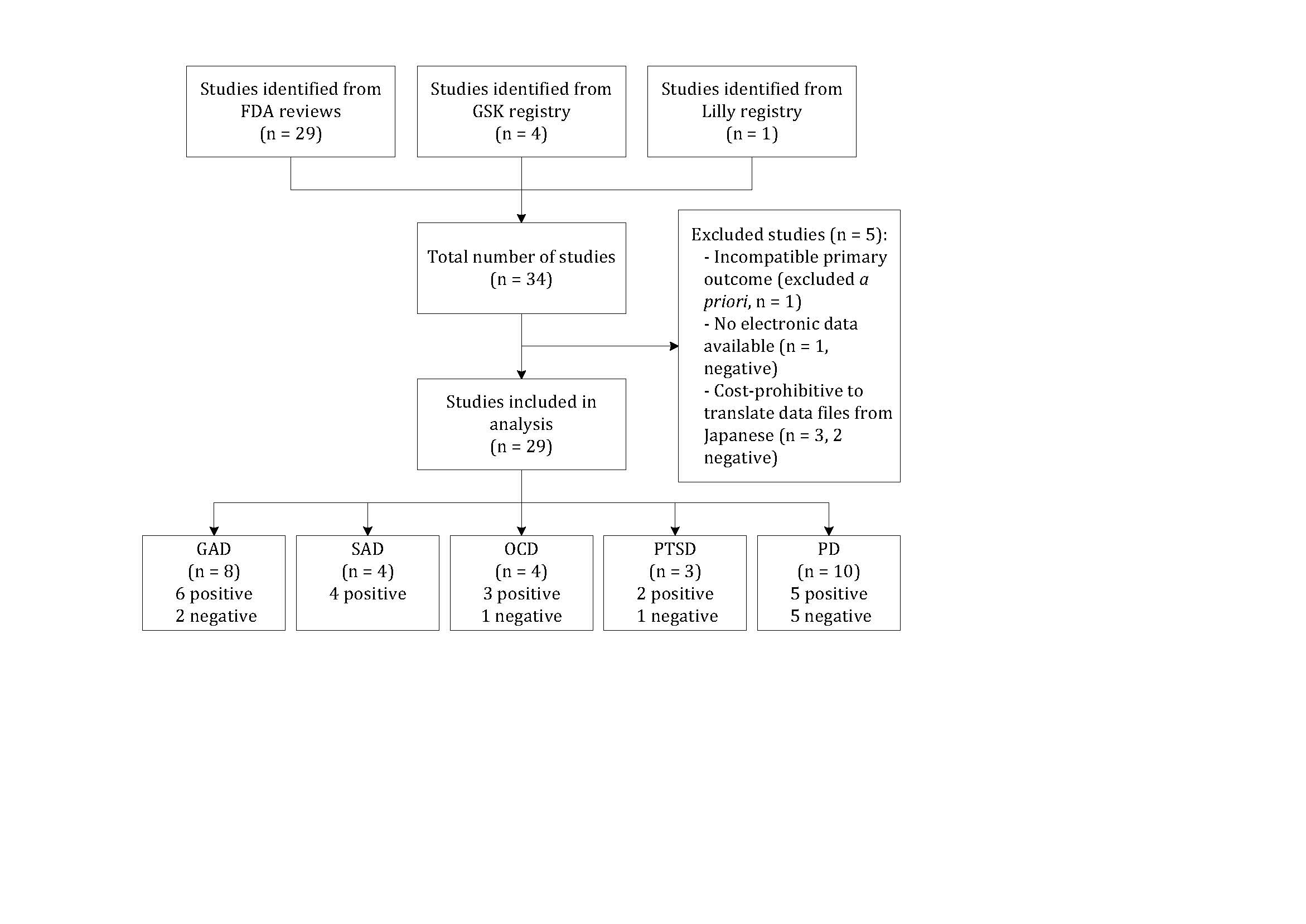
**Supplemental figure 1: Flow chart of study identification and inclusion**

