Supplement to Levine et al. Quantifying the Heterogeneity of Cognitive Functioning in Alzheimer’s Disease to extend the Placebo-Treatment Dichotomy: Latent class analysis of Individual-Participant Data from Five Pivotal Randomized Clinical Trials of Donepezil

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# eTable 1 Inclusion criteria by trial in the analytic sample

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trial | Allocation, sample, and dose information | Analytic sampleN(%) | List of visits with a scheduled ADAS-Cog administration | Trial inclusion criteria |
| Homma et al. (2000) | Placebo 132Donepezil 136 (5 mg) |  268 (12.23)  | Week 0, 4, 8, 12, 16, 20, 24 | MMSE: 10-26CDR: 1 or 2ADAS-cog: at least 15 |
| Rogers and Friedhoff (1996) | Placebo 37Donepezil 42 (1 mg)Donepezil 40 (3 mg)Donepezil 37 (5 mg) |  156 ( 7.12)  | Week 0, 1, 3, 6, 9, 12 | MMSE: 10-26CDR: 1 or 2 |
| Rogers, Doody, Mohs, and Friedhoff (1998) | Placebo 157Donepezil 160 (5 mg)Donepezil 163 (10 mg) |  480 (21.91)  | Week 0, 3, 6, 9, 12 | MMSE: 10-26CDR: 1 or 2 |
| Rogers, Farlow, Doody, Mohs, and Friedhoff (1998) | Placebo 162Donepezil 154 (5 mg)Donepezil 156 (10 mg) |  472 (21.54)  | Week 0, 6, 12, 18, 24 | MMSE: 10-26CDR: 1 or 2 |
| Burns et al. (1999) | Placebo 272Donepezil 271 (5 mg)Donepezil 272 (10 mg) |  815 (37.20)  | Week 0, 6, 12, 18, 24 | MMSE: 10-26CDR: 1 or 2 |

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale, CDR, Clinical Dementia Rating, MMSE: Mini-Mental State Examination.

# eTable 2 Supplement model fit indices

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Basis for model | Number of classes Polynomial | BIC | SABIC | Entropy | AIC | Loglik | NPM | Largest class |
| Primary analysis | 2 Linear | 47172.42 | 47121.59 | 0.77 | 47081.35 | -23524.67 | 16 | 77.23 |
| 2 Quadratic | 46988.00 | 46921.28 | 0.77 | 46868.47 | -23413.23 | 21 | 77.23 |
| 3 Linear | 47068.07 | 47007.71 | 0.84 | 46959.92 | -23460.96 | 19 | 76.22 |
| 3 Quadratic | 46891.99 | 46812.56 | 0.84 | 46749.69 | -23349.84 | 25 | 76.04 |
| 4 Linear | 47017.21 | 46947.31 | 0.79 | 46891.98 | -23423.99 | 22 | 61.94 |
| 4 Quadratic | 46813.02 | 46720.88 | 0.87 | 46647.94 | -23294.97 | 29 | 75.99 |
| 5 Linear | 46953.37 | 46873.94 | 0.81 | 46811.06 | -23380.53 | 25 | 62.21 |
| 5 Quadratic | 46809.29 | 46704.45 | 0.84 | 46621.45 | -23277.73 | 33 | 75.49 |
| 6 Linear | 46955.55 | 46866.59 | 0.82 | 46796.17 | -23370.09 | 28 | 62.07 |
| 6 Quadratic | 46721.52 | 46603.97 | 0.85 | 46510.91 | -23218.46 | 37 | 75.22 |
| Treatment group | 2 Linear | 30723.85 | 30676.20 | 0.75 | 30644.86 | -15307.43 | 15 | 76.17 |
| 2 Quadratic | 30596.41 | 30532.87 | 0.76 | 30491.08 | -15225.54 | 20 | 75.33 |
| 3 Linear | 30637.80 | 30580.62 | 0.83 | 30543.01 | -15253.50 | 18 | 75.26 |
| 3 Quadratic | 30518.81 | 30442.57 | 0.83 | 30392.42 | -15172.21 | 24 | 75.33 |
| 4 Linear | 30612.72 | 30546.01 | 0.84 | 30502.13 | -15230.07 | 21 | 75.96 |
| 4 Quadratic | 30478.48 | 30389.53 | 0.85 | 30331.03 | -15137.51 | 28 | 75.40 |
| 5 Linear | 30588.68 | 30512.44 | 0.81 | 30462.29 | -15207.15 | 24 | 62.61 |
| 5 Quadratic | 30463.84 | 30362.19 | 0.86 | 30295.33 | -15115.66 | 32 | 74.63 |
| 6 Linear | 30600.14 | 30514.37 | 0.77 | 30457.95 | -15201.98 | 27 | 61.84 |
| 6 Quadratic | 30457.31 | 30342.95 | 0.78 | 30267.73 | -15097.86 | 36 | 64.85 |
| Placebo group | 2 Linear | 16415.26 | 16367.63 | 0.81 | 16345.76 | -8157.88 | 15 | 76.58 |
| 2 Quadratic | 16372.50 | 16308.99 | 0.81 | 16279.83 | -8119.92 | 20 | 76.97 |
| 3 Linear | 16409.64 | 16352.48 | 0.74 | 16326.24 | -8145.12 | 18 | 60.39 |
| 3 Quadratic | 16289.55 | 16213.34 | 0.88 | 16178.35 | -8065.18 | 24 | 76.32 |
| 4 Linear | 16394.35 | 16327.67 | 0.78 | 16297.05 | -8127.53 | 21 | 61.71 |
| 4 Quadratic | 16282.07 | 16193.16 | 0.85 | 16152.33 | -8048.17 | 28 | 75.00 |
| 5 Linear | 16356.62 | 16280.41 | 0.80 | 16245.42 | -8098.71 | 24 | 62.37 |
| 5 Quadratic | 16306.13 | 16204.52 | 0.87 | 16157.87 | -8046.93 | 32 | 75.00 |
| 6 Linear | 16397.45 | 16311.71 | 0.78 | 16272.35 | -8109.18 | 27 | 41.18 |
| 6 Quadratic | 16303.51 | 16189.19 | 0.83 | 16136.71 | -8032.35 | 36 | 63.55 |

