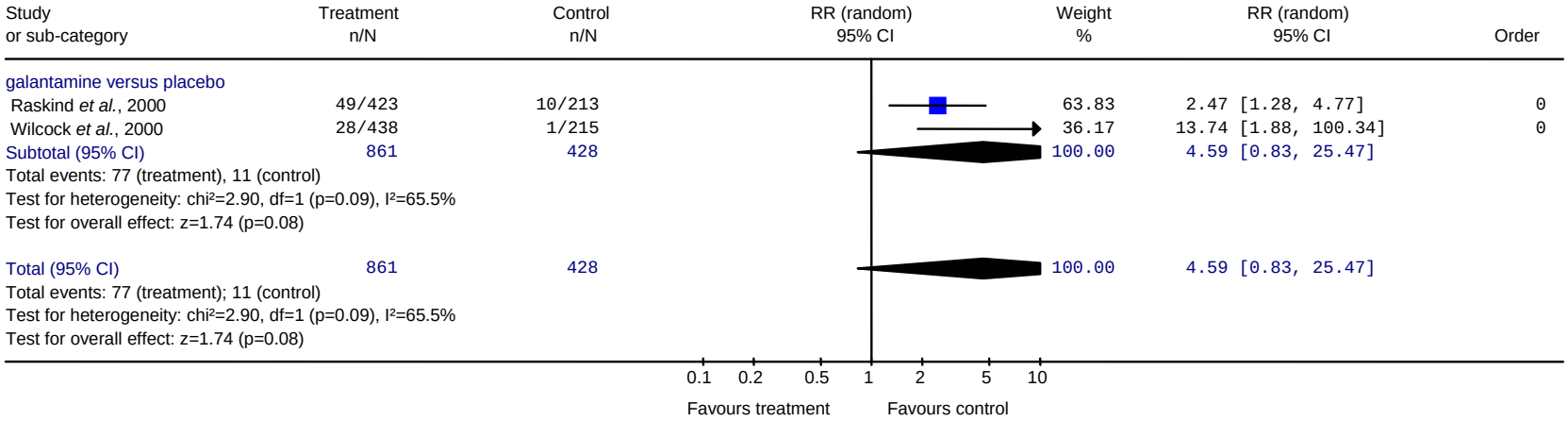


Figure 71: Pooled data for serious AE; galantamine versus placebo

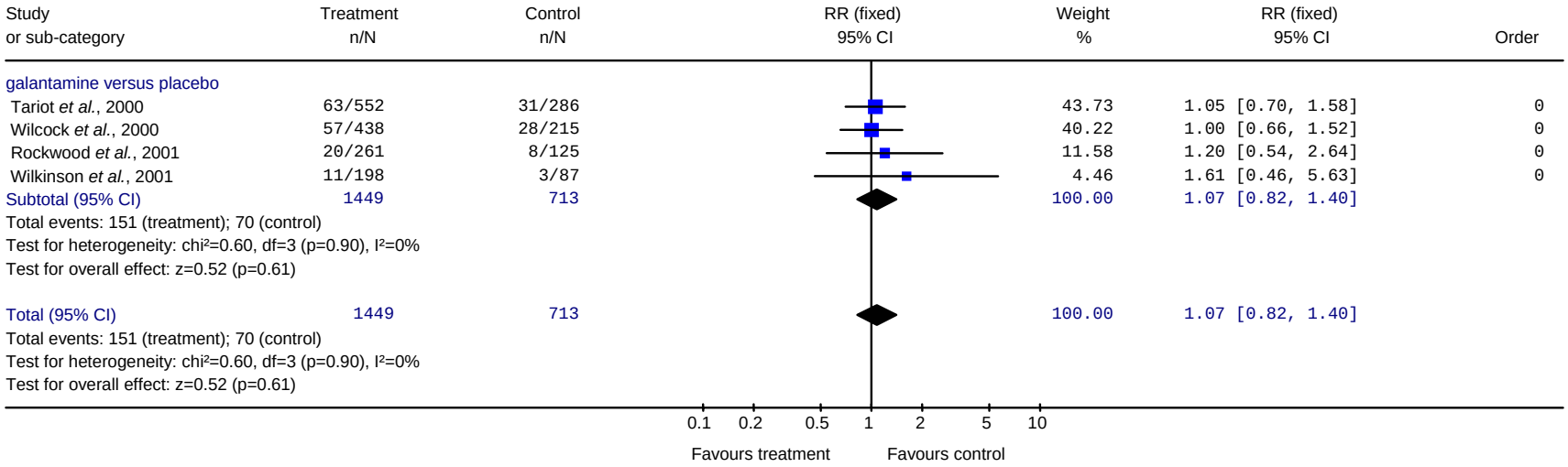


Figure 72: Pooled data for withdrawals due to AE; galantamine versus placebo

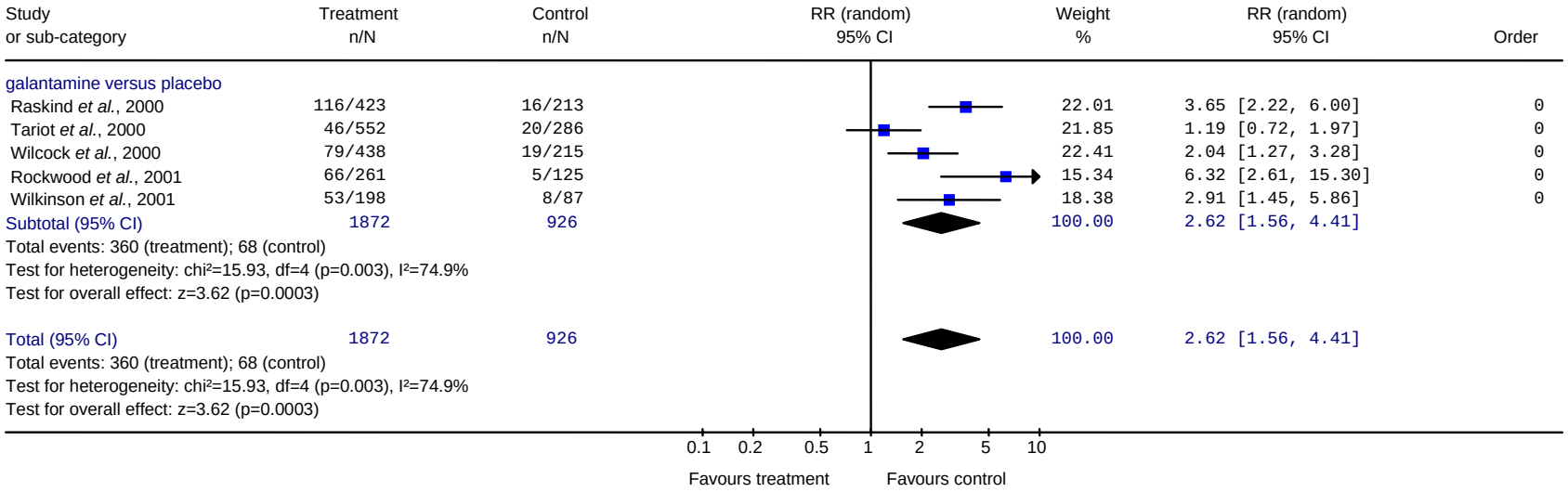