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**Supplemental table 1: Characteristics of the included studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Disorder** | **Drug** | **Trial name** | **Journal reference** | **Antidepressant dose (mg/day)** | **Trial duration (weeks)** | **Sample size for drug/ placebo** | **Mean baseline score (SD)** | **Mean age in years (SD)** | **Gender (% female)** |
| **GAD** | Duloxetine | HMBR | Koponen (2007)1 | 60  120 | 9 | 334/173 | 25.3 (7.4) | 43.8 (13.0) | 67 |
| HMDT | Rynn (2008)2 | 60 – 120 | 10 | 161/158 | 23.0 (7.7) | 41.6 (13.9) | 62 |
| HMDW | N/A3 | 60 – 120  Venlafaxine 75 – 225 | 10 | 392/163 | 27.5 (7.5) | 42.8 (12.8) | 57 |
| HMDU | Hartford (2007)4 | 60 – 120  Venlafaxine 75 – 225 | 10 | 308/158 | 25.2 (5.7) | 41.0 (13.7) | 63 |
| Paroxetine | 637 | Rickels (2006)5 | 20 – 50 | 8 | 184/184 | 25.6 (4.5) | 46.1 (14.9) | 70 |
| 641 | Rickels (2003)6 | 20  40 | 8 | 385/180 | 24.1 (3.6) | 40.5 (12.7) | 56 |
| 642 | Pollack (2001)7 | 20 – 50 | 8 | 161/163 | 24.1 (3.6) | 40.5 (12.2) | 64 |
| Paroxetine CR | 791 | N/A8 | 12.5 – 37.5 | 8 | 163/163 | 24.6 (3.7) | 39.1 (13.7) | 63 |
|  | | | | | | | | | |
| **SAD** | Paroxetine | 382 | Stein (1998)9 | 20 – 50 | 12 | 90/92 | 80.3 (23.5) | 36.4 (11.8) | 42 |
| 454 | Liebowitz (2002)10 | 20  40  60 | 12 | 275/93 | 77.3 (23.0) | 37.2 (10.1) | 41 |
| 502 | Baldwin (1999)11 | 20 – 50 | 12 | 131/145 | 86.4 (24.5) | 36.0 (11.4) | 54 |
| Paroxetine CR | 790 | Lepola (2004)12 | 12.5 – 37.5 | 12 | 185/184 | 78.5 (24.0) | 38.8 (11.0) | 50 |
|  | | | | | | | | | |
| **OCD** | Fluoxetine | HCEP | Tollefson (1994)13 | 20  40  60 | 13 | 259/88 | 24.1 (5.4) | 36.8 (11.7) | 55 |
| Paroxetine | 116 | Hollander (2003)14 | 20  40  60 | 12 | 250/88 | 25.4 (5.2) | 41.3 (13.3) | 27 |
| 118 | N/A15 | 20 – 60 | 12 | 79/75 | 24.2 (4.8) | 39.1 (11.5 | 38 |
| 136 | Zohar (1996)16 | 20 – 60 | 12 | 194/99 | 25.9 (5.2) | 37.8 (12.2) | 55 |
|  | | | | | | | | | |
| **PTSD** | Paroxetine | 627 | Stein (2003)17 | 20 – 50 | 12 | 154/159 | 77.9 (17.9) | 39.3 (11.7) | 53 |
| 648 | Tucker (2001)18 | 20 – 50 | 12 | 136/133 | 73.4 (16.1) | 41.7 (11.5) | 64 |
| 651 | Marshall (2001)19 | 20  40 | 12 | 322/167 | 74.5 (15.8) | 41.9 (11.8) | 68 |
|  | | | | | | | | | |
| **Panic disorder** | Fluoxetine | HCJC | Michelson (2001)20 | 20 – 60 | 12 | 90/90 | 7.8 (6.6) | 35.7 (10.1) | 56 |
| HCJB | N/A\* | 20 – 60 | 12 | 106/104 | 6.8 (7.1) | 37.9 (11.2) | 65 |
| HCHG | N/A\* | 10  20 | 10 | 145/63 | 10.7 (16.4) | 37.6 (10.8) | 69 |
| HCHQ | N/A\* | 20 | 8 | 56/65 | 22.4 (41.9) | 38.0 (10.9) | 59 |
| Paroxetine | 120 | Ballenger (1998)21 | 10  20  40 | 10 | 182/66 | 10.2 (15.9) | 36.7 (10.2) | 66 |
| 187 | Lecrubier (1997)22 | 20 – 60 | 12 | 109/113 | 12.5 (13.8) | 34.6 (9.0) | 60 |
| 223 | N/A23 | 10 – 60 | 10 | 68/67 | 8.4 (9.2) | 38.9 (11.6) | 65 |
| Paroxetine CR | 494 | Sheehan (2005)24 | 25 – 75 | 10 | 127/137 | 10.4 (20.9) | 37.8 (10.2) | 56 |
| 495 | Sheehan (2005)24 | 25 – 75 | 10 | 143/155 | 10.0 (12.7) | 36.6 (10.5) | 63 |
| 497 | Sheehan (2005)24 | 25 – 75 | 10 | 134/131 | 8.8 (11.8) | 39.3 (10.7) | 55 |

Caption: Characteristics of the included studies, with reference to the journal article or, in case of unpublished trials, a trial registry summary (if available). \* indicates unpublished trials for which a registry summary could not be located. These trials were identified in the Food and Drug Administration drug application package for fluoxetine for panic disorder.

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**Supplemental table 2: Minimum severity required for study entry**

|  |  |  |  |
| --- | --- | --- | --- |
| **Disorder** | **Drug** | **Trial name** | **Minimum severity required for entry** |
| **GAD** | Duloxetine | HMBR | CGI-S ≥ 4; HADS anxiety subscale ≥10; CAS ≥ 9 & CAS score greater than RDS score |
| HMDT | CGI-S ≥ 4; HADS anxiety subscale ≥10; CAS ≥ 9 & CAS score greater than RDS score |
| HMDW | CGI-S ≥ 4; HADS anxiety subscale ≥10; CAS ≥ 9 & CAS score greater than RDS score |
| HMDU | CGI-S ≥ 4; HADS anxiety subscale ≥10; CAS ≥ 9 & CAS score greater than RDS score |
| Paroxetine | 637 | HAM-A ≥ 20; HAM-A item 1 and 2 ≥ 2 |
| 641 | HAM-A ≥ 20; HAM-A item 1 and 2 ≥ 2 |
| 642 | HAM-A ≥ 20; HAM-A item 1 and 2 ≥ 2 |
| Paroxetine CR | 791 | HAM-A ≥ 20; HAM-A item 1 and 2 ≥ 2 |
|  | | | |
| **SAD** | Paroxetine | 382 | None (≥4 feared social situations, of which ≥2 interpersonal) |
| 454 | None (≥4 feared social situations, of which ≥2 interpersonal) |
| 502 | None |
| Paroxetine CR | 790 | None |
|  | | | |
| **OCD** | Fluoxetine | HCEP | CGI-S ≥ 4; Y-BOCS ≥ 16 (if both obsessions and compulsions were present) or Y-BOCS ≥ 10 (if only obsessions or only compulsions were present) |
| Paroxetine | 116 | NIMHOCS ≥ 7; Y-BOCS ≥ 16 |
| 118 | NIMHOCS ≥ 7; Y-BOCS ≥ 16 |
| 136 | NIMHOCS ≥ 7; Y-BOCS ≥ 16 |
|  | | | |
| **PTSD** | Paroxetine | 627 | CAPS ≥ 50 |
| 648 | CAPS ≥ 50 |
| 651 | CAPS ≥ 50 |
|  | | | |
| **Panic disorder** | Fluoxetine | HCJC | PDSS ≥ 12; CGI-S ≥ 4; ≥4 panic attacks in the month preceding study entry; ≥2 panic attacks during the 2-week baseline evaluation |
| HCJB | PDSS ≥ 12; CGI-S ≥ 4; ≥4 panic attacks in the month preceding study entry |
| HCHG | ≥1 panic attack/week in each of the 4 weeks preceding study entry |
| HCHQ | ≥2 panic attacks during the 2-week baseline evaluation; CGI-S ≥ 3 |
| Paroxetine | 120 | ≥2 panic attacks during the 2-week baseline evaluation |
| 187 | ≥3 panic attacks during the 3-week baseline evaluation |
| 223 | ≥2 panic attacks during the 2-week baseline evaluation |
| Paroxetine CR | 494 | ≥2 panic attacks during the 2-week baseline evaluation |
| 495 | ≥2 panic attacks during the 2-week baseline evaluation |
| 497 | ≥2 panic attacks during the 2-week baseline evaluation |

