# Contents

# Part I

# Donepezil

# 1 Overview of donepezil

## 1.1 Included trials

A total of 5 randomized comparisons which enrolled 2083 patients were identified. In all, 4 randomized comparisons concerned donepezil 10 mg/d and one donepezil 5-10 mg/d.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for donepezil 10 mg/d and in section **??** (page **??**) for donepezil 5-10 mg/d.

The average study size was 416 patients (range 208 to 994). The first study was published in 1999, and the last study was published in 2005.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

## 1.2 Summary of meta-analysis results

The meta-analysis of the available trials about donepezil provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

### 1.2.1 Donepezil 10 mg/d

**Donepezil 10 mg/d** was superior to **placebo** in terms of SIB score at 6 months (ES=0.38, 95% CI 0.25 to 0.52, p=0.0000, 3 trials), ADCS-ADL-severe at 6 months (ES=0.31, 95% CI 0.04 to 0.57, p=0.0251, 1 trial), MMSE at 6 months (ES=0.33, 95% CI 0.18 to 0.49, p=0.0000, 3 trials)and CDR-SB at 24 weeks (ES=-0.40, 95% CI -0.67 to -0.12, p=0.0052, 1 trial).
However, no significant difference was found on NPI at 6 months (ES=-0.13, 95% CI -0.43 to 0.17, p=0.4097, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0164)(ES=-0.19, 95% CI -0.46 to 0.09, p=0.1845, 1 trial)and MMSE at 12 weeks (ES=0.22, 95% CI -0.06 to 0.49, p=0.1246, 1 trial). Donepezil 10 mg/d appear to be associated with significantly greater risk of diarrhoea (RR=2.31, 95% CI 1.52 to 3.51, p=0.0000, 4 trials)and nausea (RR=2.07, 95% CI 1.19 to 3.59, p=0.0095, 4 trials).

### 1.2.2 Donepezil 5-10 mg/d

No significant difference was found between **donepezil 5-10 mg/d** and **rivastigmine** in terms of SIB score at 6 months (ES=-0.03, 95% CI -0.15 to 0.10, p=0.6952, 1 trial), ADCS-ADL-severe at 6 months (ES=-0.11, 95% CI -0.24 to 0.02, p=0.1030, 1 trial), NPI at 6 months (ES=0.03, 95% CI -0.10 to 0.16, p=0.6339, 1 trial)and MMSE at 6 months (ES=-0.08, 95% CI -0.20 to 0.05, p=0.2392, 1 trial).

***Table 1.1:*** *Main study characteristics - donepezil*

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| **Donepezil 10 mg/d** | | | |
| ***Donepezil 10 mg/d versus placebo*** | | | |
| MSAD Feldman, 2000 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] n = 144 vs. 146 | moderate to severe (MMSE between 5 and 17) | donepezil 10 mg/day **versus** placebo | double-blind parallel-group Primary endpoint: CIBIC+ |
| Study 311 10mg/d, 1999 [?, ?, ?, ?, ?] n = 103 vs. 105 | moderate to severe MMSE between 5 and 26 inclusive | donepezil 10 mg/day **versus** placebo | double-blind parallel groups Primary endpoint: NPI-NH |
| Study 315 10mg/d, 2004 [?, ?] n = 176 vs. 167 | moderate to severe AD MMSE 1-12 | donepezil 5 mg/day for 6 weeks followed by 10 mg/day thereafter **versus** placebo | double-blind parallel-group |
| Winblad, 2005 [?, ?, ?, ?, ?] n = 128 vs. 120 | severe MMSE 1-10 | donepezil 5 mg/day for 30 days followed 10 mg/day thereafter **versus** placebo | double-blind parallel-group Primary endpoint: SIB and (ADCS-ADL-severe) |
| **Donepezil 5-10 mg/d** | | | |
| ***Donepezil 5-10 mg/d versus rivastigmine*** | | | |
| EXCEED, 2005 [?] n = 499 vs. 495 | patients with moderate to moderately-severe Alzheimer's disease | donepezil 5-10 mg/day **versus** rivastigmine 3-12 mg/day | double blind parallel groups |

***Table 1.2:*** *Summary of all results for donepezil 10 mg/d*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***donepezil 10 mg/d versus placebo*** | | | | | | |
| SIB score at 6 months | ES=0.38 | 0.25;0.52 | 0.0000 | 0.9486 (0.00) | 3 | 843 |
| ADCS-ADL-severe at 6 months | ES=0.31 | 0.04;0.57 | 0.0251 | 1.0000 (0.00) | 1 | 216 |
| NPI at 6 months | ES=-0.13 [1] | -0.43;0.17 | 0.4097 | 0.0164 (0.76) † | 3 | 706 |
| withdrawals due to an adverse event at 24 weeks | RR=1.35 [2] | 0.75;2.44 | 0.3113 | 0.0367 (0.65) † | 4 | 1090 |
| agitation | RR=1.27 | 0.52;3.10 | 0.5931 | 1.0000 (0.00) | 1 | 208 |
| CIBIC-Plus or CGIC (numbers improved) at 24 weeks | RR=1.32 | 1.05;1.66 | 0.0185 | 0.6024 (0.00) | 2 | 561 |
| MMSE at 6 months | ES=0.33 | 0.18;0.49 | 0.0000 | 0.3438 (0.06) | 3 | 668 |
| CDR-SB at 12 weeks | ES=-0.19 | -0.46;0.09 | 0.1845 | 1.0000 (0.00) | 1 | 204 |
| CDR-SB at 24 weeks | ES=-0.40 | -0.67;-0.12 | 0.0052 | 1.0000 (1.00) | 1 | 204 |
| MMSE at 12 weeks | ES=0.22 | -0.06;0.49 | 0.1246 | 1.0000 (0.00) | 1 | 205 |
| diarrhoea | RR=2.31 | 1.52;3.51 | 0.0000 | 0.5840 (0.00) | 4 | 1089 |
| nausea | RR=2.07 | 1.19;3.59 | 0.0095 | 0.6187 (0.00) | 4 | 1036 |
| vomiting | RR=1.42 | 0.60;3.36 | 0.4215 | 0.1747 (0.46) | 2 | 498 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

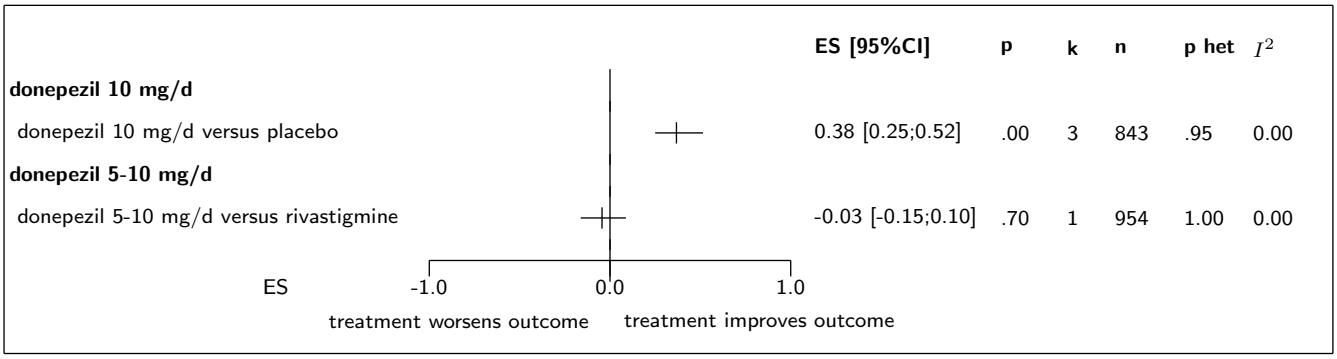
***Table 1.3:*** *Summary of all results for donepezil 5-10 mg/d*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***donepezil 5-10 mg/d versus rivastigmine*** | | | | | | |
| SIB score at 6 months | ES=-0.03 | -0.15;0.10 | 0.6952 | 1.0000 (0.00) | 1 | 954 |
| ADCS-ADL-severe at 6 months | ES=-0.11 | -0.24;0.02 | 0.1030 | 1.0000 (0.00) | 1 | 929 |
| NPI at 6 months | ES=0.03 | -0.10;0.16 | 0.6339 | 1.0000 (0.00) | 1 | 955 |
| MMSE at 6 months | ES=-0.08 | -0.20;0.05 | 0.2392 | 1.0000 (0.00) | 1 | 955 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

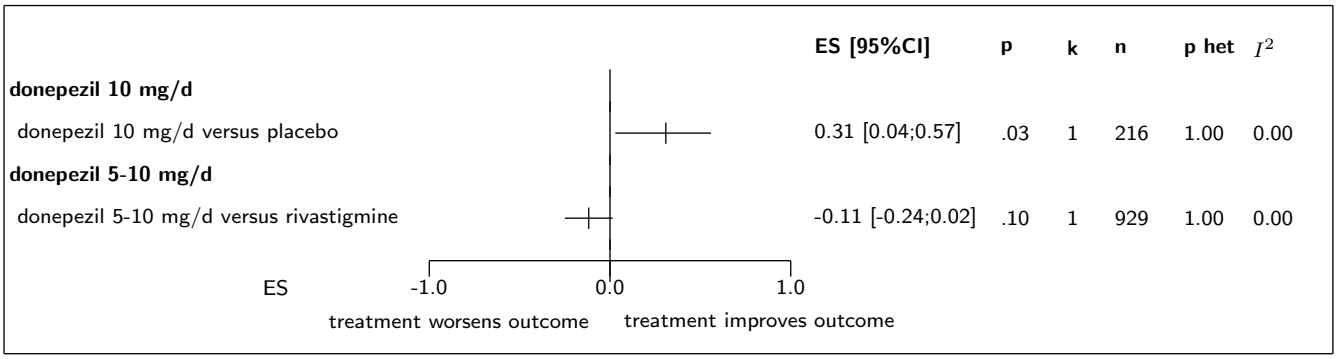
[1] with a random model ($\tau^2 = 0.054$). The results with a fixed effect model was RRFE=-0.15 95% CI -0.30;0.00
[2] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.38 95% CI 0.98;1.94

***Figure 1.1:*** *Forest's plot for SIB score at 6 months*



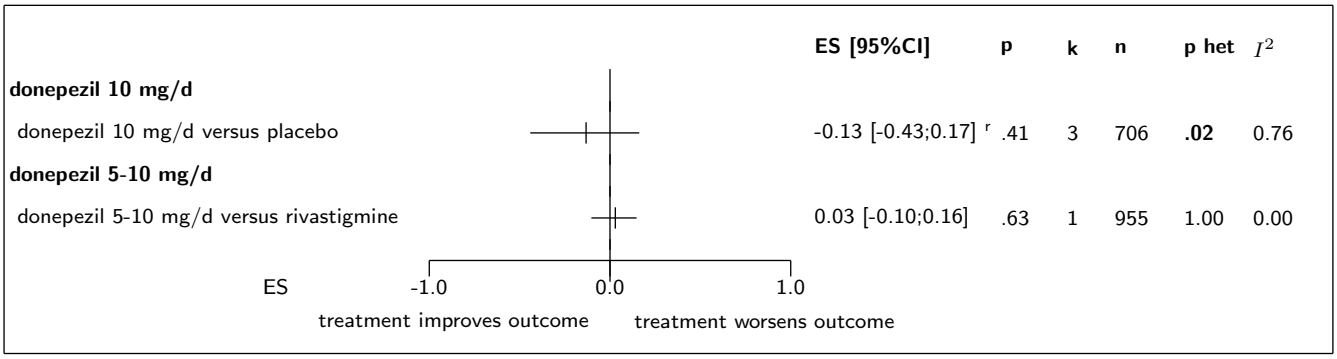

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.2:*** *Forest's plot for ADCS-ADL-severe at 6 months*



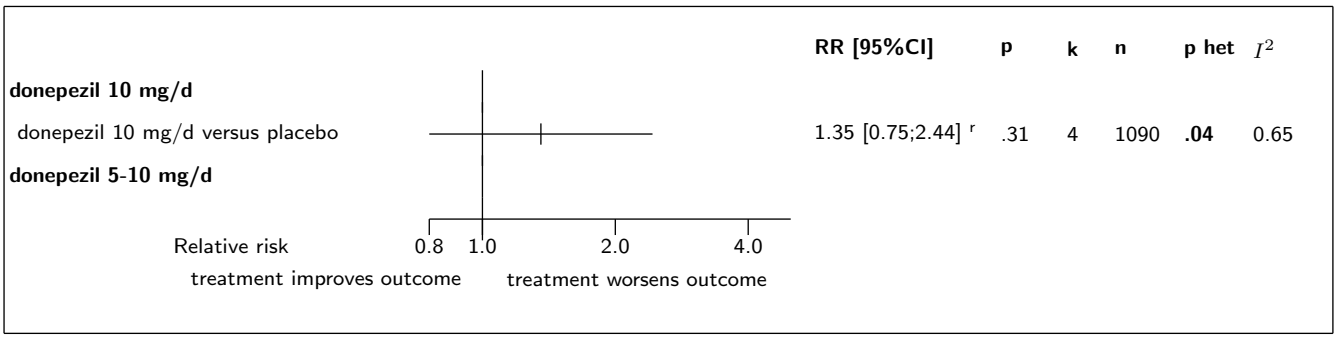

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.3:*** *Forest's plot for NPI at 6 months*