Figure 73: Pooled data for deaths; galantamine versus placebo

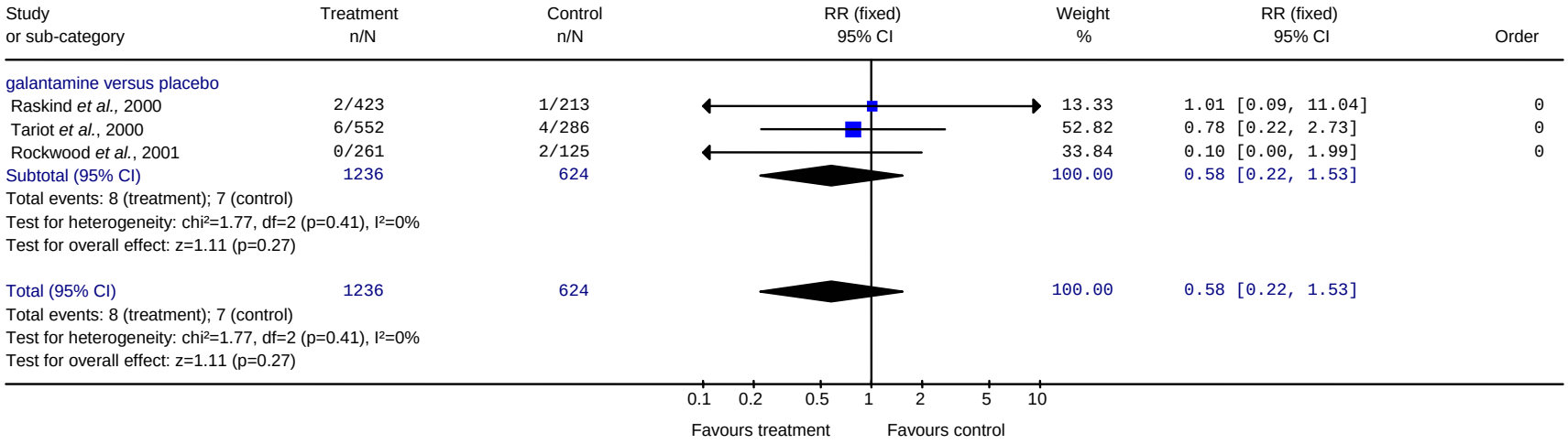


Figure 74: Pooled data for anorexia; rivastigmine versus placebo

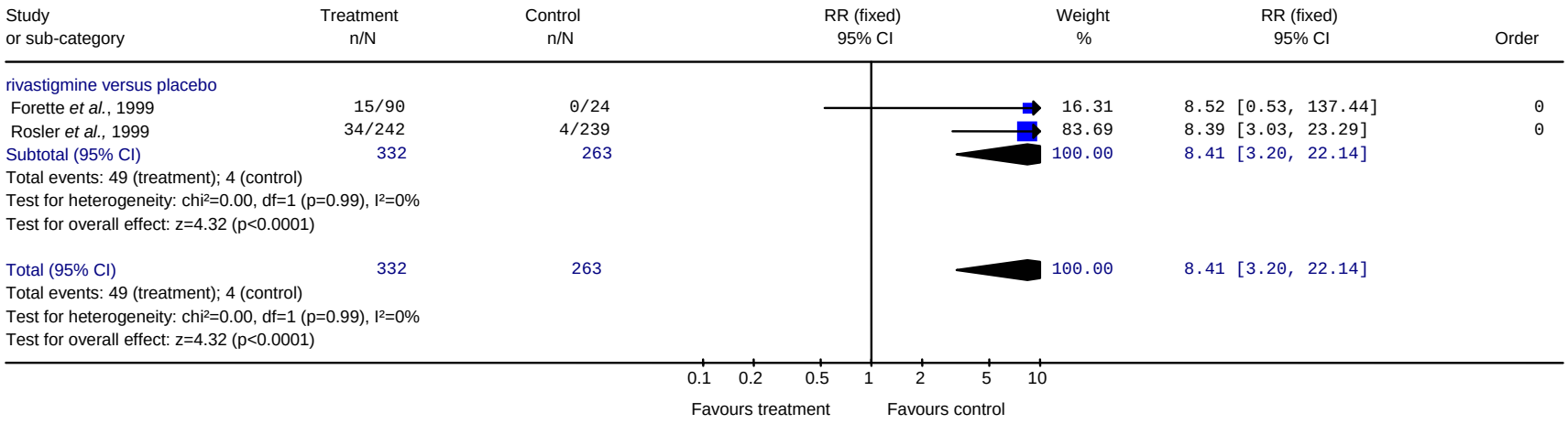