Caption: Inclusion criteria (with regard to minimum severity) of the included studies. Abbreviations: CAPS: Clinician-Administered PTSD Scale; CAS: Covi Anxiety Scale; CGI-S: Clinical Global Impression – Severity; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; NIMHOCS: National Institute of Mental Health Obsessive Compulsive Scale; PDSS: Panic Disorder Severity Scale; RDS: Raskin Depression Scale; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

**Supplemental table 3: Tables of models for primary analysis**

**GAD**

**Supplemental table 3a. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 32046.47 | 32209.12 | -16002.23 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 32044.61 | 32199.52 | -16002.31 |
| **3.** | As model 2, but without Time × Group × Baseline | 19 | **32043.03** | 32190.19 | -16002.51 |
| 4. | As model 3, but without Group × Baseline | 18 | 32058.99 | 32198.41 | -16011.49 |

**Supplemental table 3b. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.189 | 0.033 | 13639 | <0.001 |
| Time | 0.015 | 0.018 | 13639 | 0.390 |
| Time2 | -0.127 | 0.008 | 13639 | <0.001 |
| Group | 0.420 | 0.035 | 3419 | <0.001 |
| Baseline | 0.403 | 0.022 | 3419 | <0.001 |
| Time × Group | 0.019 | 0.023 | 13639 | 0.405 |
| Time2 × Group | -0.049 | 0.010 | 13639 | <0.001 |
| Time × Baseline | 0.039 | 0.010 | 13639 | <0.001 |
| Time2 × Baseline | -0.025 | 0.004 | 13639 | <0.001 |
| Group × Baseline | 0.095 | 0.022 | 3419 | <0.001 |

**Supplemental table 3c. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.189 | 0.033 | 13637 | <0.001 |
| Time | 0.015 | 0.018 | 13637 | 0.390 |
| Time2 | -0.127 | 0.008 | 13637 | <0.001 |
| Group | 0.420 | 0.035 | 3419 | <0.001 |
| Baseline | 0.391 | 0.027 | 3419 | <0.001 |
| Time × Group | 0.019 | 0.023 | 13637 | 0.408 |
| Time2 × Group | -0.049 | 0.010 | 13637 | <0.001 |
| Time × Baseline | 0.0383 | 0.016 | 13637 | 0.019 |
| Time2 × Baseline | -0.023 | 0.007 | 13637 | 0.002 |
| Group × Baseline | 0.115 | 0.035 | 3419 | <0.001 |
| Time × Group × Baseline | 0.002 | 0.021 | 13637 | 0.941 |
| Time2 × Group × Baseline | -0.004 | 0.009 | 13637 | 0.706 |

**SAD**

**Supplemental table 3d. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 10633.50 | 10778.63 | -5295.749 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 10632.75 | 10770.96 | -5296.372 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 10631.48 | 10762.79 | -5296.741 |
| **4.** | As model 3, but without Group × Baseline | 18 | **10631.06** | 10755.45 | -5297.528 |
| 5. | As model 4, but without Time2 × Baseline | 17 | 10637.17 | 10754.65 | -5301.583 |

**Supplemental table 3e. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.163 | 0.055 | 6211 | 0.003 |
| Time | -0.012 | 0.028 | 6211 | 0.672 |
| Time2 | -0.074 | 0.010 | 6211 | <0.001 |
| Group | 0.711 | 0.071 | 1189 | <0.001 |
| Baseline | 0.359 | 0.035 | 1189 | <0.001 |
| Time × Group | 0.134 | 0.037 | 6211 | <0.001 |
| Time2 × Group | -0.034 | 0.013 | 6211 | 0.008 |
| Time × Baseline | 0.059 | 0.019 | 6211 | 0.001 |
| Time2 × Baseline | -0.016 | 0.006 | 6211 | 0.010 |

**Supplemental table 3f. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.164 | 0.055 | 6209 | 0.003 |
| Time | -0.012 | 0.028 | 6209 | 0.665 |
| Time2 | -0.074 | 0.010 | 6209 | <0.001 |
| Group | 0.710 | 0.071 | 1188 | <0.001 |
| Baseline | 0.289 | 0.052 | 1188 | <0.001 |
| Time × Group | 0.134 | 0.037 | 6209 | <0.001 |
| Time2 × Group | -0.033 | 0.013 | 6209 | 0.008 |
| Time × Baseline | 0.049 | 0.028 | 6209 | 0.076 |
| Time2 × Baseline | -0.014 | 0.009 | 6209 | 0.120 |
| Group × Baseline | 0.130 | 0.070 | 1188 | 0.065 |
| Time × Group × Baseline | 0.018 | 0.037 | 6209 | 0.624 |
| Time2 × Group × Baseline | -0.004 | 0.013 | 6209 | 0.770 |

**OCD**

**Supplemental table 3g. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 13500.48 | 13646.47 | -6729.238 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 13498.79 | 13637.84 | -6729.396 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 13498.10 | 13630.19 | -6730.050 |
| **4.** | As model 3, but without Group × Baseline | 18 | **13496.15** | 13621.29 | -6730.076 |
| 5. | As model 4, but without Time2 × Baseline | 17 | 13498.81 | 13617.00 | -6732.405 |