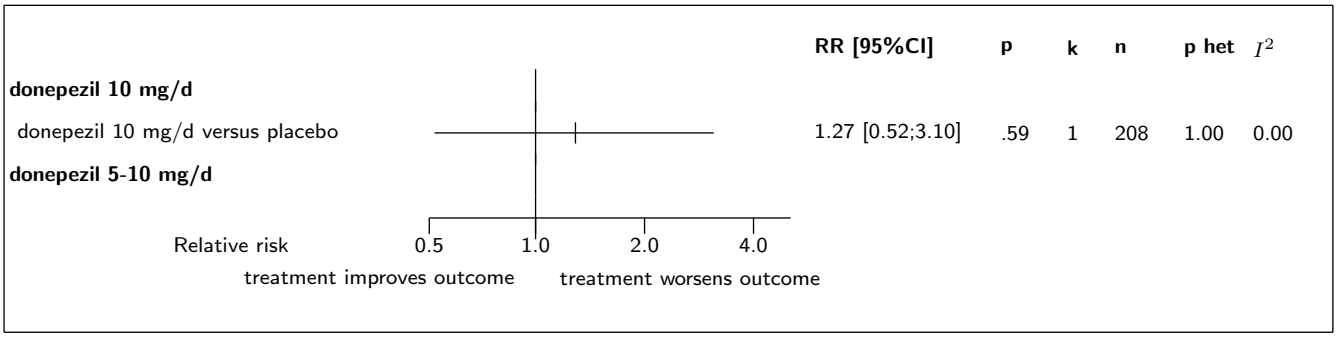

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; [r]: random effect model used

***Figure 1.4:*** *Forest's plot for withdrawals due to an adverse event at 24 weeks*



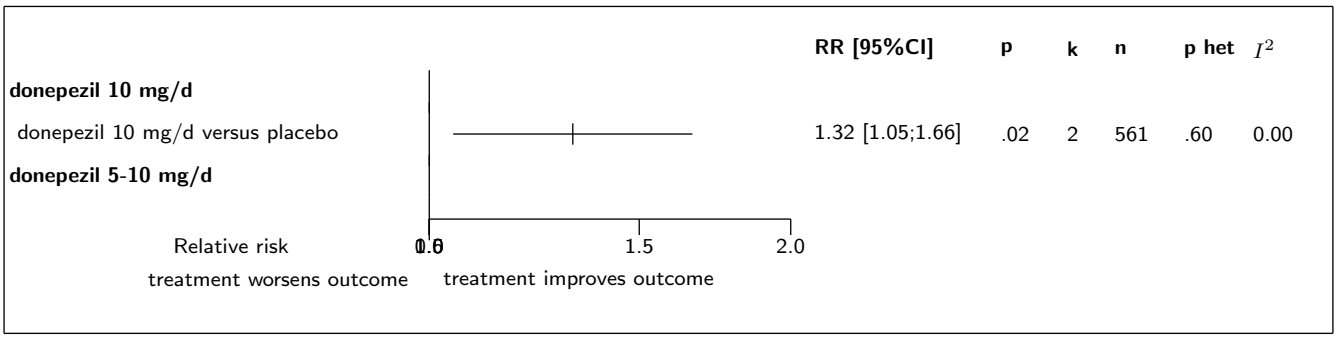

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

***Figure 1.5:*** *Forest's plot for agitation*



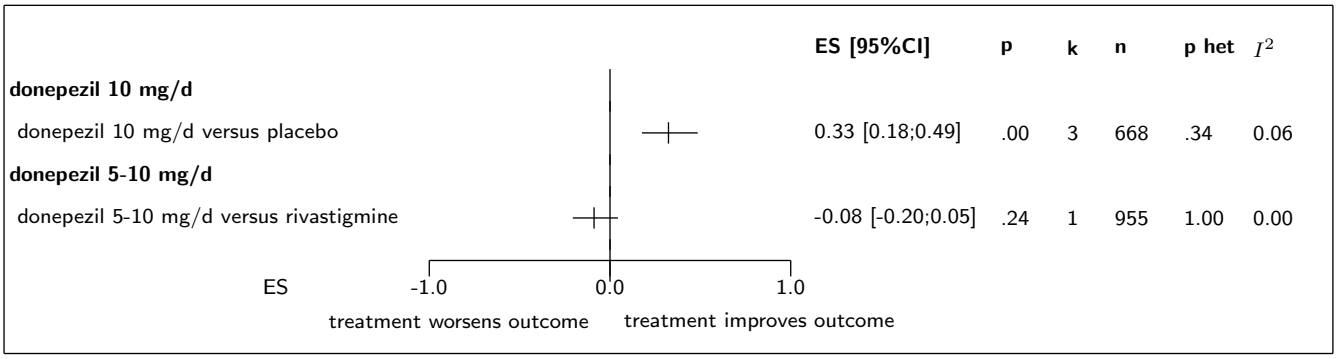

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

***Figure 1.6:*** *Forest's plot for CIBIC-Plus or CGIC (numbers improved) at 24 weeks*



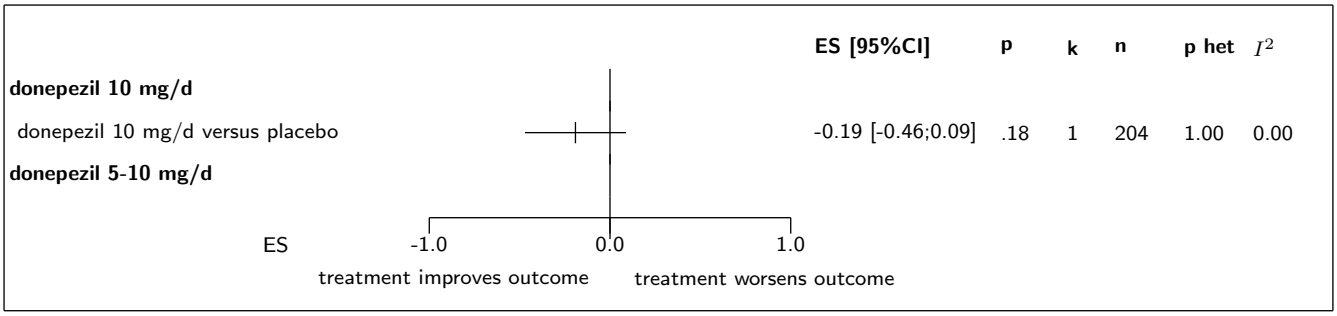

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; [r]: random effect model used

***Figure 1.7:*** *Forest's plot for MMSE at 6 months*



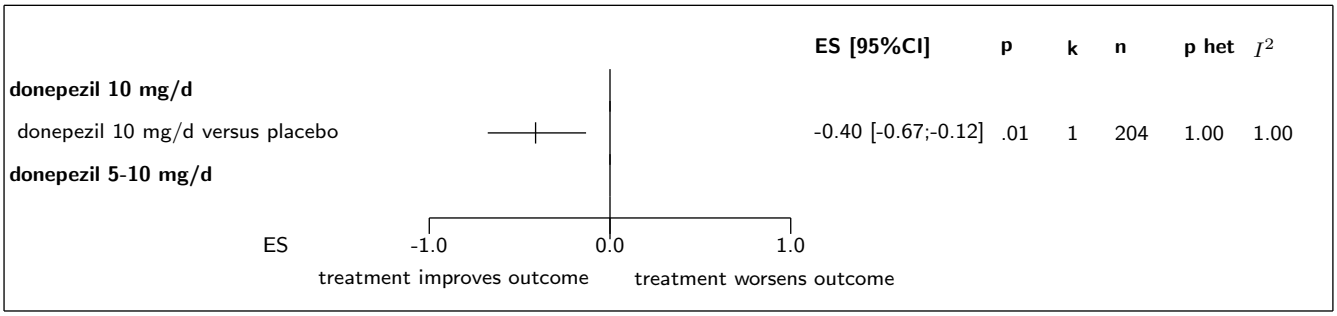

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.8:*** *Forest's plot for CDR-SB at 12 weeks*



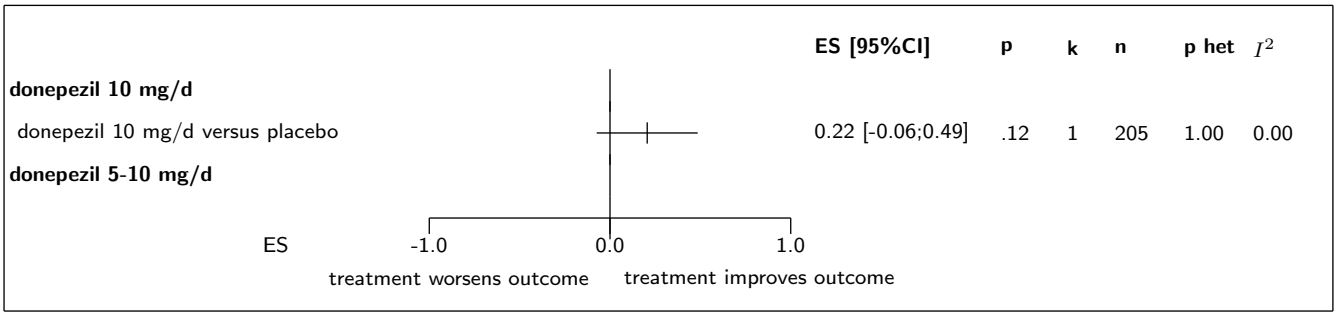

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.9:*** *Forest's plot for CDR-SB at 24 weeks*



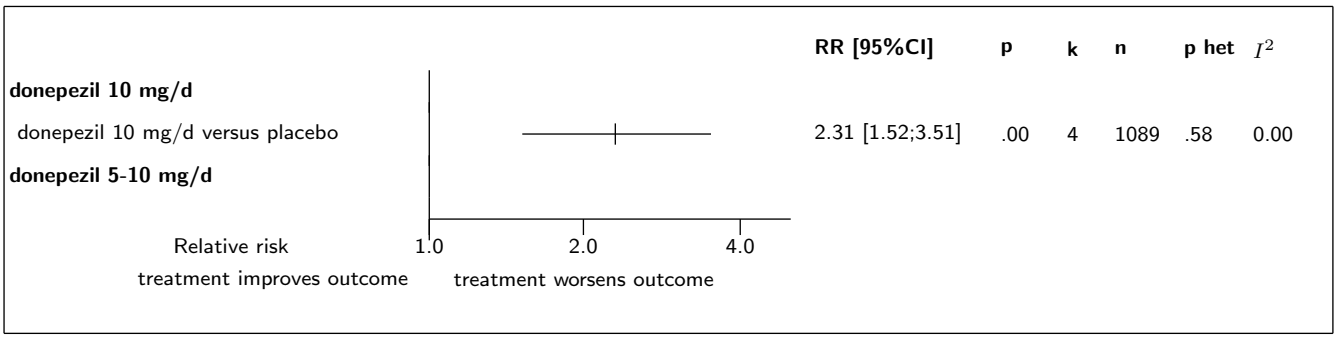

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.10:*** *Forest's plot for MMSE at 12 weeks*



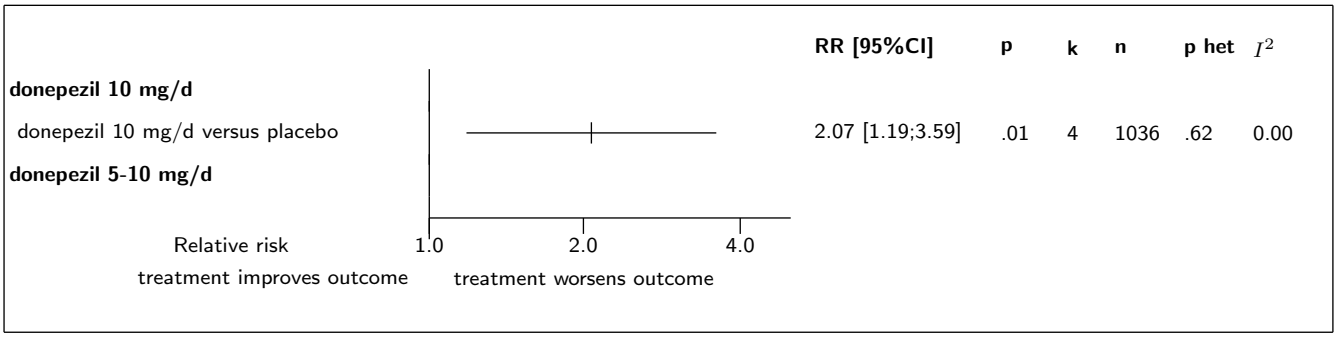

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $I^2$: inconsistance degree; $^r$: random effect model used