Figure 75: Pooled data for diarrhea; rivastigmine versus placebo

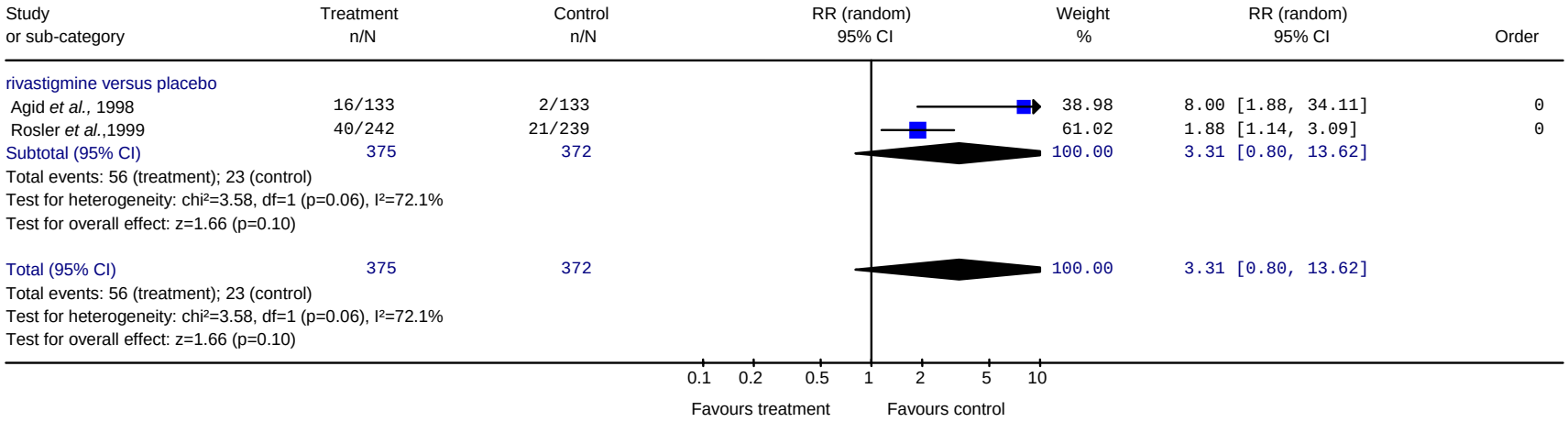


Figure 76: Pooled data for dizziness; rivastigmine versus placebo

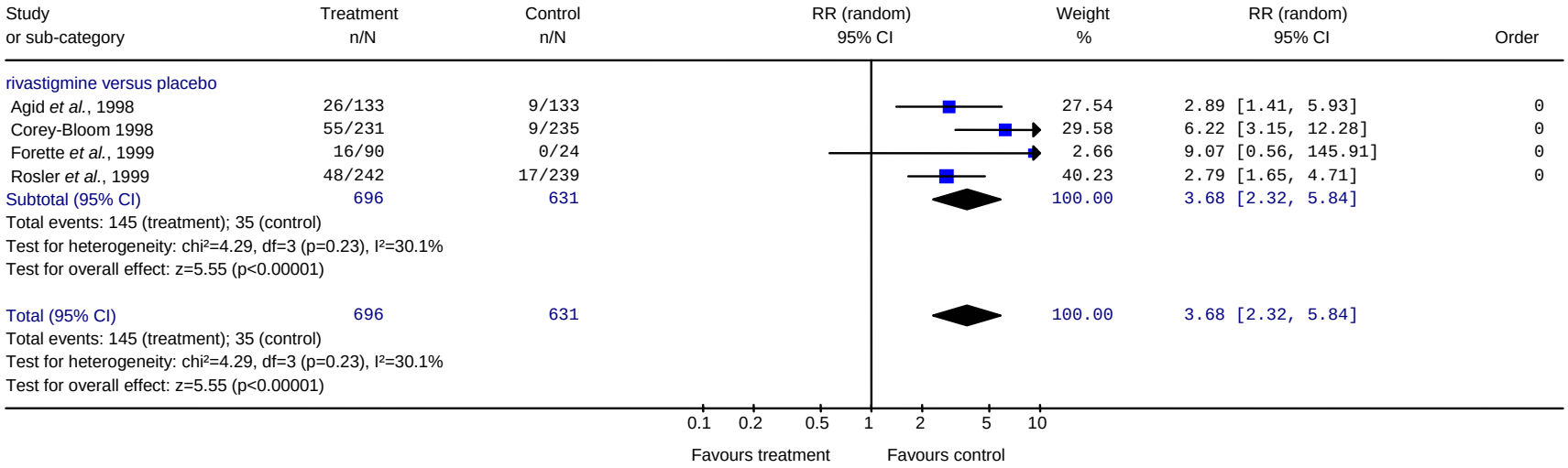


Figure 77: Pooled data for headache; rivastigmine versus placebo