Abbreviations. BIC, Bayesian information criterion, the model with the smallest BIC value is considered the most parsimonious (Schwarz, 1978). SABIC, sample-size-adjusted BIC. Entropy, higher values imply a clearer differentiation between classes (Celeux & Soromenho, 1996). AIC Akaike information criterion. AIC estimates the quality of each model, relative to each of the other models (Akaike, 1974). We relied primarily on the BIC because it is the most common index and based on prior research (Nylund, Asparouhov, & Muthén, 2007).

# eTable 3 Logistic regression models

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Analysis | Low scorers | Low scorers (i.e., less severe cognitive impairment) | Improvers | High scorers (i.e. more severe cognitive impairment) |
| Term | OR (95% CI), P-Value | OR (95% CI), P-Value | OR (95% CI), P-Value |
| Primary analysis | Intercept | 0.68 (0.25, 1.85), 0.45 | 0.01 (0.00, 0.34), 0.01 | 1.43 (0.52, 3.95), 0.49 |
| Rogers & Friedhoff (1996) | **0.55 (0.35, 0.88)**, 0.01 | 0.83 (0.11, 5.14), 0.84 | **1.88 (1.16, 3.03)**, 0.01 |
| Rogers, et al. (1998a) | **0.62 (0.43, 0.90)**, 0.01 | 1.41 (0.41, 6.46), 0.62 | **1.59 (1.09, 2.34)**, 0.02 |
| Rogers, et al. (1998b) | **0.58 (0.40, 0.83)**, 0.00 | 0.47 (0.09, 2.60), 0.37 | **1.84 (1.26, 2.70)**, 0.00 |
| Burns et al. (1999) | 0.77 (0.54, 1.09), 0.14 | 0.88 (0.26, 3.96), 0.84 | 1.32 (0.93, 1.91), 0.13 |
| Male vs. ref. Female sex | 1.10 (0.90, 1.36), 0.34 | 1.31 (0.59, 2.82), 0.50 | 0.89 (0.72, 1.09), 0.25 |
| Age | **1.02 (1.01, 1.04)**, 0.00 | 0.99 (0.94, 1.04), 0.62 | **0.98 (0.96, 0.99)**, 0.00 |
| Donepezil vs. ref. Placebo | 1.15 (0.93, 1.42), 0.18 | **6.88 (2.03, 42.95)**, 0.01 | **0.79 (0.64, 0.98)**, 0.03 |
| Donepezil analysis | Intercept | 1.76 (0.50, 6.24), 0.38 | 0.00 (0.00, 0.21), 0.01 | 0.62 (0.17, 2.23), 0.46 |
| Rogers & Friedhoff (1996) | **0.49 (0.26, 0.89)**, 0.02 | 1.07 (0.13, 9.10), 0.94 | **2.13 (1.14, 4.05)**, 0.02 |
| Rogers, et al. (1998a) | **0.50 (0.29, 0.83)**, 0.01 | 1.56 (0.38, 10.50), 0.58 | **2.00 (1.18, 3.51)**, 0.01 |
| Rogers, et al. (1998b) | **0.49 (0.29, 0.82)**, 0.01 | 0.20 (0.01, 2.09), 0.19 | **2.27 (1.34, 3.98)**, 0.00 |
| Burns et al. (1999) | 0.62 (0.37, 1.00), 0.06 | 0.94 (0.23, 6.28), 0.94 | **1.68 (1.02, 2.90)**, 0.05 |
| Male vs. ref. Female sex | 1.11 (0.86, 1.43), 0.42 | 1.56 (0.64, 3.75), 0.31 | 0.86 (0.67, 1.11), 0.26 |
| Age | 1.02 (1.00, 1.03), 0.08 | 1.02 (0.96, 1.09), 0.46 | **0.98 (0.97, 1.00)**, 0.04 |
| Placebo analysis | Intercept | 0.25 (0.05, 1.32), 0.10 |   | 3.95 (0.76, 20.82), 0.10 |
| Rogers & Friedhoff (1996) | 0.72 (0.31, 1.73), 0.44 |   | 1.39 (0.58, 3.18), 0.44 |
| Rogers, et al. (1998a) | 0.73 (0.41, 1.28), 0.27 |  N/A | 1.37 (0.78, 2.43), 0.27 |
| Rogers, et al. (1998b) | 0.80 (0.45, 1.39), 0.43 |   | 1.26 (0.72, 2.21), 0.43 |
| Burns et al. (1999) | 0.89 (0.53, 1.47), 0.66 |   | 1.12 (0.68, 1.89), 0.66 |
| Male vs. ref. Female sex | 1.10 (0.78, 1.56), 0.60 |   | 0.91 (0.64, 1.29), 0.60 |
| Age | **1.04 (1.02, 1.06)**, 0.00 |   | **0.96 (0.94, 0.98)**, 0.00 |

Note. Statistically significant (P<.05) values in bold for readability.

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