***Figure 1.11:*** *Forest's plot for diarrhoea*



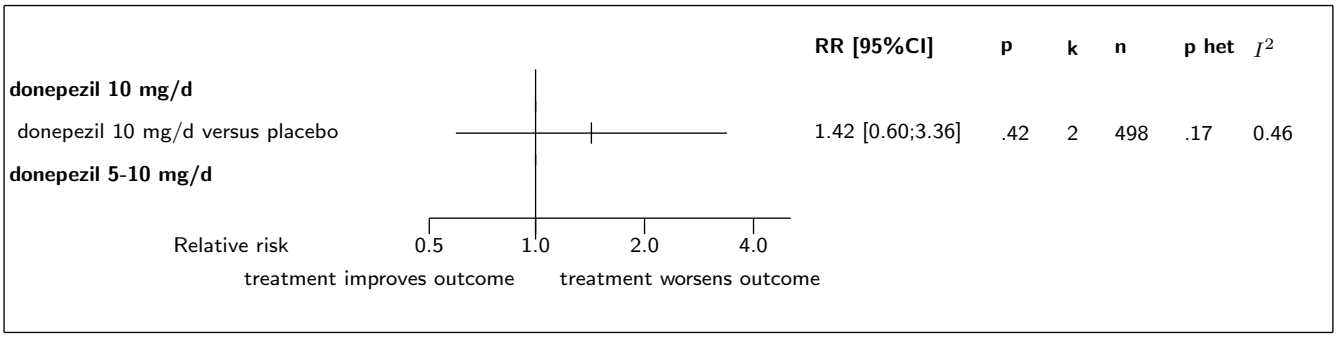

Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^r$: random effect model used

***Figure 1.12:*** *Forest's plot for nausea*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

***Figure 1.13:*** *Forest's plot for vomiting*




Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; $^{r}$: random effect model used

# 2 Detailed results for donepezil 10 mg/d

## 2.1 Available trials

A total of 4 RCTs which randomized 1089 patients were identified: all compared donepezil 10 mg/d with placebo.
The average study size was 272 patients (range 208 to 343). The first study was published in 1999, and the last study was published in 2005.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
NPI at 6 months data was reported in 3 trials; 3 trials reported data on SIB score at 6 months; 3 trials reported data on MMSE at 6 months; 2 trials reported data on CIBIC-Plus or CGIC (numbers improved) at 24 weeks; 1 trials reported data on MMSE at 12 weeks; 1 trials reported data on CDR-SB at 12 weeks; 1 trials reported data on CDR-SB at 24 weeks; 1 trials reported data on ADCS-ADL-severe at 6 months; 4 trials reported data on diarrhoea; 4 trials reported data on nausea; 4 trials reported data on withdrawals due to an adverse event at 24 weeks; 2 trials reported data on vomiting; and 1 trials reported data on agitation.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of donepezil 10 mg/d.

***Table 2.1:*** *Treatment description - donepezil - donepezil 10 mg/d*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Donepezil 10 mg/d versus placebo** | | |
| MSAD Feldman (2000) [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | donepezil 10 mg/day<br>donepezil 5 mg/day for the first 28 days and 10 mg/day thereafter as per the clinician's judgment | placebo |
| Study 311 10mg/d (1999) [?, ?, ?, ?, ?] | donepezil 10 mg/day | placebo |
| Study 315 10mg/d (2004) [?, ?] | donepezil 5 mg/day for 6 weeks followed by 10 mg/day thereafter | placebo |
| Winblad (2005) [?, ?, ?, ?, ?] | donepezil 5 mg/day for 30 days followed 10 mg/day thereafter | placebo |

***Table 2.2:*** *Descriptions of participants - donepezil - donepezil 10 mg/d*

| Trial | Patients |
|---|---|
| **Donepezil 10 mg/d versus placebo** | |

continued...

| Trial | Patients | |
|---|---|---|
| MSAD Feldman (2000) [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | Moderate to severe (MMSE between 5 and 17) | |
| | **Inclusion criteria:** eligible patients had a diagnosis of probable or possible AD, of moderate or severe severity, according to the NINCDS-ADRDA criteria with no clinical or laboratory evidence of a cause other than AD for their dementia. MMSE between 5 and 17. All participants had a reliable caregiver. | **Exclusion criteria:** delirium, depression or other illness that may interfere with the study. Other neurologic or psychiatric diagnosis. History of drug or alcohol misuse. hypersensitivity to AChE inhibitors. Clinically obstructive airway disease, asthma, haematologic or oncologic disorder within last 2 years. B12 or folate deficiency, active gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease. Most concomitant medications were allowed except those with notable cholinomimetic or anticholinergic effects. |
| Study 311 10mg/d (1999) [?, ?, ?, ?, ?] | Moderate to severe MMSE between 5 and 26 inclusive | |
| | **Inclusion criteria:** MMSE between 5 and 26 inclusive, residence in nursing home, at least one NPI symptom reported at a frequency of at least several times per week. Exclusion: most concomitant medications were allowed except those with significant cholinergic or anticholinergic effects | **Exclusion criteria:** most concomitant medications were allowed except those with significant cholinergic or anticholinergic effects |
| Study 315 10mg/d (2004) [?, ?] | Moderate to severe AD MMSE 1-12 | |
| | **Inclusion criteria:** eligible patients had a diagnosis of probable AD, according to the NINCDS-ADRDA criteria and DSM-IV. MMSE 1-12, Functional Assessment Staging Score (FAST) >= 6, modified Hachinski <= 6 | **Exclusion criteria:** none given |
| Winblad (2005) [?, ?, ?, ?, ?] | Severe MMSE 1-10 | |
| | **Inclusion criteria:** CT or MRI scan at time of diagnosis, MMSE 1-10, functional assessment staging (FAST) 5-7c, | **Exclusion criteria:** other dementias, or primary psychiatric and neurological disorders |

***Table 2.3:*** *Main patients characteristics - donepezil - donepezil 10 mg/d*

| Trial | Characteristics |
|---|---|
| **Donepezil 10 mg/d versus placebo** | |
| MSAD Feldman, 2000 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | |
| Study 311 10mg/d, 1999 [?, ?, ?, ?, ?] | |
| Study 315 10mg/d, 2004 [?, ?] | |
| Winblad, 2005 [?, ?, ?, ?, ?] | |

***Table 2.4:*** *Design and methodological quality of trials - donepezil - donepezil 10 mg/d*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Donepezil 10 mg/d versus placebo** | | | | |
| MSAD Feldman, 2000 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] n=290 | parallel-group double-blind | 24-week | | CIBIC+ |
| Study 311 10mg/d, 1999 [?, ?, ?, ?, ?] n=208 | Parallel groups double-blind | 24-week | | NPI-NH |
| Study 315 10mg/d, 2004 [?, ?] n=343 | parallel-group double-blind | 24-week | | |
| Winblad, 2005 [?, ?, ?, ?, ?] n=248 | parallel-group double-blind | | | SIB and (ADCS-ADL-severe) |

## 2.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Donepezil 10 mg/d versus placebo

A total of 3 of the 4 studies eligible for this comparison provided data on **SIB score at 6 months**. The analysis detected a statistically significant difference in favor of donepezil 10 mg/d in SIB score at 6 months, with a ES of 0.38 (95% CI 0.25 to 0.52, p=0.0000). No heterogeneity was detected (p = 0.9486, $I^2$ = 0.00%).

Only one of the 4 studies eligible for this comparison provided data on **ADCS-ADL-severe at 6 months**. The analysis detected a statistically significant difference in favor of donepezil 10 mg/d in ADCS-ADL-severe at 6 months, with a ES of 0.31 (95% CI 0.04 to 0.57, p=0.0251).

A total of 3 of the 4 studies eligible for this comparison provided data on **NPI at 6 months**. When pooled together, there was no statistically significant difference between the groups in NPI at 6 months, with a ES of -0.13 (95% CI -0.43 to 0.17, p=0.4097). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0164, $I^2$ = 0.76%).

A total of 2 of the 4 studies eligible for this comparison provided data on **CIBIC-Plus or CGIC (numbers improved) at 24 weeks**. The analysis detected a statistically significant difference in favor of donepezil 10 mg/d in CIBIC-Plus or CGIC (numbers improved) at 24 weeks, with a RR of 1.32 (95% CI 1.05 to 1.66, p=0.0185). No heterogeneity was detected (p = 0.6024, $I^2$ = 0.00%).

A total of 3 of the 4 studies eligible for this comparison provided data on **MMSE at 6 months**. The analysis detected a statistically significant difference in favor of donepezil 10 mg/d in MMSE at 6 months, with a ES of 0.33 (95% CI 0.18 to 0.49, p=0.0000). No heterogeneity was detected (p = 0.3438, $I^2$ = 0.06%).

Only one of the 4 studies eligible for this comparison provided data on **CDR-SB at 12 weeks**. No statistically significant difference between the groups was found in CDR-SB at 12 weeks, with a ES of -0.19 (95% CI -0.46 to 0.09, p=0.1845).
Only one of the 4 studies eligible for this comparison provided data on **CDR-SB at 24 weeks**. The analysis detected a statistically significant difference in favor of donepezil 10 mg/d in CDR-SB at 24 weeks, with a ES of -0.40 (95% CI -0.67 to -0.12, p=0.0052).
Only one of the 4 studies eligible for this comparison provided data on **MMSE at 12 weeks**. No statistically significant difference between the groups was found in MMSE at 12 weeks, with a ES of 0.22 (95% CI -0.06 to 0.49, p=0.1246).

***Table 2.5:*** *Results details - donepezil - donepezil 10 mg/d*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***donepezil 10 mg/d versus placebo*** | | | | | | |
| SIB score at 6 months | ES=0.38 | [0.25;0.52] | 0.0000 | 0.9486 ($I^2$=0.00) | 3 | 843 |
| ADCS-ADL-severe at 6 months | ES=0.31 | [0.04;0.57] | 0.0251 | 1.0000 ($I^2$=0.00) | 1 | 216 |
| NPI at 6 months | ES=-0.13 | [-0.43;0.17] | 0.4097 | 0.0164 ($I^2$=0.76) | 3 | 706 |
| withdrawals due to an adverse event at 24 weeks | RR=1.35 | [0.75;2.44] | 0.3113 | 0.0367 ($I^2$=0.65) | 4 | 1090 |
| agitation | RR=1.27 | [0.52;3.10] | 0.5931 | 1.0000 ($I^2$=0.00) | 1 | 208 |
| CIBIC-Plus or CGIC (numbers improved) at 24 weeks | RR=1.32 | [1.05;1.66] | 0.0185 | 0.6024 ($I^2$=0.00) | 2 | 561 |
| MMSE at 6 months | ES=0.33 | [0.18;0.49] | 0.0000 | 0.3438 ($I^2$=0.06) | 3 | 668 |
| CDR-SB at 12 weeks | ES=-0.19 | [-0.46;0.09] | 0.1845 | 1.0000 ($I^2$=0.00) | 1 | 204 |
| CDR-SB at 24 weeks | ES=-0.40 | [-0.67;-0.12] | 0.0052 | 1.0000 ($I^2$=1.00) | 1 | 204 |
| MMSE at 12 weeks | ES=0.22 | [-0.06;0.49] | 0.1246 | 1.0000 ($I^2$=0.00) | 1 | 205 |
| diarrhoea | RR=2.31 | [1.52;3.51] | 0.0000 | 0.5840 ($I^2$=0.00) | 4 | 1089 |
| nausea | RR=2.07 | [1.19;3.59] | 0.0095 | 0.6187 ($I^2$=0.00) | 4 | 1036 |
| vomiting | RR=1.42 | [0.60;3.36] | 0.4215 | 0.1747 ($I^2$=0.46) | 2 | 498 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 2.1:*** *Forest's plot for SIB score at 6 months*