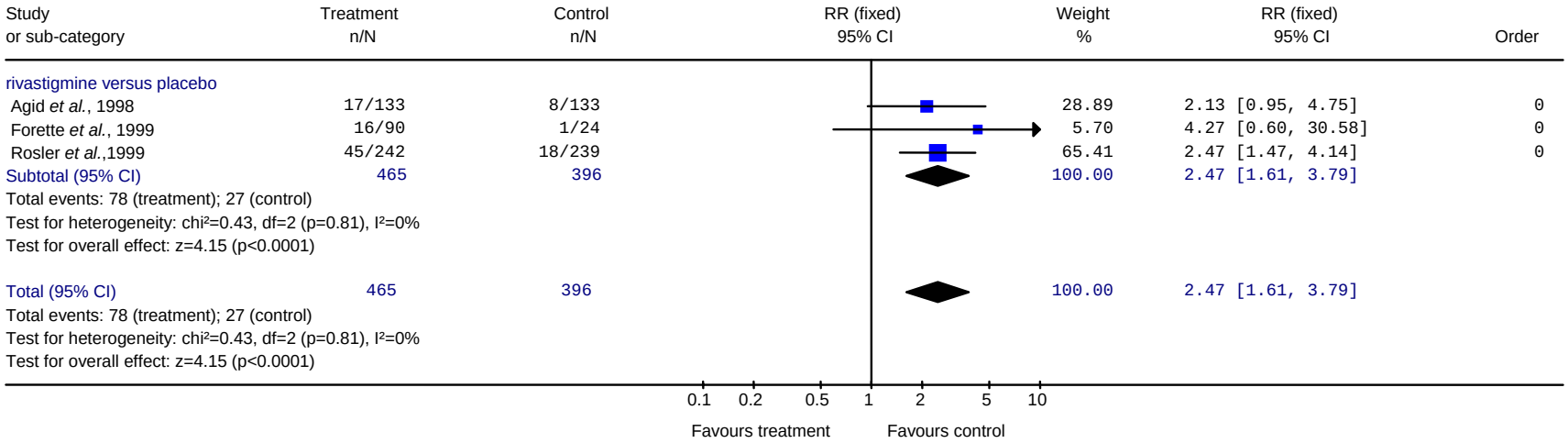


Figure 78: Pooled data for nausea; rivastigmine versus placebo

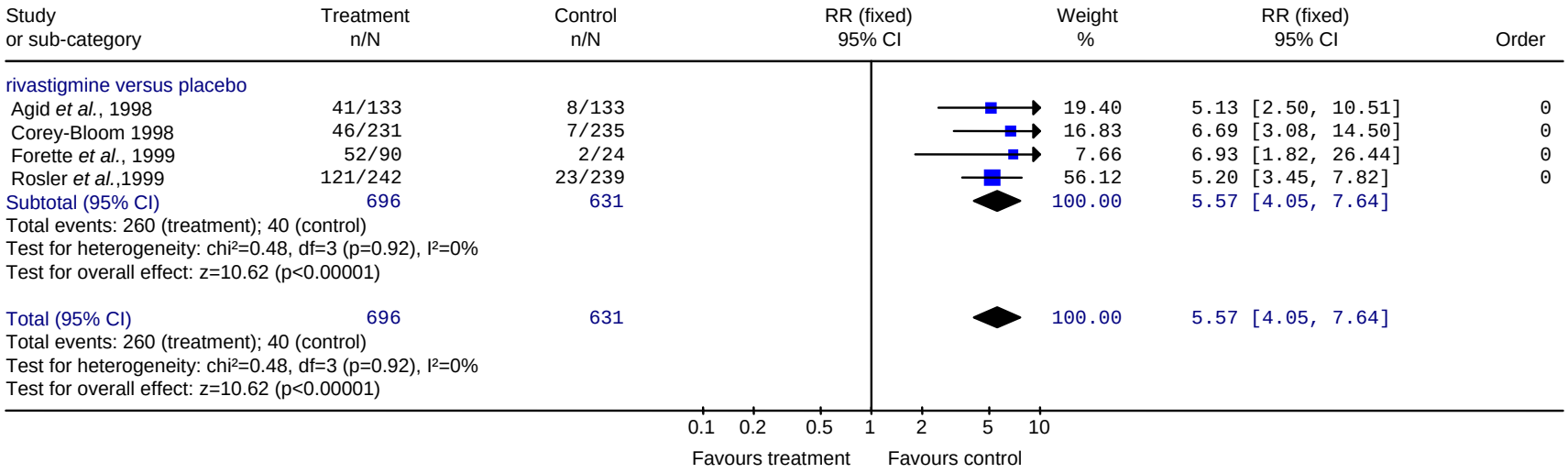


Figure 79: Pooled data for vomiting; rivastigmine versus placebo

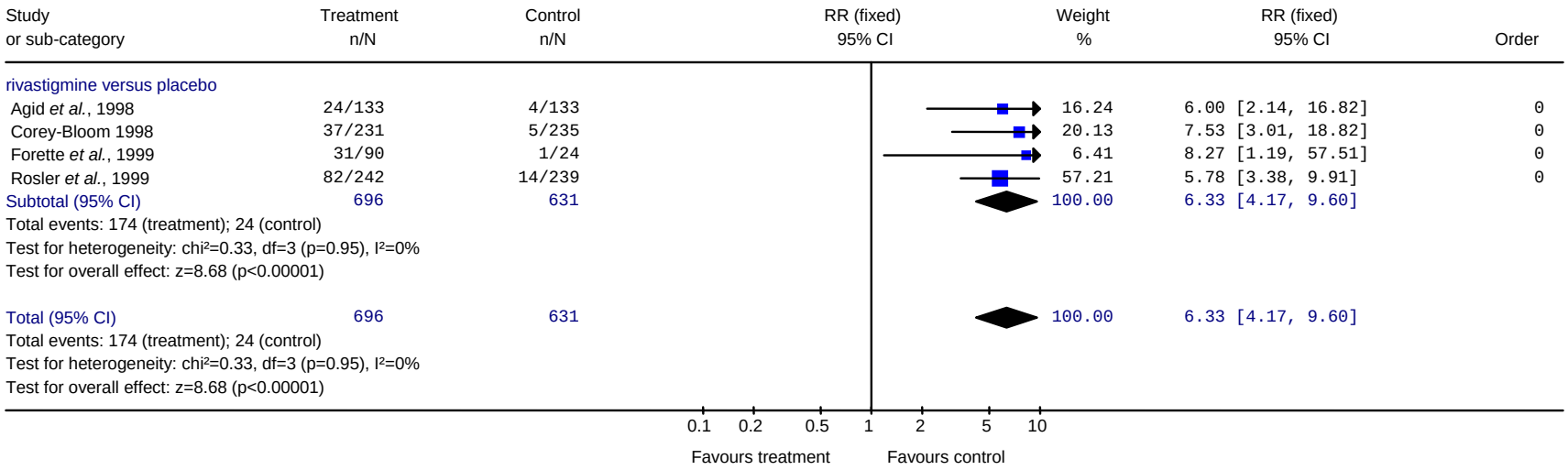