**Supplemental table 3h. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.0.63 | 0.067 | 6587 | 0.346 |
| Time | -0.045 | 0.044 | 6587 | 0.305 |
| Time2 | -0.066 | 0.015 | 6587 | <0.001 |
| Group | 0.562 | 0.080 | 1126 | <0.001 |
| Baseline | 0.178 | 0.037 | 1126 | <0.001 |
| Time × Group | 0.072 | 0.052 | 6587 | 0.166 |
| Time2 × Group | -0.047 | 0.018 | 6587 | 0.010 |
| Time × Baseline | -0.006 | 0.024 | 6587 | 0.813 |
| Time2 × Baseline | -0.018 | 0.008 | 6587 | 0.034 |

**Supplemental table 3i. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.058 | 0.067 | 6585 | 0.380 |
| Time | -0.045 | 0.044 | 6585 | 0.304 |
| Time2 | -0.066 | 0.015 | 6585 | <0.001 |
| Group | 0.559 | 0.080 | 1125 | <0.001 |
| Baseline | 0.102 | 0.069 | 1125 | 0.142 |
| Time × Group | 0.072 | 0.052 | 6585 | 0.163 |
| Time2 × Group | -0.046 | 0.018 | 6585 | 0.011 |
| Time × Baseline | -0.010 | 0.046 | 6585 | 0.833 |
| Time2 × Baseline | -0.010 | 0.016 | 6585 | 0.520 |
| Group × Baseline | 0.107 | 0.082 | 1125 | 0.195 |
| Time × Group × Baseline | 0.005 | 0.054 | 6585 | 0.928 |
| Time2 × Group × Baseline | -0.011 | 0.019 | 6585 | 0.552 |

**PTSD**

**Supplemental table 3j. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 7152.29 | 7281.26 | -3555.15 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 7150.42 | 7273.25 | -3555.21 |
| 3. | As model 2, but without Time2 × Baseline | 19 | 7149.29 | 7265.97 | -3555.64 |
| 4. | As model 3, but without Time × Group × Baseline | 18 | 7148.57 | 7259.12 | -3556.29 |
| 5. | As model 4, but without Group × Baseline | 17 | 7146.98 | 7251.38 | -3556.49 |
| **6.** | As model 5, but without Time2 × Baseline | 16 | **7146.47** | 7244.74 | -3557.24 |
| 7. | As model 6, but without Time × Baseline | 15 | 7149.19 | 7241.32 | -3559.60 |

**Supplemental table 3k. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.129 | 0.104 | 2359 | 0.216 |
| Time | 0.025 | 0.035 | 2359 | 0.481 |
| Time2 | -0.084 | 0.012 | 2359 | <0.001 |
| Group | 0.425 | 0.071 | 1066 | <0.001 |
| Baseline | 0.159 | 0.035 | 1066 | <0.001 |
| Time × Group | 0.068 | 0.025 | 2359 | 0.006 |
| Time × Baseline | -0.026 | 0.012 | 2359 | 0.034 |

**Supplemental table 3l. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.127 | 0.104 | 2355 | 0.220 |
| Time | 0.055 | 0.047 | 2355 | 0.241 |
| Time2 | -0.072 | 0.017 | 2355 | <0.001 |
| Group | 0.423 | 0.071 | 1065 | <0.001 |
| Baseline | 0.103 | 0.056 | 1065 | 0.062 |
| Time × Group | 0.016 | 0.062 | 2355 | 0.796 |
| Time2 × Group | -0.020 | 0.022 | 2355 | 0.355 |
| Time × Baseline | -0.011 | 0.047 | 2355 | 0.816 |
| Time2 × Baseline | -0.008 | 0.016 | 2355 | 0.610 |
| Group × Baseline | 0.095 | 0.072 | 1065 | 0.185 |
| Time × Group × Baseline | 0.006 | 0.061 | 2355 | 0.923 |
| Time2 × Group × Baseline | -0.008 | 0.021 | 2355 | 0.721 |

**Panic disorder**

Note: for panic disorder, time was grand-mean centered rather than centered at trial endpoint, due to convergence issues.

**Supplemental table 3m. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Deviance** |
| 1. | Full model | 17 | 38269.0 | 38390.9 | 38235.0 |
| 2. | As model 1, but without Time2 × Group × Baseline | 16 | 38269.1 | 38383.9 | 38237.1 |
| 3. | As model 2, but without Time2 × Group | 15 | 38267.8 | 38375.4 | 38237.8 |
| 4. | As model 3, but without Time × Group × Baseline | 14 | 38267.2 | 38367.6 | 38239.2 |
| 5. | As model 4, but without Group × Baseline | 13 | 38267.8 | 38361.0 | 38241.8 |
| **6.** | As model 5, but without Time2 × Baseline | 12 | **38268.6** | 38354.6 | 38244.6 |
| 7. | As model 6, but without Time2 | 11 | 38274.7 | 38353.6 | 38252.7 |

**Supplemental table 3n. Best-fitting model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.435 | 0.069 | <0.001 |
| Time | -0.673 | 0.068 | <0.001 |
| Time2 | 0.033 | 0.011 | 0.004 |
| Group | -0.464 | 0.068 | <0.001 |
| Baseline | 0.903 | 0.032 | <0.001 |
| Time × Group | -0.362 | 0.039 | <0.001 |
| Time × Baseline | 0.114 | 0.018 | <0.001 |

**Supplemental table 3o. Full model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.446 | 0.070 | <0.001 |
| Time | -0.671 | 0.030 | <0.001 |
| Time2 | 0.027 | 0.030 | 0.084 |
| Group | -0.493 | 0.071 | <0.001 |
| Baseline | 0.846 | 0.045 | <0.001 |
| Time × Group | -0.357 | 0.040 | <0.001 |
| Time2 × Group | 0.027 | 0.023 | 0.241 |
| Time × Baseline | 0.092 | 0.024 | <0.001 |
| Time2 × Baseline | -0.004 | 0.011 | 0.722 |
| Group × Baseline | 0.144 | 0.065 | 0.026 |
| Time × Group × Baseline | 0.037 | 0.035 | 0.295 |
| Time2 × Group × Baseline | -0.024 | 0.017 | 0.148 |