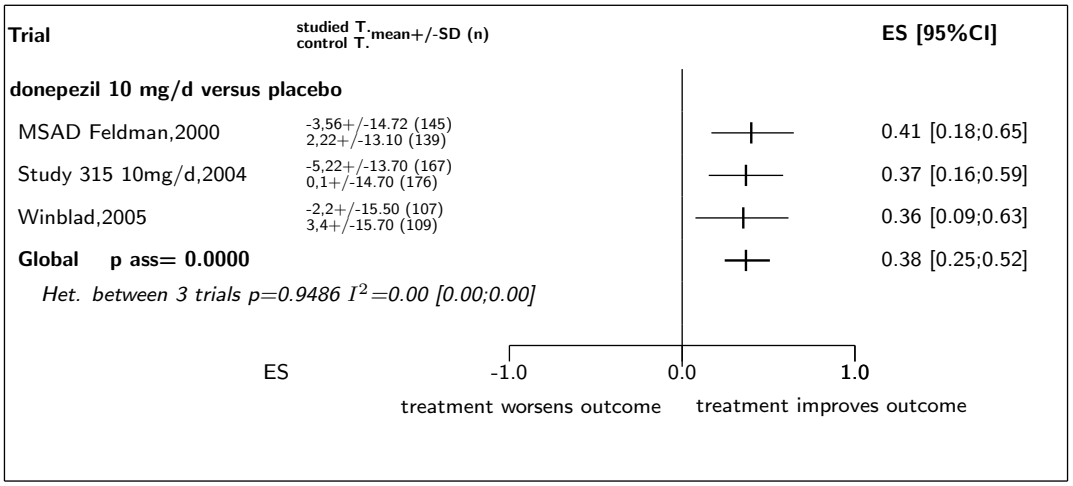


***Figure 2.2:*** *Forest's plot for ADCS-ADL-severe at 6 months*

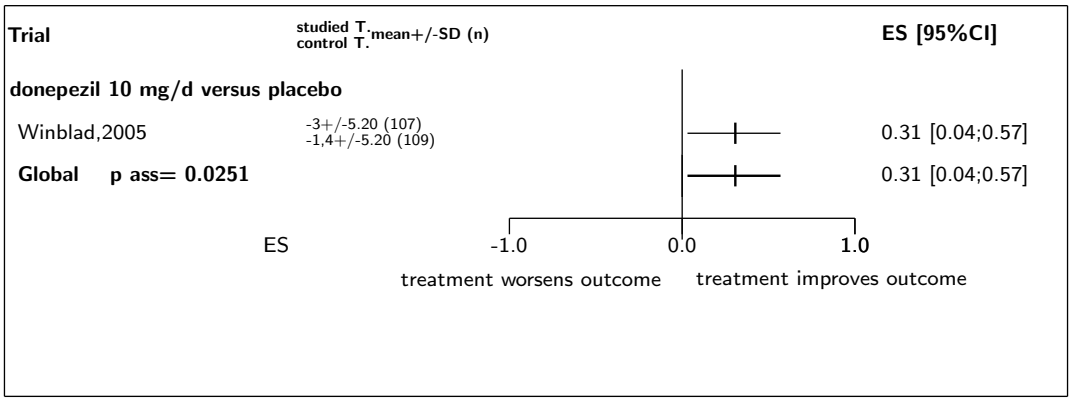



***Figure 2.3:*** *Forest's plot for NPI at 6 months*

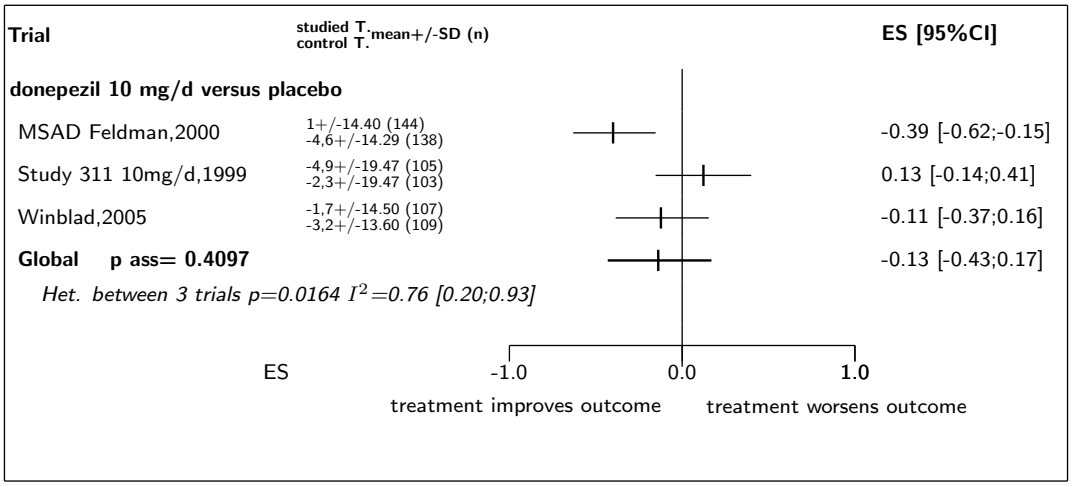


***Figure 2.4:*** *Forest's plot for withdrawals due to an adverse event at 24 weeks*

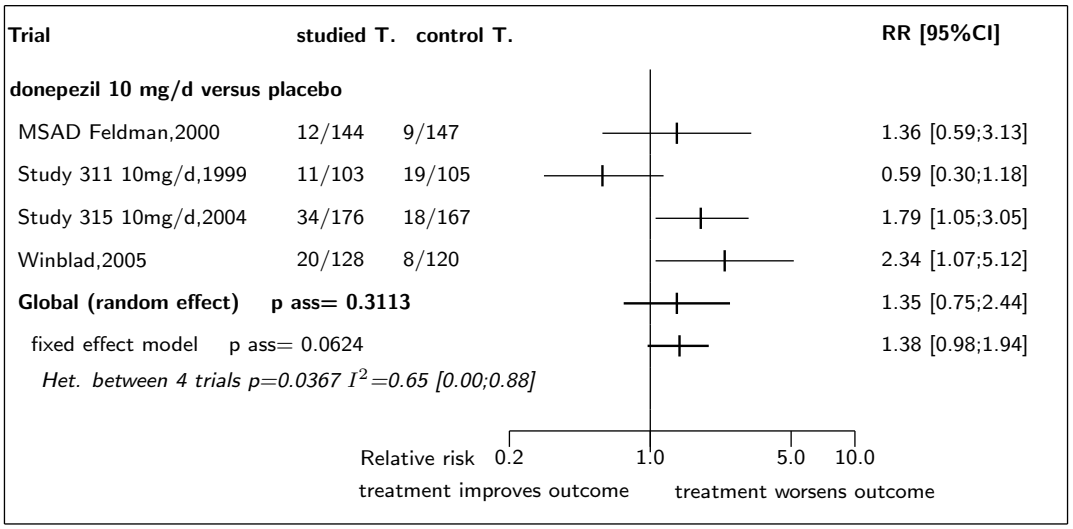



***Figure 2.5:*** *Forest's plot for agitation*

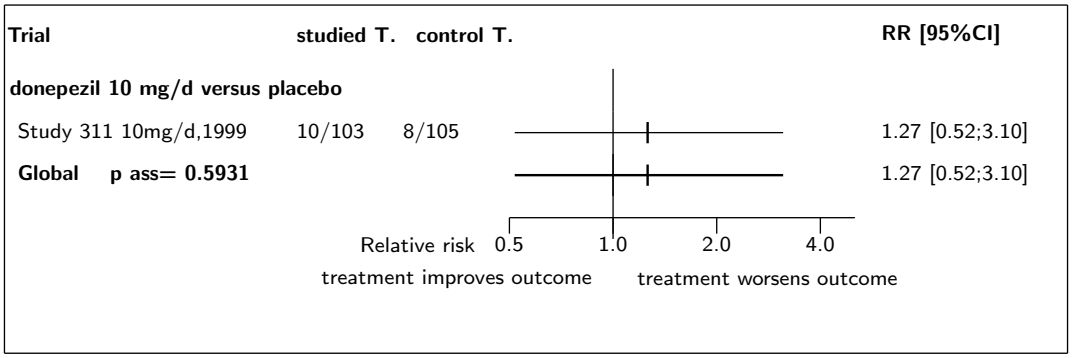



***Figure 2.6:*** *Forest's plot for CIBIC-Plus or CGIC (numbers improved) at 24 weeks*

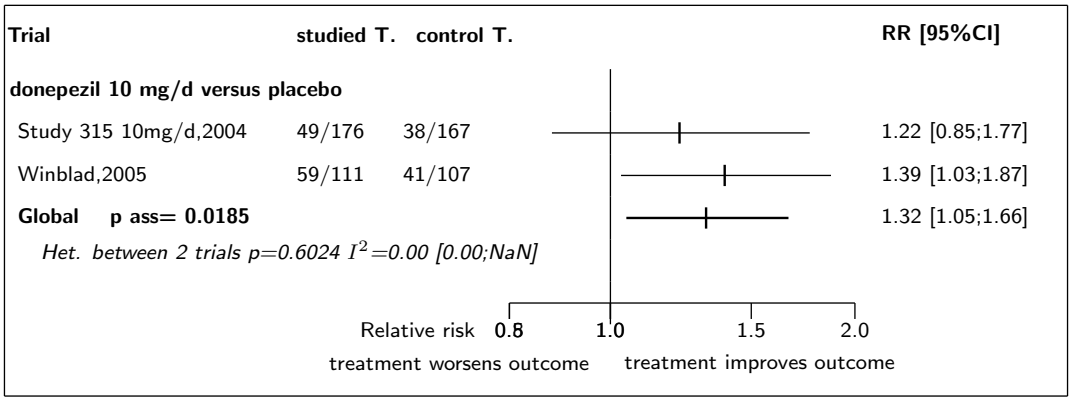


***Figure 2.7:*** *Forest's plot for MMSE at 6 months*

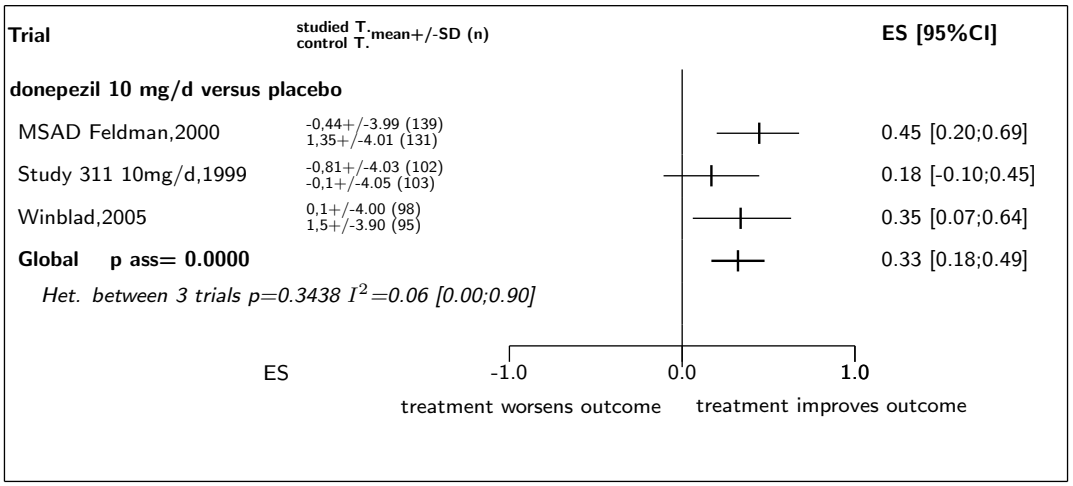



***Figure 2.8:*** *Forest's plot for CDR-SB at 12 weeks*

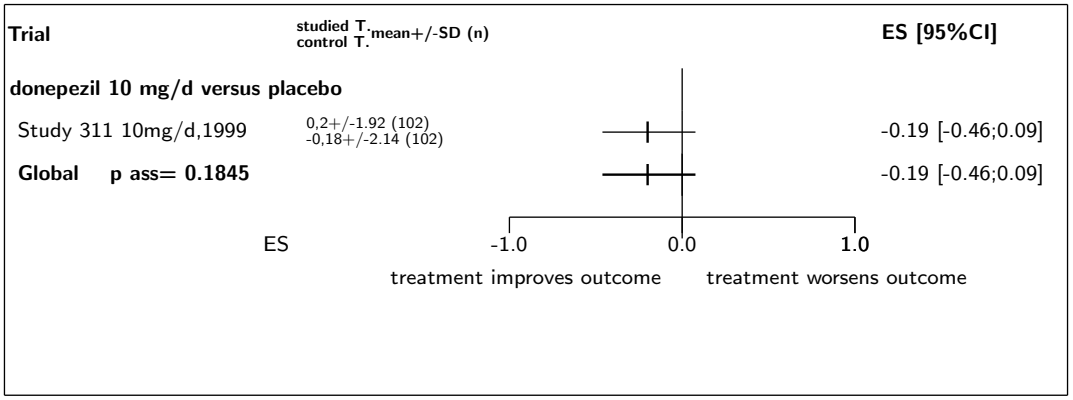



***Figure 2.9:*** *Forest's plot for CDR-SB at 24 weeks*

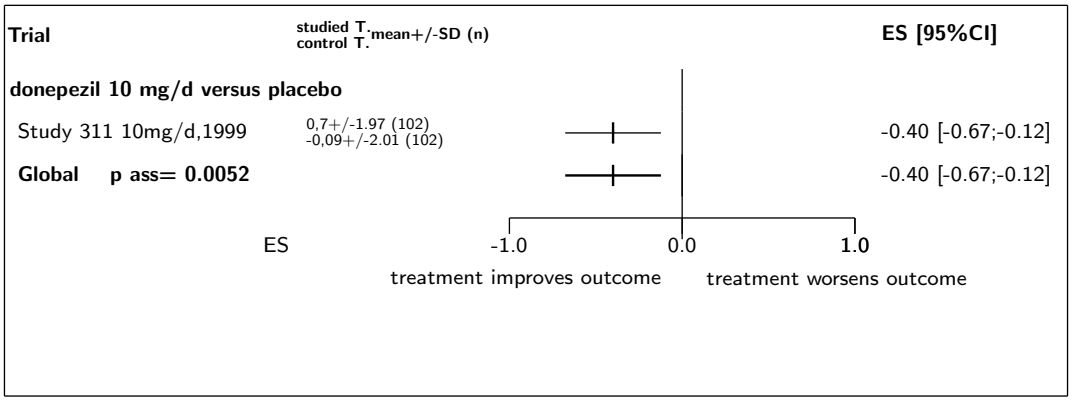


***Figure 2.10:*** *Forest's plot for MMSE at 12 weeks*

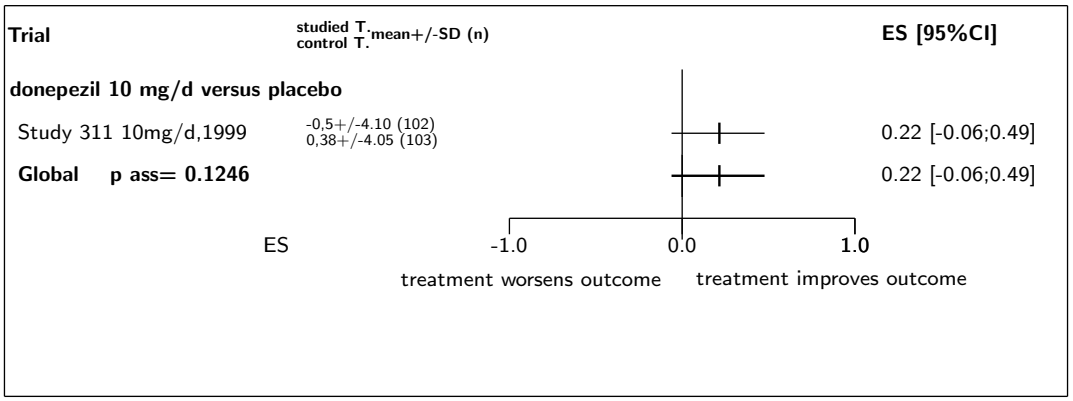



***Figure 2.11:*** *Forest's plot for diarrhoea*

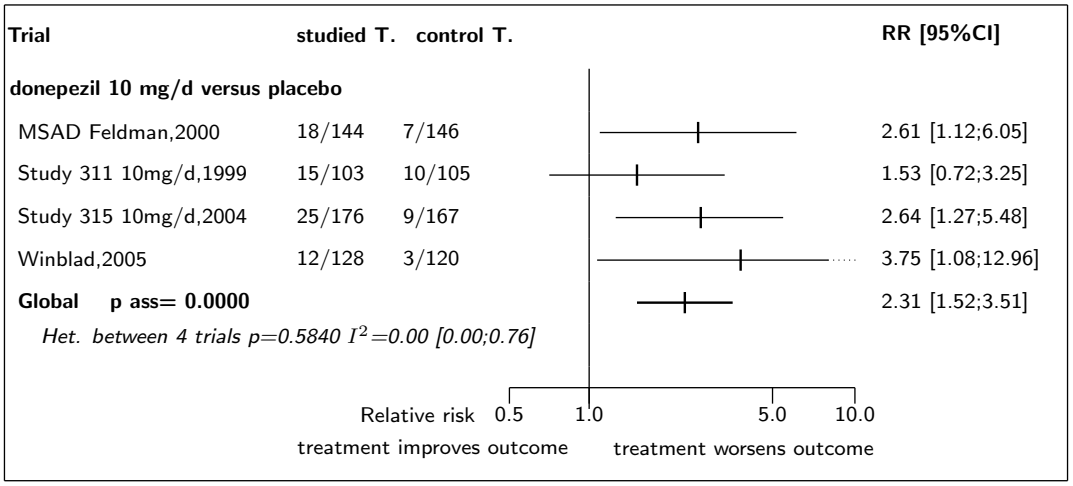



***Figure 2.12:*** *Forest's plot for nausea*

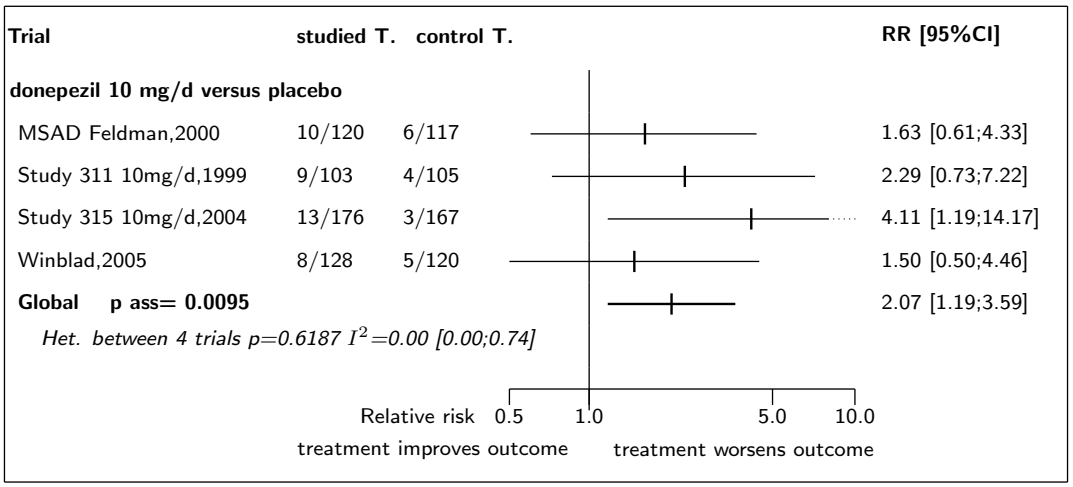
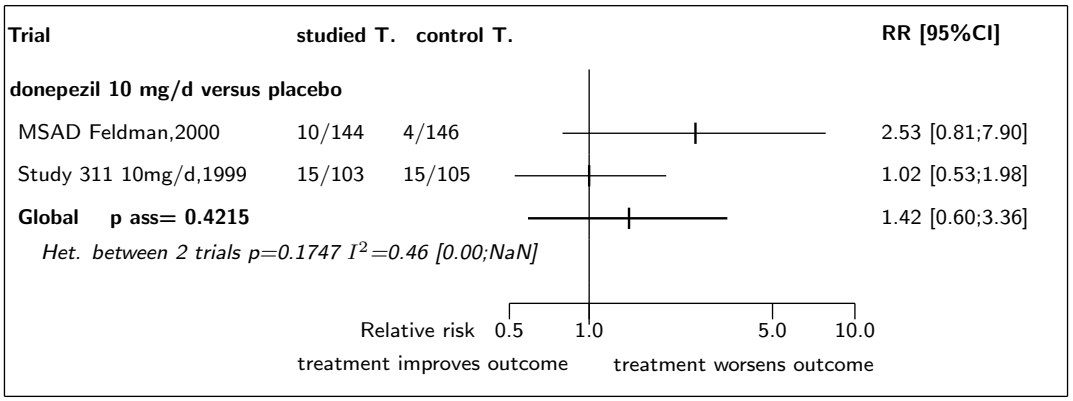


***Figure 2.13:*** *Forest's plot for vomiting*




# References

[1] Feldman H,. Therapeutic benefits of acetylcholinesterase inhibitor therapy in the moderate to severe stage of Alzheimer's disease. Proceedings of the Sixth International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 Apr 5-8, Stockholm 2000.

[2] Feldman H,Gauthier S,Hecker J,Vellas B,Emir B,Mastey V,Subbiah P,. Donepezil treatment benefits caregivers of patients with moderate to severe Alzheimer's disease (AD). European Journal of Neurology 2002; 9: 34-.

[3] Feldman H,Gauthier S,Hecker J,Vellas B,Emir B,Mastey V,Subbiah P,. 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. Journal of the American Geriatrics Society 2003; 51: 737-744. [PMID=12757558]

[4] Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Emir B, Subbiah P, Mastery V,. Improved health outcomes with donepezil in moderate to severe Alzheimer's disease are associated with economic benefits. The 8th conference on Alzheimer's disease and related disorders, July 20-25, 2002, Stockholm, Sweden 2002 , 285.

[5] Feldman H,Gauthier S,Hecker J,Vellas B,Hux M,Xu Y,Schwam EM,Shah S,Mastey V,. Economic evaluation of donepezil in moderate to severe Alzheimer disease. Neurology 2004; 63: 644-650. [PMID=15326236]

[6] Feldman H,Gauthier S,Hecker J,Vellas B,Ieni J,Xu Y,Schwam E,. Treatment Benefits of Donepezil in Patients with Severe Alzheimer's Disease and Their Caregivers. 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005 2005b:P02.097 2005; -.

[7] 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. Proceedings of the Sixth International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy; 2000 Apr 5-8, Stockholm 2000 ,.

[8] 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. Proceedings of the World Alzheimer Congress; 2000 Jul 9-13, Washington DC 2000 ,.

[9] Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E,. Benefits of Donepezil on global function, behavior, cognition and ADLs in patients with moderate to severe Alzheimer's disease. Neurology 2000 , A469.

[10] Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001 Aug 28;57:613-20. [PMID=11524468]

[11] Feldman H,Gauthier S,Hecker J,Vellas B,Xu Y,Ieni JR,Schwam EM,. Efficacy and safety of donepezil in patients with more severe Alzheimer's disease: a subgroup analysis from a randomized, placebo-controlled trial. International Journal of Geriatric Psychiatry 2005; 20: 559-69. [PMID=15920715]