Figure 80: Pooled data for serious AE; rivastigmine versus placebo

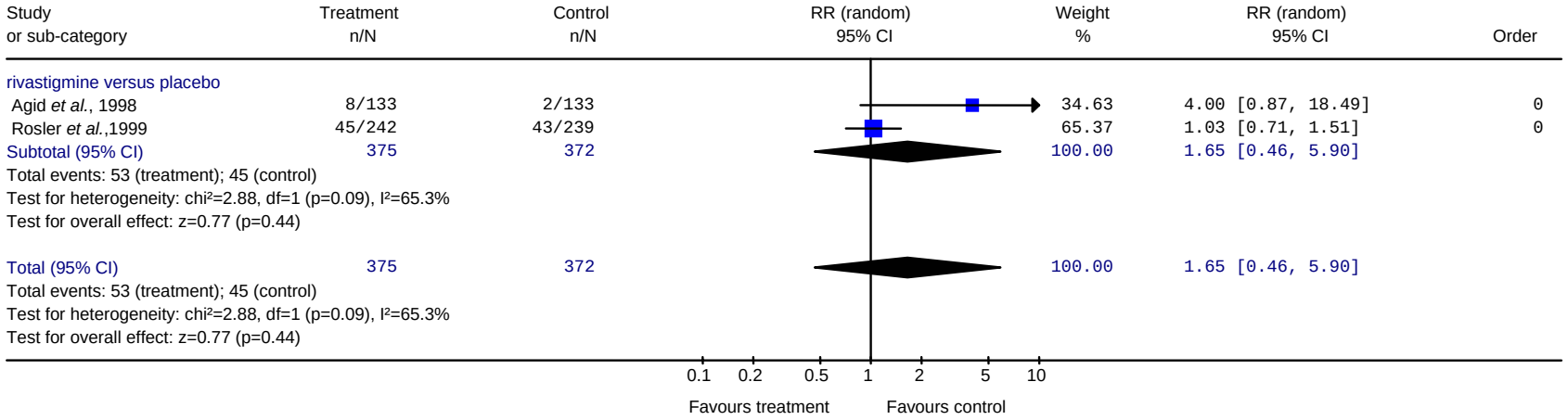


Figure 81: Pooled data for withdrawals due to AE; rivastigmine versus placebo

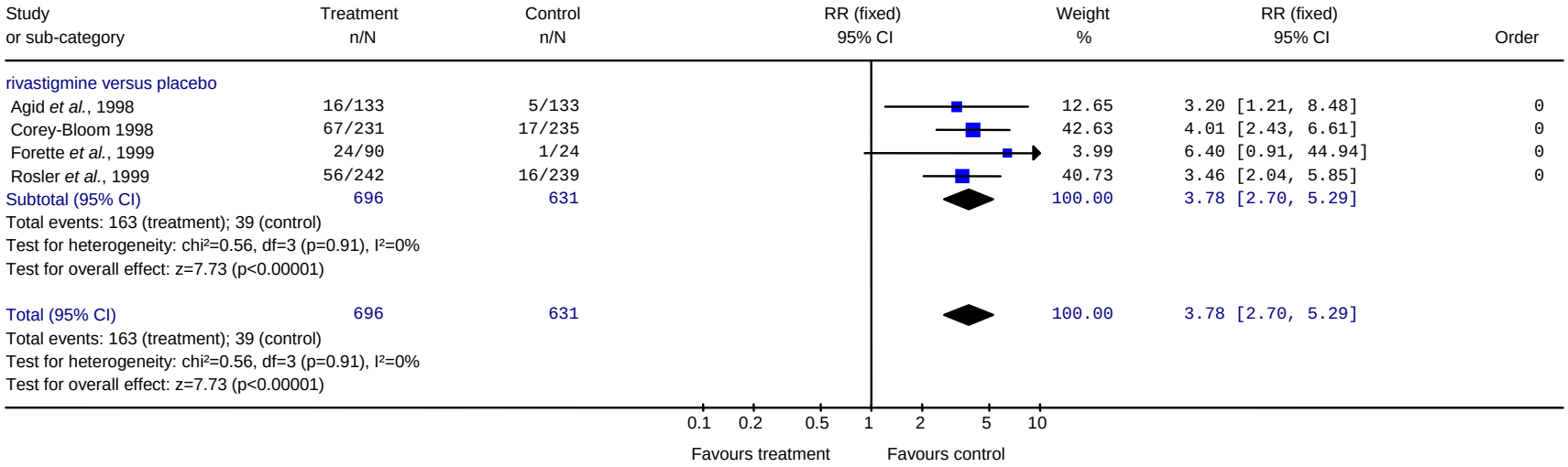