**Supplemental table 4: Tables of models for analyses excluding unapproved low dosages**

**GAD (without low doses)**

**Supplemental table 4a. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 31466.51 | 31628.70 | -15712.25 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 31465.12 | 31619.59 | -15712.56 |
| **3.** | As model 2, but without Time × Group × Baseline | 19 | **31463.50** | 31610.24 | -15712.75 |
| 4. | As model 3, but without Group × Baseline | 18 | 31479.51 | 31618.53 | -15721.76 |

**Supplemental table 4b. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.194 | 0.033 | 13348 | <0.001 |
| Time | 0.015 | 0.018 | 13348 | 0.408 |
| Time2 | -0.126 | 0.008 | 13348 | <0.001 |
| Group | 0.423 | 0.035 | 3336 | <0.001 |
| Baseline | 0.403 | 0.022 | 3336 | <0.001 |
| Time × Group | 0.013 | 0.023 | 13348 | 0.580 |
| Time2 × Group | -0.052 | 0.010 | 13348 | <0.001 |
| Time × Baseline | 0.034 | 0.010 | 13348 | 0.001 |
| Time2 × Baseline | -0.027 | 0.005 | 13348 | <0.001 |
| Group × Baseline | 0.095 | 0.022 | 3336 | <0.001 |

**Supplemental table 4c. Full model model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.194 | 0.033 | 13346 | <0.001 |
| Time | 0.015 | 0.018 | 13346 | 0.412 |
| Time2 | -0.126 | 0.008 | 13346 | <0.001 |
| Group | 0.423 | 0.035 | 3336 | <0.001 |
| Baseline | 0.389 | 0.027 | 3336 | <0.001 |
| Time × Group | 0.013 | 0.023 | 13346 | 0.576 |
| Time2 × Group | -0.052 | 0.010 | 13346 | <0.001 |
| Time × Baseline | 0.038 | 0.016 | 13346 | 0.020 |
| Time2 × Baseline | -0.023 | 0.007 | 13346 | 0.002 |
| Group × Baseline | 0.120 | 0.035 | 3336 | <0.001 |
| Time × Group × Baseline | -0.006 | 0.021 | 13346 | 0.777 |
| Time2 × Group × Baseline | -0.007 | 0.010 | 13346 | 0.433 |

**OCD (without low doses)**

**Supplemental table 4d. Model comparisons**

**Supplemental table 4e. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.078 | 0.067 | 6047 | 0.239 |
| Time | -0.047 | 0.043 | 6047 | 0.280 |
| Time2 | -0.066 | 0.015 | 6047 | <0.001 |
| Group | 0.615 | 0.081 | 1042 | <0.001 |
| Baseline | 0.183 | 0.038 | 1042 | <0.001 |
| Time × Group | 0.079 | 0.052 | 6047 | 0.126 |
| Time2 × Group | -0.051 | 0.018 | 6047 | 0.006 |
| Time × Baseline | 0.043 | 0.013 | 6047 | 0.001 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 12331.25 | 12475.48 | -6144.625 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 12329.55 | 12466.90 | -6144.773 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 12329.83 | 12460.32 | -6145.917 |
| 4. | As model 3, but without Group × Baseline | 18 | 12328.13 | 12451.75 | -6146.066 |
| **5.** | As model 4, but without Time2 × Baseline | 17 | **12329.74** | 12446.49 | -6147.869 |

**Supplemental table 4f. Full model model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.074 | 0.067 | 6044 | 0.268 |
| Time | -0.045 | 0.043 | 6044 | 0.303 |
| Time2 | -0.066 | 0.015 | 6044 | <0.001 |
| Group | 0.612 | 0.081 | 1041 | <0.001 |
| Baseline | 0.101 | 0.069 | 1041 | 0.145 |
| Time × Group | 0.075 | 0.052 | 6044 | 0.152 |
| Time2 × Group | -0.052 | 0.018 | 6044 | 0.004 |
| Time × Baseline | -0.010 | 0.045 | 6044 | 0.831 |
| Time2 × Baseline | -0.010 | 0.016 | 6044 | 0.513 |
| Group × Baseline | 0.140 | 0.084 | 1041 | 0.094 |
| Time × Group × Baseline | 0.017 | 0.054 | 6044 | 0.749 |
| Time2 × Group × Baseline | -0.010 | 0.019 | 6044 | 0.609 |

**Panic disorder (without low doses)**

Note: for panic disorder, time was grand-mean centered rather than centered at trial endpoint, due to convergence issues.

**Supplemental table 4g. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Deviance** |
| 1. | Full model | 17 | 34931.5 | 35051.9 | 34897.5 |
| 2. | As model 1, but without Time2 × Group × Baseline | 16 | 34932.9 | 35046.2 | 34900.9 |
| 3. | As model 2, but without Time2 × Group | 15 | 34931.6 | 35037.9 | 34901.6 |
| 4. | As model 3, but without Time × Group × Baseline | 14 | 34930.6 | 35029.7 | 34902.6 |
| 5. | As model 4, but without Group × Baseline | 13 | 34931.4 | 35023.5 | 34905.4 |
| **6** | As model 5, but without Time2 × Baseline | **12** | **34932.8** | **35017.8** | **34908.8** |
| 7 | As model 6, but without Time2 | 11 | 34937.9 | 35015.8 | 34915.9 |

**Supplemental table 4h. Best-fitting model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.426 | 0.072 | <0.001 |
| Time | -0.680 | 0.031 | <0.001 |
| Time2 | 0.032 | 0.012 | 0.007 |
| Group | -0.511 | 0.071 | <0.001 |
| Baseline | 0.891 | 0.034 | <0.001 |
| Time × Group | -0.389 | 0.042 | <0.001 |
| Time × Baseline | 0.110 | 0.019 | <0.001 |