[12] Gauthier S,. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate-to-severe Alzheimer's disease, and impact on caregiver burden. Geriatrics and Aging 2004; 7: 34-36.

[13] Gauthier S,Feldman H,Hecker J,Vellas B,Ames D,Subbiah P,Whalen E,Emir B,. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. International Psychogeriatrics 2002; 14: 389-404. [PMID=12670060]

[14] Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, McGill PS,. Exploratory analysis of the effects af donepezil in moderate and severe Alzheimer's disease patients. The 8th conference on Alzheimer's disease and related disorders, July 20-25, 2002, Stockholm, Sweden 2002 , 277.

[15] Gauthier S,Feldman H,Hecker J,Vellas B,Emir B,Subbiah P,. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2002; 18: 347-354.

[16] 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. Proceedings of the World Alzheimer Congress; 2000 Jul 9-13, Washington DC 2000 ,.

[17] 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. Journal of the European College of Neuropsychopharmacology 2000; S359-.

[18] Gauthier S, Feldman H, Vellas B, Subbiah P,. Efficacy of donepezil on functional, behavioural and cognitive symptoms in patients with moderate to severe Alzheimer's disease. Journal of the American Geriatrics Society 2000 , S2.

[19] Hecker J, Foti D, Gauthier S, Vellas B, Subbiah P, Whalen E,. Benefits of donepezil in the treatment of behavioural problems in moderate to severe Alzheimer's disease. Proceedings of the World Alzheimer Congress; 2000 Jul 9-13, Washington DC 2000 ,.

[20] Luckmann R,. Donepezil improved the clinical state and quality of life in moderate-to-severe Alzheimer disease. ACP-Journal-Club 2002 . 59. [PMID=11874284]

[21] Panisset M, Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E,. Use of the severe impairment battery in a clinical trial of donepezil in moderate to severe Alzheimers disease. Proceedings of the World Alzheimer Congress; 2000 Jul 9-13, Washington 2000 ,.

[22] Shah SN,Feldman H,Gauthier S,Hecker J,Vellas B,Hux M,Xu Y,Schwam E,Leaderer M,Pfizer Inc,New York,NY ,USA ,. Pharmacoeconomic Benefits of Donepezil Treatment in Severe Alzheimer's Disease. NeuroBiology of Aging 2004; 25: 208-.

[23] Vellas B, Feldman H, Gauthier S, Hecker J, Subbiah P, Whalen E, Mastey V,. Donepezil treatment in patients with moderate to severe Alzheimer's disease reduces caregiver stress. Proceedings of the World Alzheimer Congress; 2000 Jul 9-13, Washington 2000 ,.

[24] Steinman MA,Covinsky KE,Tariot PN,Cummings JL,Katz IR,Mintzer J,Perdomo CA,Schwam EM,Whalen E,. Donepezil for nursing home patients with dementia: a reinterpretation of the evidence. Journal of the American Geriatrics Society 2003; 51: 132-133. [PMID=12534859]

[25] Tariot P,Cummings JL,Katz IR,Perdomo CA,Whalen E,Sovel MA,Schwam EM,. Donepezil was well-tolerated and enhanced cognition in nursing home patients with alzheimer's disease. Journal of the American Geriatrics Society 1999; 47: S3-.

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

[27] Tariot PN,Cummings JL,Katz IR,Mintzer J,Perdomo CA,Schwam EM,Whalen E,. A randomised, double-blind, placebo-controlled study of the efficacy and safety of Donepezil in patients with Alzheimer's disease in the nursing home setting. Journal of the American Geriatrics Society 2001; 49: 1590-9. [PMID=11843990]

[28] Tariot PN,Cummings JL,Katz IR,Mintzer J,Perdomo CA,Schwam EM,Whalen E,. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting J Am Geriatr Soc 2001;49:1590-9. Journal of the American Geriatrics Society 2003; 51: 133-134.