Figure 82: Pooled data for deaths; rivastigmine versus placebo

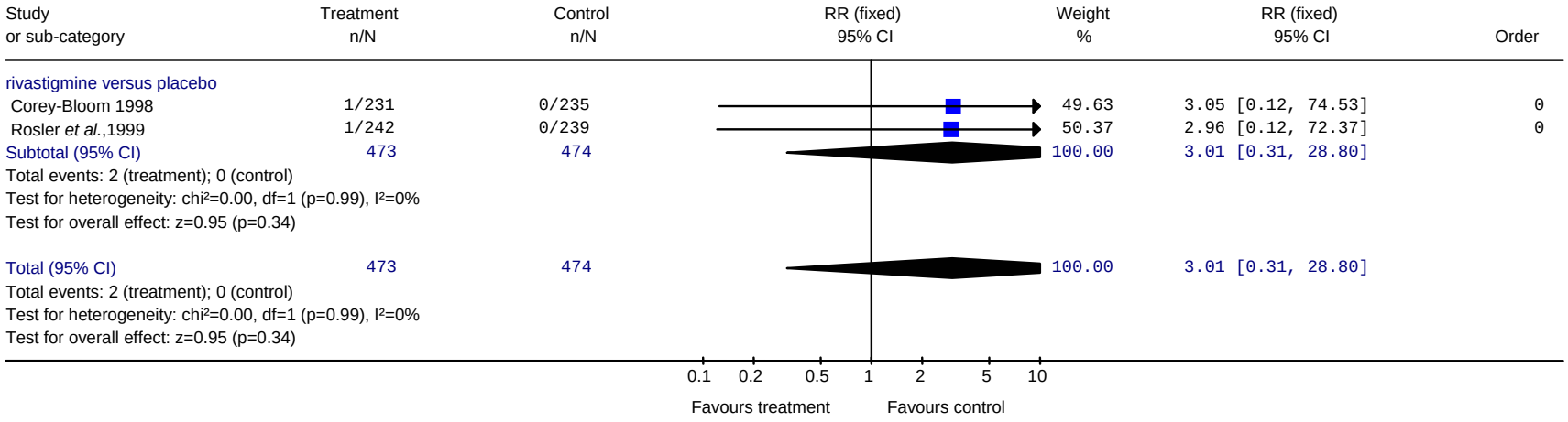


Figure 83: Pooled data for nausea; galantamine versus donepezil

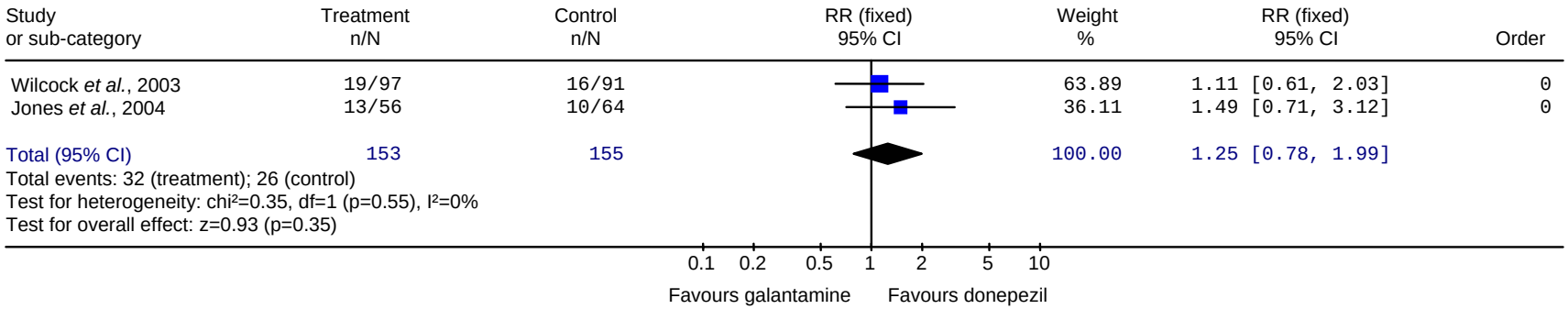


Figure 84: Pooled data for vomiting; galantamine versus donepezil