**Supplemental table 4i. Full model model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.437 | 0.073 | <0.001 |
| Time | -0.678 | 0.031 | <0.001 |
| Time2 | 0.023 | 0.016 | 0.098 |
| Group | -0.544 | 0.074 | <0.001 |
| Baseline | 0.840 | 0.045 | <0.001 |
| Time × Group | -0.381 | 0.042 | <0.001 |
| Time2 × Group | 0.031 | 0.024 | 0.189 |
| Time × Baseline | 0.093 | 0.024 | <0.001 |
| Time2 × Baseline | -0.004 | 0.011 | 0.730 |
| Group × Baseline | 0.150 | 0.069 | 0.029 |
| Time × Group × Baseline | 0.030 | 0.037 | 0.426 |
| Time2 × Group × Baseline | -0.032 | 0.018 | 0.065 |

**Supplemental table 5: Tables of models after excluding participants with very low baseline scores**

**GAD (HAM-A ≥ 10)**

**Supplemental table 5a. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 31986.16 | 32148.72 | -15972.08 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 31984.28 | 32139.10 | -15972.14 |
| **3.** | As model 2, but without Time × Group × Baseline | 19 | **31982.53** | 32129.62 | -15972.26 |
| 4. | As model 3, but without Group × Baseline | 18 | 31997.69 | 32137.03 | -15980.85 |

**Supplemental table 5b. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.189 | 0.033 | 13585 | <0.001 |
| Time | 0.015 | 0.018 | 13585 | 0.393 |
| Time2 | -0.127 | 0.008 | 13585 | <0.001 |
| Group | 0.423 | 0.035 | 3400 | <0.001 |
| Baseline | 0.396 | 0.022 | 3400 | <0.001 |
| Time × Group | 0.019 | 0.023 | 13585 | 0.397 |
| Time2 × Group | -0.049 | 0.010 | 13585 | <0.001 |
| Time × Baseline | 0.039 | 0.010 | 13585 | <0.001 |
| Time2 × Baseline | -0.026 | 0.005 | 13585 | <0.001 |
| Group × Baseline | 0.093 | 0.023 | 3400 | <0.001 |

**Supplemental table 5c. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.189 | 0.033 | 13583 | <0.001 |
| Time | 0.015 | 0.018 | 13583 | 0.393 |
| Time2 | -0.127 | 0.008 | 13583 | <0.001 |
| Group | 0.423 | 0.035 | 3400 | <0.001 |
| Baseline | 0.387 | 0.027 | 3400 | <0.001 |
| Time × Group | 0.019 | 0.023 | 13583 | 0.399 |
| Time2 × Group | -0.049 | 0.010 | 13583 | <0.001 |
| Time × Baseline | 0.039 | 0.017 | 13583 | 0.019 |
| Time2 × Baseline | -0.024 | 0.007 | 13583 | 0.001 |
| Group × Baseline | 0.110 | 0.035 | 3400 | 0.002 |
| Time × Group × Baseline | 0.000 | 0.021 | 13583 | 0.987 |
| Time2 × Group × Baseline | -0.003 | 0.010 | 13583 | 0.734 |

**GAD (HAM-A ≥ 15)**

**Supplemental table 5d. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 31487.38 | 31649.53 | -15722.69 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 31486.07 | 31640.50 | -15723.03 |
| **3.** | As model 2, but without Time × Group × Baseline | 19 | **31484.24** | 31630.94 | -15723.12 |
| 4. | As model 3, but without Group × Baseline | 18 | 31499.56 | 31638.55 | -15731.78 |

**Supplemental table 5e. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.199 | 0.033 | 13337 | <0.001 |
| Time | 0.015 | 0.018 | 13337 | 0.411 |
| Time2 | -0.129 | 0.008 | 13337 | <0.001 |
| Group | 0.425 | 0.036 | 3321 | <0.001 |
| Baseline | 0.366 | 0.022 | 3321 | <0.001 |
| Time × Group | 0.025 | 0.023 | 13337 | 0.288 |
| Time2 × Group | -0.046 | 0.010 | 13337 | <0.001 |
| Time × Baseline | 0.036 | 0.010 | 13337 | <0.001 |
| Time2 × Baseline | -0.025 | 0.005 | 13337 | <0.001 |
| Group × Baseline | 0.095 | 0.023 | 3321 | <0.001 |

**Supplemental table 5f. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.198 | 0.033 | 13335 | <0.001 |
| Time | 0.015 | 0.018 | 13335 | 0.412 |
| Time2 | -0.129 | 0.008 | 13335 | <0.001 |
| Group | 0.425 | 0.036 | 3321 | <0.001 |
| Baseline | 0.354 | 0.027 | 3321 | <0.001 |
| Time × Group | 0.025 | 0.023 | 13335 | 0.282 |
| Time2 × Group | -0.046 | 0.010 | 13335 | <0.001 |
| Time × Baseline | 0.042 | 0.016 | 13335 | 0.011 |
| Time2 × Baseline | -0.020 | 0.007 | 13335 | 0.007 |
| Group × Baseline | 0.116 | 0.035 | 3321 | 0.001 |
| Time × Group × Baseline | -0.009 | 0.021 | 13335 | 0.666 |
| Time2 × Group × Baseline | -0.008 | 0.010 | 13335 | 0.405 |

**GAD (HAMA ≥ 20)**

**Supplemental table 5g. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 29342.69 | 29503.35 | -14650.34 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 29342.06 | 29495.07 | -14651.03 |
| **3.** | As model 2, but without Time × Group × Baseline | 19 | **29340.08** | 29485.44 | -14651.04 |
| 4. | As model 3, but without Group × Baseline | 18 | 29354.03 | 29491.75 | -14659.02 |

**Supplemental table 5h. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.208 | 0.035 | 12455 | <0.001 |
| Time | 0.010 | 0.020 | 12455 | 0.595 |
| Time2 | -0.133 | 0.008 | 12455 | <0.001 |
| Group | 0.435 | 0.038 | 3062 | <0.001 |
| Baseline | 0.326 | 0.024 | 3062 | <0.001 |
| Time × Group | 0.028 | 0.024 | 12455 | 0.251 |
| Time2 × Group | -0.044 | 0.010 | 12455 | <0.001 |
| Time × Baseline | 0.042 | 0.011 | 12455 | <0.001 |
| Time2 × Baseline | -0.019 | 0.005 | 12455 | <0.001 |
| Group × Baseline | 0.096 | 0.024 | 3062 | <0.001 |