[29] Pfizer ,. E2020-A001-315: A 24 week multinational RCT evaluating the efficacy and safety of donepezil in severe AD. http://www.marc.soton.ac.uk/Research%20Page.htm.

[30] Richardson S,. A 24 Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Donepezil Hydrochloride (E2020) in Patients with Severe Alzheimer's Disease Followed by a 12 Week Open-Label Extension Period. http://www.clinicaltrials.gov/ct/show/NCT00096473 2004.

[31] Batsman S,Minthon L,Eeriksson S,Kilander L,jansson-Blixt C,Wetterholm A,Haglund A,Winblad B,. Study design and baseline patients characteristics in a randomized controlled trial of the efficacy and tolerability of donepezil in severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[32] Eriksson S,Winblad B,Kilander L,Batsman S,Jansson-Blixt C,Wetterholm A,Haglund A,Minthon L,. Efficacy of donepezil on secondary end points in a randomized, double-blind placebo-controlled study in severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[33] Kilander L,Winblad B,Minthon L,Batsman S,Jansson-Blixt C,Cronlund A,Haglund A,Eriksson S,. Donepezil is well tolerated in patients with severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[34] Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL, Jansson-Blixt C, Haglund A. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006 Apr 1;367:1057-65. [PMID=16581404]

[35] Winblad B,Minthon L,Eriksson S,Batsman S,Jansoon-Blixt C,Wetterholm A,Haglund A,Kilander L,. Efficacy of donepezil on primary end points in a randomized, double-blind placebo-controlled study in severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

# 3 Detailed results for donepezil 5-10 mg/d

## 3.1 Available trials

Only one trial which randomized 994 patients was identified: it compared donepezil 5-10 mg/d with rivastigmine.
This trial included 994 patients and was published in 2005.
This trial was double blind in design.
It was reported in English language.
ADCS-ADL-severe at 6 months data was reported in 1 trials; 1 trials reported data on MMSE at 6 months; 1 trials reported data on NPI at 6 months; and 1 trials reported data on SIB score at 6 months.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of donepezil 5-10 mg/d.

***Table 3.1:*** *Treatment description - donepezil - donepezil 5-10 mg/d*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Donepezil 5-10 mg/d versus rivastigmine** | | |
| EXCEED (2005) [**?**] | donepezil 5-10 mg/day | rivastigmine 3-12 mg/day |

***Table 3.2:*** *Descriptions of participants - donepezil - donepezil 5-10 mg/d*

| Trial | Patients |
|---|---|
| **Donepezil 5-10 mg/d versus rivastigmine** | |
| EXCEED (2005) [**?**] | Patients with moderate to moderately-severe Alzheimer's disease |

***Table 3.3:*** *Main patients characteristics - donepezil - donepezil 5-10 mg/d*

| Trial | Characteristics |
|---|---|
| **Donepezil 5-10 mg/d versus rivastigmine** | |
| EXCEED, 2005 [**?**] | |

***Table 3.4:*** *Design and methodological quality of trials - donepezil - donepezil 5-10 mg/d*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Donepezil 5-10 mg/d versus rivastigmine** | | | | |

continued...

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| EXCEED, 2005 [?] n=994 | Parallel groups Double blind | 2 years | | |

## 3.2 Meta-analysis results

The results are detailed in table ?? (page ??). This table is followed by the Forest's plot corresponding to each endpoint.

### Donepezil 5-10 mg/d versus rivastigmine

The single study eligible for this comparison provided data on **SIB score at 6 months**. No statistically significant difference between the groups was found in SIB score at 6 months, with a ES of -0.03 (95% CI -0.15 to 0.10, p=0.6952).
The single study eligible for this comparison provided data on **ADCS-ADL-severe at 6 months**. No statistically significant difference between the groups was found in ADCS-ADL-severe at 6 months, with a ES of -0.11 (95% CI -0.24 to 0.02, p=0.1030).
The single study eligible for this comparison provided data on **NPI at 6 months**. No statistically significant difference between the groups was found in NPI at 6 months, with a ES of 0.03 (95% CI -0.10 to 0.16, p=0.6339).
The single study eligible for this comparison provided data on **MMSE at 6 months**. No statistically significant difference between the groups was found in MMSE at 6 months, with a ES of -0.08 (95% CI -0.20 to 0.05, p=0.2392).

***Table 3.5:*** *Results details - donepezil - donepezil 5-10 mg/d*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***donepezil 5-10 mg/d versus rivastigmine*** | | | | | | |
| SIB score at 6 months | ES=-0.03 | [-0.15;0.10] | 0.6952 | 1.0000 ($I^2$=0.00) | 1 | 954 |
| ADCS-ADL-severe at 6 months | ES=-0.11 | [-0.24;0.02] | 0.1030 | 1.0000 ($I^2$=0.00) | 1 | 929 |
| NPI at 6 months | ES=0.03 | [-0.10;0.16] | 0.6339 | 1.0000 ($I^2$=0.00) | 1 | 955 |
| MMSE at 6 months | ES=-0.08 | [-0.20;0.05] | 0.2392 | 1.0000 ($I^2$=0.00) | 1 | 955 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 3.1:*** *Forest's plot for SIB score at 6 months*

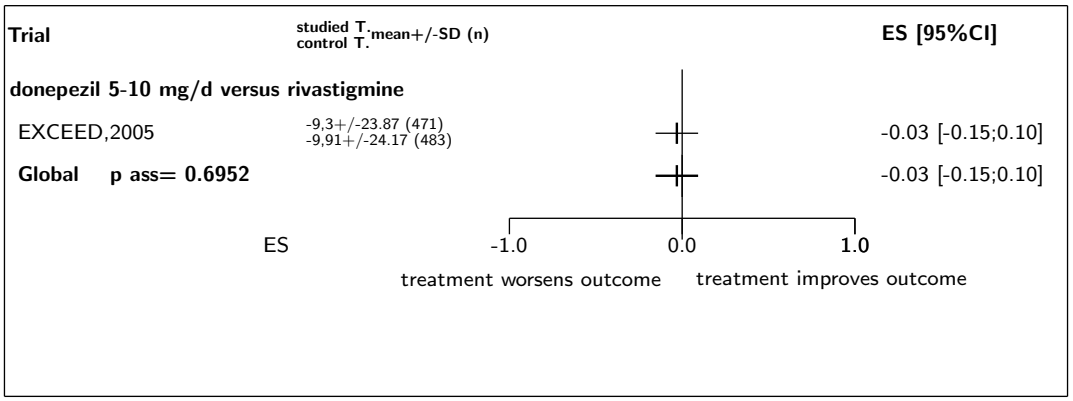



***Figure 3.2:*** *Forest's plot for ADCS-ADL-severe at 6 months*

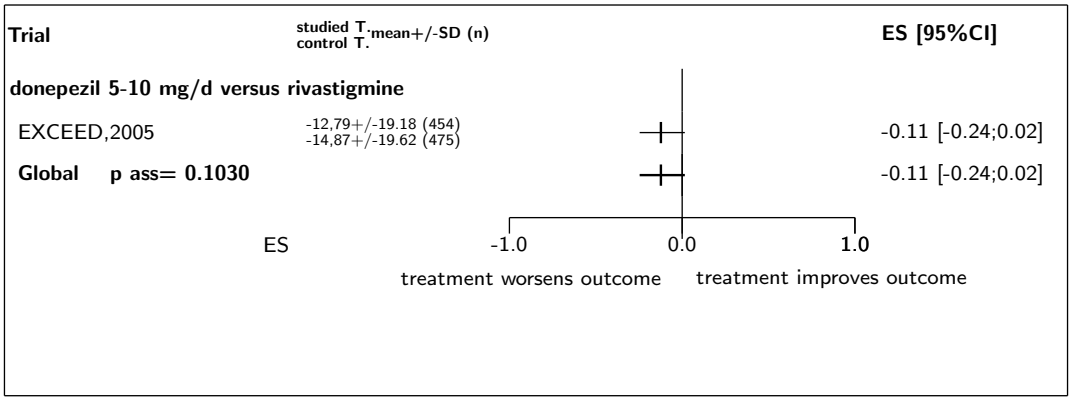



***Figure 3.3:*** *Forest's plot for NPI at 6 months*

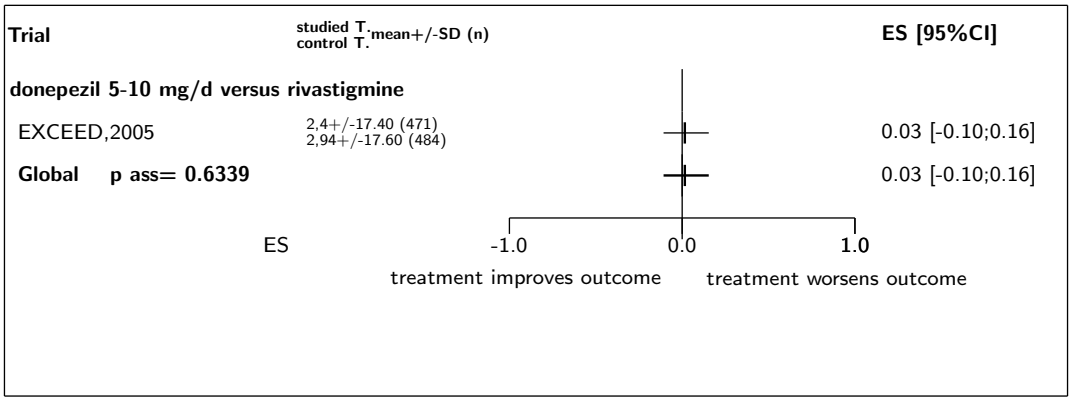
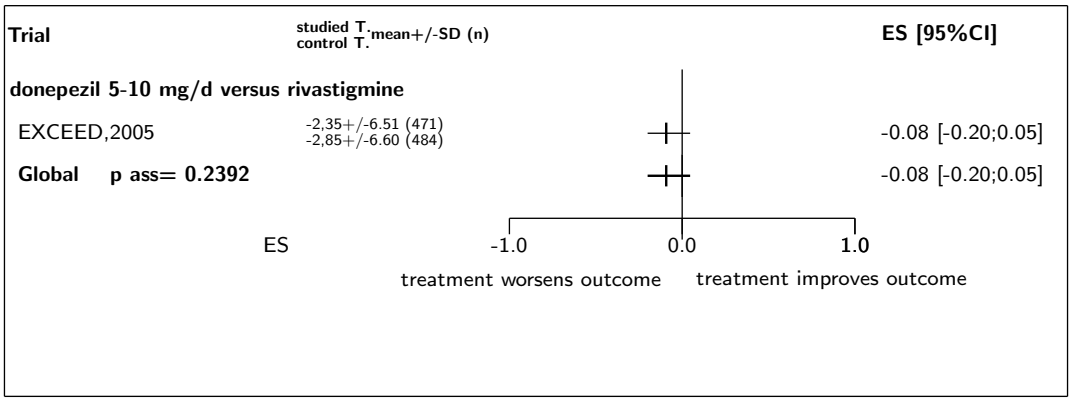


***Figure 3.4:*** *Forest's plot for MMSE at 6 months*




# References

[1] Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin 2005 Aug;21:1317-27. [PMID=16083542]

# 4 Global meta-analysis: all donepezil

## 4.1 Global meta-analysis: all donepezil versus placebo

***Table 4.1:*** *All donepezilversus placebo*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| SIB score at 6 months | ES=0.38 | 0.25;0.52 | 0.0000 | 0.9486 (0.00) | 3 | 843 |
| ADCS-ADL-severe at 6 months | ES=0.31 | 0.04;0.57 | 0.0251 | 1.0000 (0.00) | 1 | 216 |
| NPI at 6 months | ES=-0.13 [1] | -0.43;0.17 | 0.4097 | 0.0164 (0.76) † | 3 | 706 |
| CIBIC-Plus or CGIC (numbers improved) at 24 weeks | RR=1.32 | 1.05;1.66 | 0.0185 | 0.6024 (0.00) | 2 | 561 |
| MMSE at 6 months | ES=0.33 | 0.18;0.49 | 0.0000 | 0.3438 (0.06) | 3 | 668 |
| CDR-SB at 12 weeks | ES=-0.19 | -0.46;0.09 | 0.1845 | 1.0000 (0.00) | 1 | 204 |
| CDR-SB at 24 weeks | ES=-0.40 | -0.67;-0.12 | 0.0052 | 1.0000 (1.00) | 1 | 204 |
| MMSE at 12 weeks | ES=0.22 | -0.06;0.49 | 0.1246 | 1.0000 (0.00) | 1 | 205 |

[1] with a random model ($\tau^2 = 0.054$). The results with a fixed effect model was RRFE=-0.15 95% CI -0.30;0.00

legend B

## 4.2 Global meta-analysis: all donepezil versus rivastigmine

***Table 4.2:*** *All donepezilversus rivastigmine*

| **Endpoint** | **Effect** | **95% CI** | **p ass** | **p het ($I^2$)** | **k** | **n** |
|---|---|---|---|---|---|---|
| SIB score at 6 months | ES=-0.03 | -0.15;0.10 | 0.6952 | 1.0000 (0.00) | 1 | 954 |
| ADCS-ADL-severe at 6 months | ES=-0.11 | -0.24;0.02 | 0.1030 | 1.0000 (0.00) | 1 | 929 |
| NPI at 6 months | ES=0.03 | -0.10;0.16 | 0.6339 | 1.0000 (0.00) | 1 | 955 |
| MMSE at 6 months | ES=-0.08 | -0.20;0.05 | 0.2392 | 1.0000 (0.00) | 1 | 955 |

legend B

# 5 Ongoing studies of donepezil

No ongoing trial was identified.