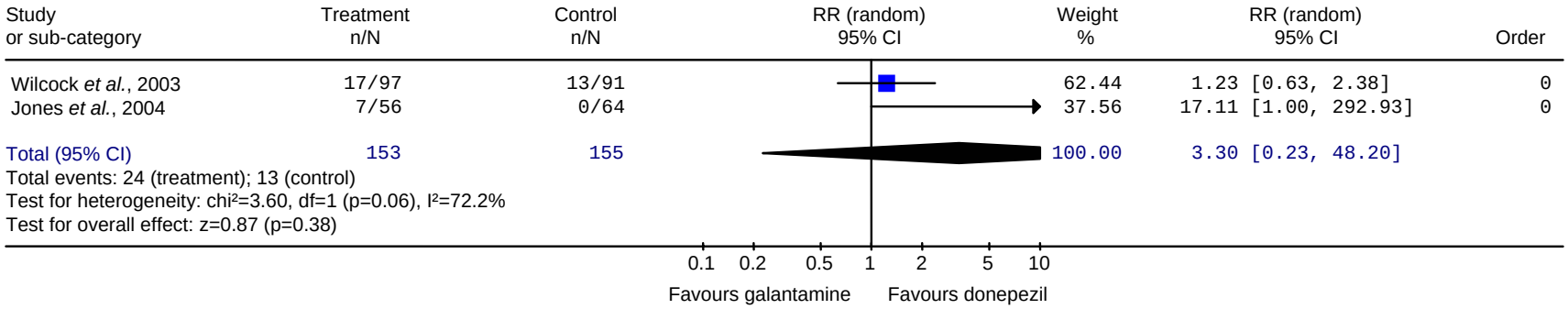


Figure 85: Pooled data for headache; galantamine versus donepezil

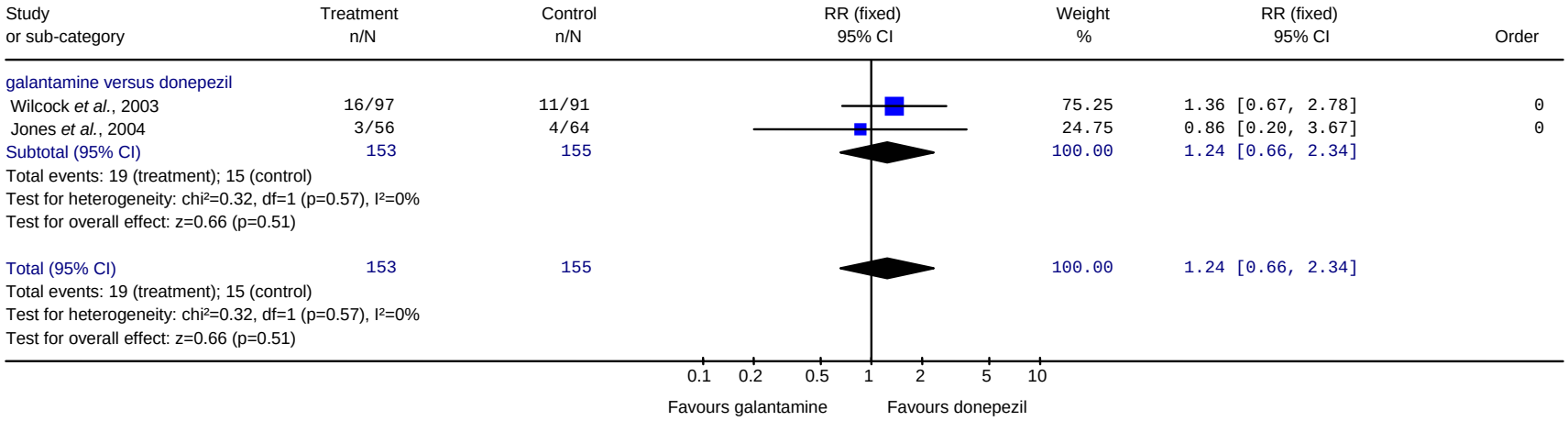


Figure 86: Pooled data for participants with serious AE; galantamine versus donepezil