**Supplemental table 5i. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.207 | 0.035 | 12453 | <0.001 |
| Time | 0.009 | 0.020 | 12453 | 0.639 |
| Time2 | -0.133 | 0.008 | 12453 | <0.001 |
| Group | 0.437 | 0.038 | 3062 | <0.001 |
| Baseline | 0.315 | 0.029 | 3062 | <0.001 |
| Time × Group | 0.030 | 0.025 | 12453 | 0.220 |
| Time2 × Group | -0.044 | 0.010 | 12453 | <0.001 |
| Time × Baseline | 0.054 | 0.018 | 12453 | 0.003 |
| Time2 × Baseline | -0.012 | 0.008 | 12453 | 0.128 |
| Group × Baseline | 0.114 | 0.037 | 3062 | 0.002 |
| Time × Group × Baseline | -0.020 | 0.023 | 12453 | 0.386 |
| Time2 × Group × Baseline | -0.012 | 0.010 | 12453 | 0.242 |

**SAD (LSAS ≥ 50)**

**Supplemental table 5j. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 9473.09 | 9615.86 | -4715.55 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 9471.17 | 9607.14 | -4715.59 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 9470.14 | 9599.32 | -4716.07 |
| **4.** | As model 3, but without Group × Baseline | 18 | **9468.86** | 9591.24 | -4716.43 |
| 5. | As model 4, but without Time2 × Baseline | 17 | 9470.17 | 9585.74 | -4718.08 |
| 6. | As model 5, but without Time2 × Group | 16 | 9472.36 | 9581.14 | -4720.18 |

**Supplemental table 5k. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.175 | 0.058 | 5552 | 0.002 |
| Time | -0.012 | 0.031 | 5552 | 0.689 |
| Time2 | -0.078 | 0.010 | 5552 | <0.001 |
| Group | 0.723 | 0.076 | 1062 | <0.001 |
| Baseline | 0.272 | 0.035 | 1062 | <0.001 |
| Time × Group | 0.146 | 0.040 | 5552 | <0.001 |
| Time2 × Group | -0.029 | 0.013 | 5552 | 0.029 |
| Time × Baseline | 0.087 | 0.010 | 5552 | <0.001 |

**Supplemental table 5l. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.177 | 0.058 | 5549 | 0.002 |
| Time | -0.011 | 0.031 | 5549 | 0.713 |
| Time2 | -0.078 | 0.010 | 5549 | <0.001 |
| Group | 0.723 | 0.076 | 1061 | <0.001 |
| Baseline | 0.235 | 0.056 | 1061 | <0.001 |
| Time × Group | 0.144 | 0.040 | 5549 | <0.001 |
| Time2 × Group | -0.030 | 0.013 | 5549 | 0.026 |
| Time × Baseline | 0.056 | 0.030 | 5549 | 0.066 |
| Time2 × Baseline | -0.008 | 0.010 | 5549 | 0.454 |
| Group × Baseline | 0.107 | 0.075 | 1061 | 0.157 |
| Time × Group × Baseline | 0.001 | 0.040 | 5549 | 0.974 |
| Time2 × Group × Baseline | -0.008 | 0.013 | 5549 | 0.542 |

**SAD (LSAS ≥ 60)**

**Supplemental table 5m. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 8296.15 | 8436.11 | -4127.08 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 8294.47 | 8427.76 | -4127.23 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 8294.10 | 8420.73 | -4128.05 |
| **4.** | As model 3, but without Group × Baseline | 18 | **8292.88** | 8412.85 | -4128.44 |
| 5. | As model 4, but without Time2 × Baseline | 17 | 8292.10 | 8405.40 | -4129.05 |
| 6. | As model 5, but without Time2 × Group | 16 | 8294.86 | 8401.49 | -4131.43 |

**Supplemental table 5n. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.199 | 0.061 | 4857 | 0.001 |
| Time | -0.002 | 0.033 | 4857 | 0.960 |
| Time2 | -0.079 | 0.011 | 4857 | <0.001 |
| Group | 0.710 | 0.081 | 927 | <0.001 |
| Baseline | 0.251 | 0.038 | 927 | <0.001 |
| Time × Group | 0.135 | 0.043 | 4857 | 0.002 |
| Time2 × Group | -0.031 | 0.014 | 4857 | 0.031 |
| Time × Baseline | 0.082 | 0.011 | 4857 | <0.001 |

**Supplemental table 5o. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.201 | 0.061 | 4854 | 0.001 |
| Time | -0.001 | 0.032 | 4854 | 0.967 |
| Time2 | -0.079 | 0.011 | 4854 | <0.001 |
| Group | 0.709 | 0.081 | 926 | <0.001 |
| Baseline | 0.194 | 0.060 | 926 | 0.001 |
| Time × Group | 0.134 | 0.043 | 4854 | 0.002 |
| Time2 × Group | -0.031 | 0.014 | 4854 | 0.030 |
| Time × Baseline | 0.052 | 0.032 | 4854 | 0.106 |
| Time2 × Baseline | -0.005 | 0.011 | 4854 | 0.631 |
| Group × Baseline | 0.133 | 0.081 | 926 | 0.101 |
| Time × Group × Baseline | 0.016 | 0.043 | 4854 | 0.707 |
| Time2 × Group × Baseline | -0.006 | 0.014 | 4854 | 0.684 |

**OCD (Y-BOCS ≥ 16)**

**Supplemental table 5p. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 13261.41 | 13407.06 | -6609.71 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 13262.22 | 13400.93 | -6611.11 |
| 3. | As model 2, but without Time × Group × Baseline | 19 | 13260.70 | 13392.48 | -6611.349 |
| **4.** | As model 3, but without Group × Baseline | 18 | **13260.35** | 13385.19 | -6612.17 |
| 5. | As model 4, but without Time2 × Baseline | 17 | 13257.94 | 13375.84 | -6611.97 |
| 5. | As model 5, but without Time2 × Group | 16 | 13265.98 | 13376.95 | -6616.99 |