# 6 Excluded studies for donepezil

No trial was excluded.

# Part II

# NMDA-receptor antagonist

# 7 Overview of NMDA-receptor antagonist

## 7.1 Included trials

A total of 2 randomized comparisons which enrolled 602 patients were identified. In all, 2 randomized comparisons concerned Memantine.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for Memantine.

The average study size was 335 patients (range 252 to 404). The first study was published in 2003, and the last study was published in 2004.
Erreur ??? 0 et 0.
All included studies were reported in English language. We found one unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

## 7.2 Summary of meta-analysis results

The meta-analysis of the available trials about NMDA-receptor antagonist provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

### 7.2.1 Association memantine and donepezil

### 7.2.2 Memantine

No significant difference was found between **Memantine** and **placebo** in terms of CIBIC+ score at 6 months (ES=0.01, 95% CI -0.53 to 0.56, p=0.9627, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0000)(ES=0.28, 95% CI -0.11 to 0.67, p=0.1565, 2 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0184)(ES=0.20, 95% CI -0.02 to 0.41, p=0.0745, 2 trials)and NPI at 6 months (ES=-0.07, 95% CI -0.32 to 0.18, p=0.5925, 2 trials). There is a statistically significant difference in favour of Memantine for agitation (RR=0.60, 95% CI 0.42 to 0.86, p=0.0052, 2 trials).

***Table 7.1:*** *Main study characteristics - NMDA-receptor antagonist*

| Trial | Patients | Treatments | Trial design and method |
|---|---|---|---|
| **Association memantine and donepezil** | | | |
| **Memantine** | | | |
| ***Memantine versus placebo*** | | | |
| 9605/Reisberg, 2003 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] n = 126 vs. 126 | alzheimer's disease by DSM-IV and NINCDS-ADRDA | memantine 20 mg /day **versus** placebo | Primary endpoint: CIBIC-Plus and ADCS-ADLsev |
| MD-01, 2004 [?, ?, ?] n = 178 vs. 172 | alzheimers disease by NlNCDS-ADRDA; | 20 mg memantine daily **versus** placebo | Primary endpoint: SIB and ADL |

***Table 7.2:*** *Summary of all results for Association memantine and donepezil*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

***Table 7.3:*** *Summary of all results for Memantine*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| ***Memantine versus placebo*** | | | | | | |
| CIBIC+ score at 6 months | ES=0.01 [1] | -0.53;0.56 | 0.9627 | 0.0000 (0.91) † | 2 | 570 |
| SIB score at 6 months | ES=0.28 [2] | -0.11;0.67 | 0.1565 | 0.0184 (0.82) † | 2 | 582 |
| ADCS-ADL-severe at 6 months | ES=0.20 | -0.02;0.41 | 0.0745 | 0.1863 (0.43) | 2 | 583 |
| NPI at 6 months | ES=-0.07 | -0.32;0.18 | 0.5925 | 0.1315 (0.56) | 2 | 554 |
| withdrawals due to an adverse event at 24 weeks | RR=0.99 | 0.91;1.07 | 0.7693 | 0.6268 (0.00) | 2 | 602 |
| agitation | RR=0.60 | 0.42;0.86 | 0.0052 | 0.7657 (0.00) | 2 | 602 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

[1] with a random model ($\tau^2 = 0.141$). The results with a fixed effect model was RRFE=0.06 95% CI -0.11;0.22

[2] with a random model ($\tau^2 = 0.065$). The results with a fixed effect model was RRFE=0.26 95% CI 0.09;0.42

# 8 Detailed results for Association memantine and donepezil

## 8.1 Available trials

A total of 0 RCTs which randomized 0 patients were identified: .
This trial included 404 patients and was published in 2004.
Erreur ??? 0 et 0.
It was reported in English language.
ADCS-ADL-severe at 6 months data was reported in 1 trials; 1 trials reported data on CIBIC+ score at 6 months; 1 trials reported data on NPI at 6 months; 1 trials reported data on SIB score at 6 months; 1 trials reported data on withdrawals due to an adverse event at 24 weeks; and 1 trials reported data on agitation.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trial including in this systematic review of randomized trials of Association memantine and donepezil.

***Table 8.1:*** *Treatment description - NMDA-receptor antagonist - Association memantine and donepezil*

| Trial | Studied treatment | Control treatment |
|---|---|---|

***Table 8.2:*** *Descriptions of participants - NMDA-receptor antagonist - Association memantine and donepezil*

| Trial | Patients |
|---|---|

***Table 8.3:*** *Main patients characteristics - NMDA-receptor antagonist - Association memantine and donepezil*

| Trial | Characteristics |
|---|---|

***Table 8.4:*** *Design and methodological quality of trials - NMDA-receptor antagonist - Association memantine and donepezil*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|

## 8.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

***Table 8.5:*** *Results details - NMDA-receptor antagonist - Association memantine and donepezil*

| Comparison | Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|---|

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

# References

# 9 Detailed results for Memantine

## 9.1 Available trials

A total of 2 RCTs which randomized 602 patients were identified: all compared Memantine with placebo.
The average study size was 301 patients (range 252 to 350). The first study was published in 2003, and the last study was published in 2004.
Erreur ??? 0 et 0.
All included studies were reported in English language. We found one unpublished trial.
ADCS-ADL-severe at 6 months data was reported in 2 trials; 2 trials reported data on CIBIC+ score at 6 months; 2 trials reported data on NPI at 6 months; 2 trials reported data on SIB score at 6 months; 2 trials reported data on withdrawals due to an adverse event at 24 weeks; and 2 trials reported data on agitation.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of Memantine.

***Table 9.1:*** *Treatment description - NMDA-receptor antagonist - Memantine*

| Trial | Studied treatment | Control treatment |
|---|---|---|
| **Memantine versus placebo** | | |
| 9605/Reisberg (2003) [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | memantine 20 mg /day | Placebo |
| MD-01 (2004) [?, ?, ?] | 20 mg memantine daily | placebo |

***Table 9.2:*** *Descriptions of participants - NMDA-receptor antagonist - Memantine*

| Trial | Patients | |
|---|---|---|
| **Memantine versus placebo** | | |
| 9605/Reisberg (2003) [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | Alzheimer's disease by DSM-IV and NINCDS-ADRDA<br>**Inclusion criteria:** MMSE:3-14; GDS:6; FAST: 6 | **Exclusion criteria:** vascular dementia, or other clinically significant neurological disease, major depressive disorder, or a score greater than 4 on the Modified Hachinski Ischaemia Rating Scale. |
| MD-01 (2004) [?, ?, ?] | Alzheimers disease by NlNCDS-ADRDA;<br>**Inclusion criteria:** MMSE: 5-14. Age at least 50. | **Exclusion criteria:** |

***Table 9.3:*** *Main patients characteristics - NMDA-receptor antagonist - Memantine*

| Trial | Characteristics |
|---|---|
| **Memantine versus placebo** | |
| 9605/Reisberg, 2003 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] | |
| MD-01, 2004 [?, ?, ?] | |

***Table 9.4:*** *Design and methodological quality of trials - NMDA-receptor antagonist - Memantine*

| Trial | Design | Duration | Centre | Primary endpoint |
|---|---|---|---|---|
| **Memantine versus placebo** | | | | |
| 9605/Reisberg, 2003 [?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?, ?] n=252 | | 28 weeks | | CIBIC-Plus and ADCS-ADLsev |
| MD-01, 2004 [?, ?, ?] n=350 | | 24 weeks | | SIB and ADL |

## 9.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

### Memantine versus placebo

All the 2 studies had extractable data about the number of participants with **CIBIC+ score at 6 months**. There was no statistically significant difference in CIBIC+ score at 6 months between Memantine and placebo, with a ES of 0.01 (95%CI -0.53 to 0.56, p=0.9627) in favour of placebo. In other words, CIBIC+ score at 6 months was slightly lower in the Memantine group , but this was not statistically significant. A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0000, $I^2$ = 0.91%).
All the 2 studies had extractable data about the number of participants with **SIB score at 6 months**. When pooled together, there was no statistically significant difference between the groups in SIB score at 6 months, with a ES of 0.28 (95% CI -0.11 to 0.67, p=0.1565). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0184, $I^2$ = 0.82%).
All the 2 studies had extractable data about the number of participants with **ADCS-ADL-severe at 6 months**. When pooled together, there was no statistically significant difference between the groups in ADCS-ADL-severe at 6 months, with a ES of 0.20 (95% CI -0.02 to 0.41, p=0.0745). No heterogeneity was detected (p = 0.1863, $I^2$ = 0.43%).
All the 2 studies had extractable data about the number of participants with **NPI at 6 months**. When pooled together, there was no statistically significant difference between the groups in NPI

at 6 months, with a ES of -0.07 (95% CI -0.32 to 0.18, p=0.5925). No heterogeneity was detected (p = 0.1315, $I^2$ = 0.56%).

***Table 9.5:*** *Results details - NMDA-receptor antagonist - Memantine*

| Comparison Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| ***Memantine versus placebo*** | | | | | | |
| CIBIC+ score at 6 months | ES=0.01 | [-0.53;0.56] | 0.9627 | 0.0000 ($I^2$=0.91) | 2 | 570 |
| SIB score at 6 months | ES=0.28 | [-0.11;0.67] | 0.1565 | 0.0184 ($I^2$=0.82) | 2 | 582 |
| ADCS-ADL-severe at 6 months | ES=0.20 | [-0.02;0.41] | 0.0745 | 0.1863 ($I^2$=0.43) | 2 | 583 |
| NPI at 6 months | ES=-0.07 | [-0.32;0.18] | 0.5925 | 0.1315 ($I^2$=0.56) | 2 | 554 |
| withdrawals due to an adverse event at 24 weeks | RR=0.99 | [0.91;1.07] | 0.7693 | 0.6268 ($I^2$=0.00) | 2 | 602 |
| agitation | RR=0.60 | [0.42;0.86] | 0.0052 | 0.7657 ($I^2$=0.00) | 2 | 602 |

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; $I^2$: inconsistance degree