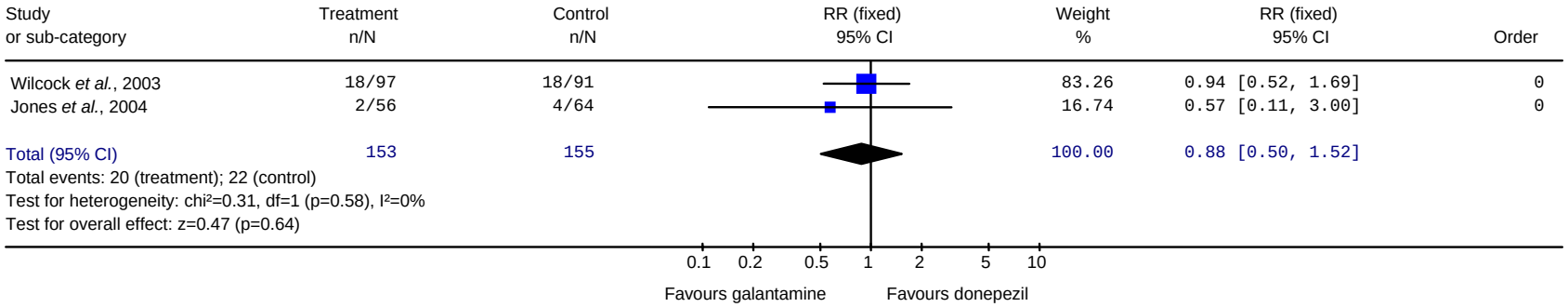


Figure 87: Pooled data for withdrawals due to AE; galantamine versus donepezil

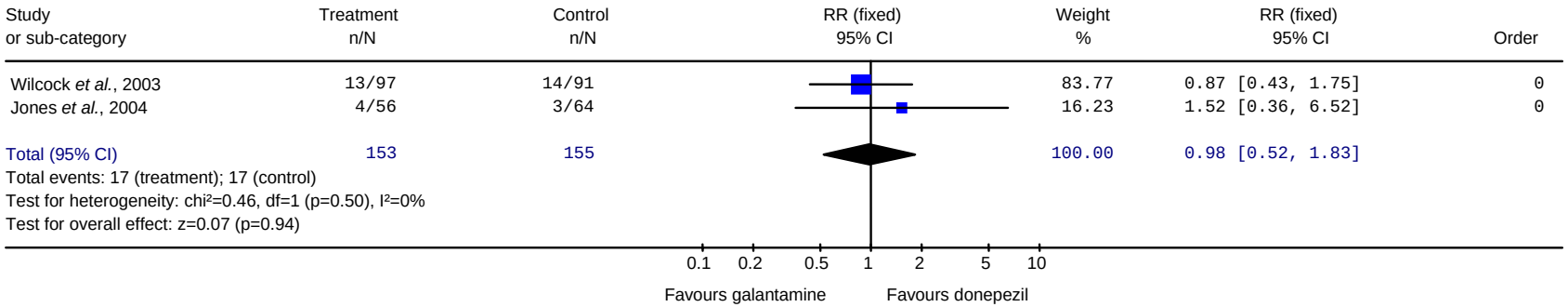


Figure 88: Pooled data for vomiting; rivastigmine versus donepezil

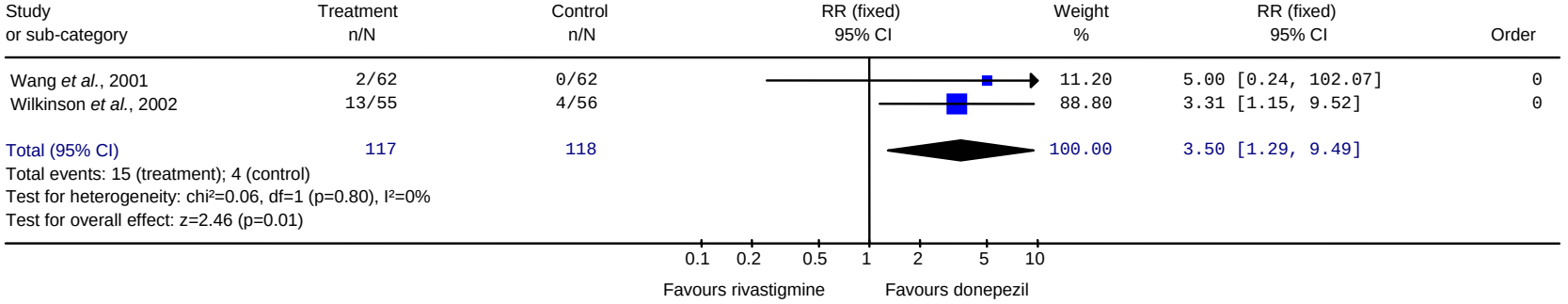


Figure 89: Pooled data for participants with serious AE; rivastigmine versus donepezil

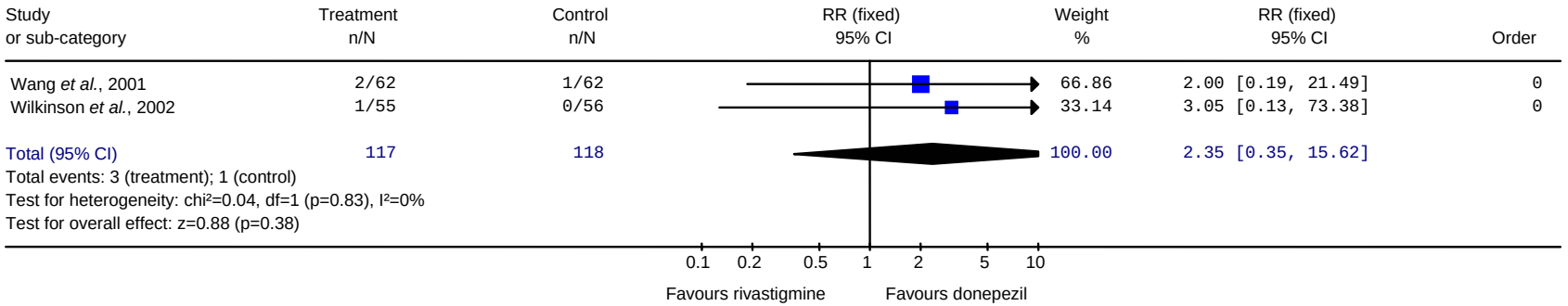


Figure 90: Pooled data for withdrawals due to AE; rivastigmine versus donepezil