***Figure 9.1:*** *Forest's plot for CIBIC+ score at 6 months*

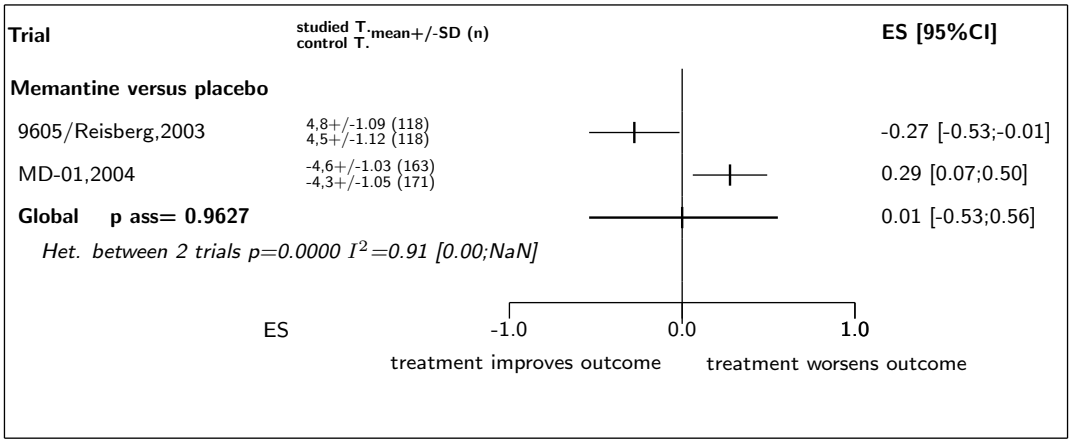



***Figure 9.2:*** *Forest's plot for SIB score at 6 months*

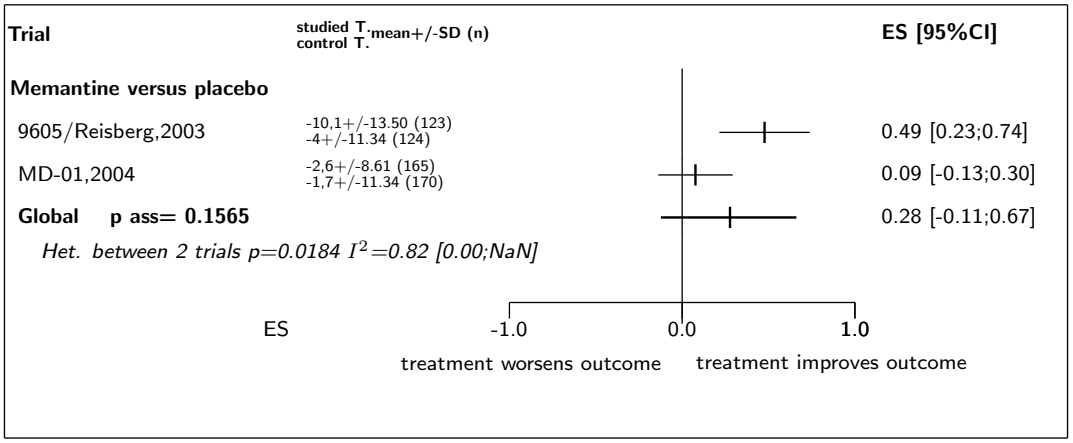


***Figure 9.3:*** *Forest's plot for ADCS-ADL-severe at 6 months*

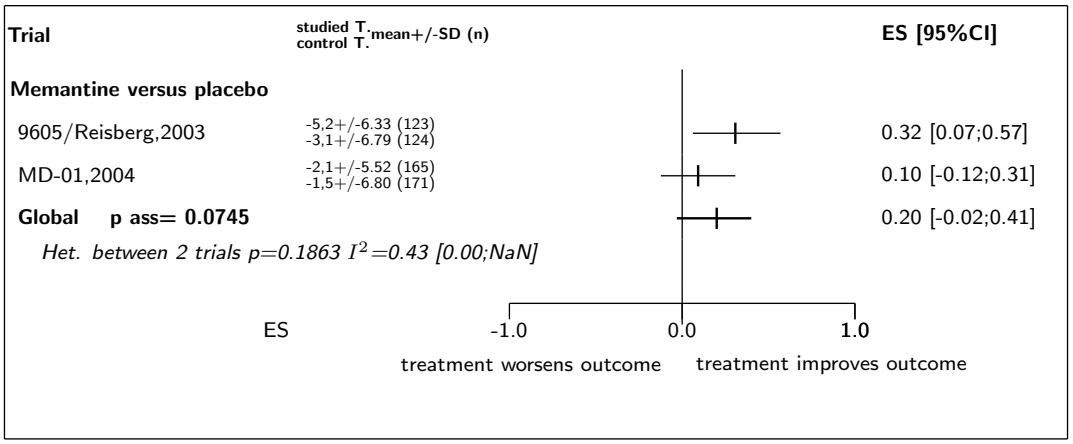



***Figure 9.4:*** *Forest's plot for NPI at 6 months*

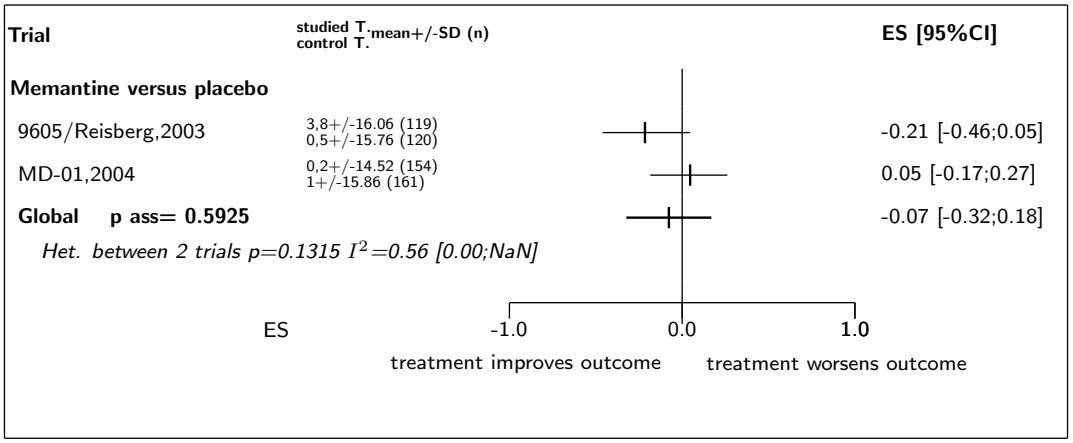



***Figure 9.5:*** *Forest's plot for withdrawals due to an adverse event at 24 weeks*

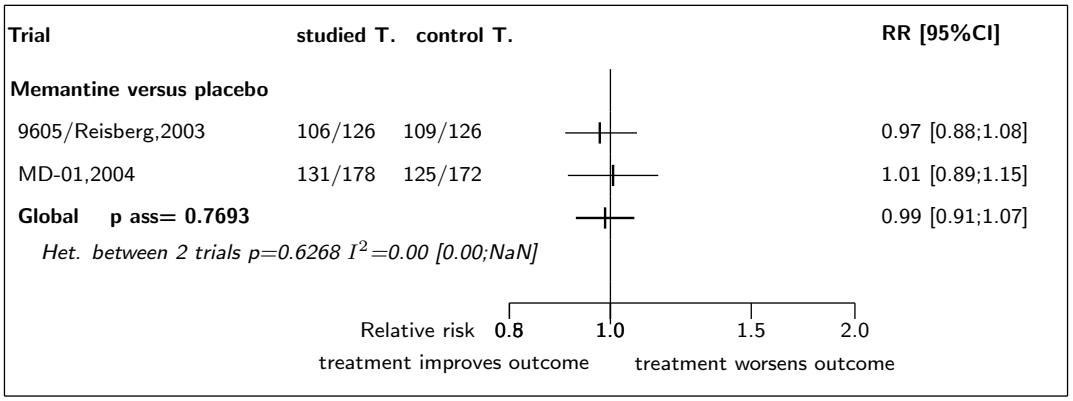
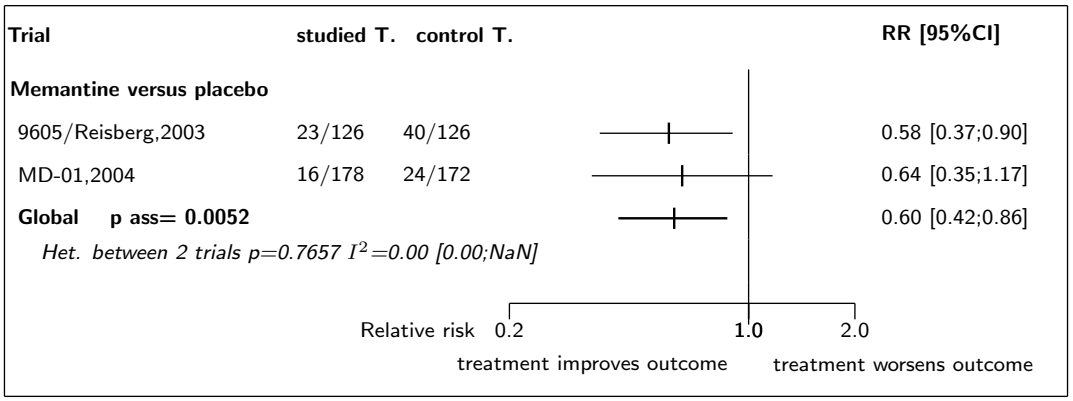


***Figure 9.6:*** *Forest's plot for agitation*




# References

[1] Doody R,Wirth Y,Schmitt F,Mobius H J,. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. Dementia and geriatric cognitive disorders 2004; 18: 227-32. [PMID=15256834]

[2] Doody R,Wirth Y,Schmitt F,Moebius HJ,. Functional benefits of memantine treatment for patients with moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[3] Feldman H,Schmitt FA,Doraiswamy PM,Graham SM,Bell JM,. Memantine and Individual Activities of Daily Living in Moderate to Severe Alzheimer's Disease. In: 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005 2005; -.

[4] Feldman H,Schmitt FA,PFeiffer E,Graham SM,Bell JM,. Memantine and individual activities of daily living in moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[5] Ferris S,. Clinical trial of memantine in severe Alzheimer disease: rationale and design. Proceedings of the 9th Congress of the International Psychogeriatric Association, Aug 15-20 1999, Vancouver 1999; -.

[6] Gauthier S,Wirth Y,Mobius HJ,. Effects of memantine on behavioural symptoms in alzheimer's disease patients: an analysis of the neuropsychiatric inventory (npi) data of two randomised, controlled studies. International Journal of Geriatric Psychiatry 2005; 20: 459-64. [PMID=15852444]

[7] Gauthier S,Wirth Y,Stockholm ,Sweden ,20-24 September 2005 2005,. Positive behavioural effects of memantine treatment in patients with Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005 2005; -.

[8] Moebius HJ,Wirth Y,Gauthier S,. Memantine: Behavioral Benefits for Moderate to Severe Alzheimer's Patients. 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005 2005; P02.095-.

[9] Reisberg B,Doody R,Stöffler A,Schimitt F,Ferris S,. Memantine in Moderate to Severe Alzheimers Disease. The New England Journal of Medicine 2003; 348: 1333-1341. [PMID=12672860]

[10] Reisberg B,Ferris S,. Experimental therapeutic shows promise for people with moderately severe to severe Alzheimer's disease. World Alzheimer Congress 2000 2000; -.

[11] Reisberg B,Ferris S,Sahin K,Windscheif U,Möbius HJ,. Results of a placebo-controlled 6 month trial with memantine in moderate to severe Alzheimer's disease. Journal of the European College of Neuropsychopharmacology 2000; 10: S363-4.

[12] Reisberg B,Möbius HJ,Stöffler A,Schmitt F,Doody R,Ferris S,. Long treatment with the NMDA antagonist memantine results of a 24 week open label extension study in moderately severe to severe Alzheimer's disease. The 8th Conference on Alzheimer's disease and related disorders, July 20-25, 2002, Stockholm, Sweden 2002; -.

[13] Reisberg B,Stöffler A,Ferris SH,Schmitt F,Doody RS,. A placebo controlled study of memantine in advanced Alzheimer's disease. Proceedings of the 15th Annual Meeting of the American Psychiatric Association; 2001 May 5-10, New Orleans 2001; -.

[14] Reisberg B,Windscheif U,Ferris SH,Hingorani VN,Stöffler A,Möbius HJ,. Memantine in moderately severe to severe Alzheimer's disease: Results of a placebo-controlled 6 month trial. Conference proceedings Worl Alzheimer Congress; 9-13 July, 2000. Washington 2000; -.

[15] Reisberg B,Windscheif U,Ferris SH,Stöffler A,. Treatment of advanced Alzheimer's disease with memantine, an NMDA antagonist: results of a 6 month multicenter randomized controlled trial. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology; Dec 10-14, 2000. San Juan, Puerto Rico 2000; -.

[16] Wimo A,Winblad B,Stoeffler A,Wirth Y,Moebius HJ,. Effect of long term treatment with memantine, an NMDA antagonist, on costs associated with advanced Alzheimer's disease: results of a 28-week randomized double-blind, placebo-controlled study. Proceedings of the 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 July 20-25, Stockholm, Sweden 2002; Abstract No 167.

[17] Wimo A,Winblad B,Stoeffler A,Wirth Y,Moebius HJ,. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. PharmacoEconomics 2003; 21: 327-40. [PMID=12627986]

[18] . FDA. Peripheral and Central Nervous System Drugs Advisory Committee September 24, 2003. Presentation by Forest, Slide 28. http://www.fda.gov/ohrms/dockets/ac/03/slides/3979S1$_0$1$_F$ − *Forest* − *Backup.ppt*.

[19] Forest Laboratories I,. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate to severe dementia of the Alzheimer's type. http://www.forestclinicaltrials.com/CTR/CTRController/CTRCompletedListStudies 2005.

[20] Peterson L,. American Neurological Association. November 2003. http://www.trends-in-medicine.com/Nov2003/AmNeuro113p.pdf.

# 10 Global meta-analysis: all NMDA-receptor antagonist

## 10.1 Global meta-analysis: all NMDA-receptor antagonist versus placebo

***Table 10.1:*** *All NMDA-receptor antagonistversus placebo*

| Endpoint | Effect | 95% CI | p ass | p het ($I^2$) | k | n |
|---|---|---|---|---|---|---|
| CIBIC+ score at 6 months | ES=0.01 [1] | -0.53;0.56 | 0.9627 | 0.0000 (0.91) † | 2 | 570 |

continued...

[1] with a random model ($\tau^2 = 0.141$). The results with a fixed effect model was RRFE=0.06 95% CI -0.11;0.22

| Endpoint | Effect | 95% CI | p ass | p het | k | n |
|---|---|---|---|---|---|---|
| SIB score at 6 months | ES=0.28 [2] | -0.11;0.67 | 0.1565 | 0.0184 (0.82) † | 2 | 582 |
| ADCS-ADL-severe at 6 months | ES=0.20 | -0.02;0.41 | 0.0745 | 0.1863 (0.43) | 2 | 583 |
| NPI at 6 months | ES=-0.07 | -0.32;0.18 | 0.5925 | 0.1315 (0.56) | 2 | 554 |

legend B

# 11 Ongoing studies of NMDA-receptor antagonist

No ongoing trial was identified.

# 12 Excluded studies for NMDA-receptor antagonist

No trial was excluded.

[2]with a random model ($\tau^2 = 0.065$). The results with a fixed effect model was RRFE=0.26 95% CI 0.09;0.42