**Supplemental table 5q. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.054 | 0.067 | 6484 | 0.419 |
| Time | -0.050 | 0.044 | 6484 | 0.256 |
| Time2 | -0.068 | 0.015 | 6484 | <0.001 |
| Group | 0.559 | 0.081 | 1103 | <0.001 |
| Baseline | 0.150 | 0.037 | 1103 | <0.001 |
| Time × Group | 0.076 | 0.052 | 6484 | 0.148 |
| Time2 × Group | -0.046 | 0.018 | 6484 | 0.012 |
| Time × Baseline | 0.036 | 0.013 | 6484 | 0.005 |

**Supplemental table 5r. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | -0.051 | 0.067 | 6481 | 0.444 |
| Time | -0.050 | 0.044 | 6481 | 0.263 |
| Time2 | -0.068 | 0.015 | 6481 | <0.001 |
| Group | 0.557 | 0.081 | 1102 | <0.001 |
| Baseline | 0.082 | 0.070 | 1102 | 0.239 |
| Time × Group | 0.074 | 0.053 | 6481 | 0.162 |
| Time2 × Group | -0.047 | 0.018 | 6481 | 0.011 |
| Time × Baseline | 0.002 | 0.047 | 6481 | 0.972 |
| Time2 × Baseline | -0.007 | 0.016 | 6481 | 0.660 |
| Group × Baseline | 0.112 | 0.083 | 1102 | 0.177 |
| Time × Group × Baseline | 0.003 | 0.055 | 6481 | 0.950 |
| Time2 × Group × Baseline | -0.008 | 0.019 | 6481 | 0.661 |

**PTSD (CAPS ≥ 50)**

**Supplemental table 5s. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 7114.75 | 7243.62 | -3536.38 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 7112.86 | 7235.60 | -3536.43 |
| 3. | As model 2, but without Time2 × Baseline | 19 | 7111.83 | 7228.42 | -3536.92 |
| 4. | As model 3, but without Time × Group × Baseline | 18 | 7110.75 | 7221.21 | -3537.38 |
| 5. | As model 4, but without Group × Baseline | 17 | 7109.37 | 7213.69 | -3537.68 |
| **6.** | As model 5, but without Time2 × Baseline | 16 | **7108.69** | 7206.87 | -3538.35 |
| 7. | As model 6, but without Time × Baseline | 15 | 7111.08 | 7203.13 | -3540.54 |

**Supplemental table 5t. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.130 | 0.103 | 2349 | 0.209 |
| Time | 0.024 | 0.034 | 2349 | 0.483 |
| Time2 | -0.084 | 0.012 | 2349 | <0.001 |
| Group | 0.426 | 0.070 | 1059 | <0.001 |
| Baseline | 0.153 | 0.035 | 1059 | <0.001 |
| Time × Group | 0.068 | 0.024 | 2349 | 0.005 |
| Time × Baseline | 0.024 | 0.012 | 2349 | 0.044 |

**Supplemental table 5u. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.126 | 0.102 | 2345 | 0.219 |
| Time | 0.053 | 0.047 | 2345 | 0.257 |
| Time2 | -0.072 | 0.017 | 2345 | <0.001 |
| Group | 0.429 | 0.071 | 1058 | <0.001 |
| Baseline | 0.103 | 0.055 | 1058 | 0.064 |
| Time × Group | 0.017 | 0.062 | 2345 | 0.789 |
| Time2 × Group | -0.021 | 0.022 | 2345 | 0.350 |
| Time × Baseline | -0.008 | 0.047 | 2345 | 0.868 |
| Time2 × Baseline | -0.007 | 0.016 | 2345 | 0.647 |
| Group × Baseline | 0.090 | 0.072 | 1058 | 0.206 |
| Time × Group × Baseline | 0.004 | 0.061 | 2345 | 0.953 |
| Time2 × Group × Baseline | -0.008 | 0.021 | 2345 | 0.724 |

**Panic disorder (>0 panic attacks / 2 weeks)**

Note: for panic disorder, time was grand-mean centered rather than centered at trial endpoint, due to convergence issues.

**Supplemental table 5v. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Deviance** |
| 1. | Full model | 17 | 38131.0 | 38252.8 | 38097.0 |
| 2. | As model 1, but without Time2 × Group × Baseline | 16 | 38131.2 | 38245.8 | 38099.2 |
| 3. | As model 2, but without Time2 × Group | 15 | 38130.0 | 38237.5 | 38100.0 |
| 4. | As model 3, but without Time × Group × Baseline | 14 | 38129.4 | 38229.7 | 38101.4 |
| 5. | As model 4, but without Group × Baseline | 13 | 38130.0 | 38223.2 | 48104.0 |
| **6.** | As model 5, but without Time2 × Baseline | 12 | **38131.0** | 38217.0 | 38107.0 |
| 7. | As model 6, but without Time2 | 11 | 38137 | 38216 | 38115 |

**Supplemental table 5w. Best-fitting model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.451 | 0.071 | <0.001 |
| Time | -0.671 | 0.030 | <0.001 |
| Time2 | 0.033 | 0.011 | 0.004 |
| Group | -0.465 | 0.068 | <0.001 |
| Baseline | 0.897 | 0.032 | <0.001 |
| Time × Group | -0.363 | 0.039 | <0.001 |
| Time × Baseline | 0.113 | 0.018 | <0.001 |

**Supplemental table 5x. Full model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.462 | 0.072 | <0.001 |
| Time | -0.670 | 0.030 | <0.001 |
| Time2 | 0.027 | 0.016 | 0.086 |
| Group | -0.496 | 0.071 | <0.001 |
| Baseline | 0.839 | 0.045 | <0.001 |
| Time × Group | -0.357 | 0.040 | <0.001 |
| Time2 × Group | 0.028 | 0.023 | 0.218 |
| Time × Baseline | 0.092 | 0.024 | <0.001 |
| Time2 × Baseline | -0.004 | 0.011 | 0.721 |
| Group × Baseline | 0.147 | 0.065 | 0.024 |
| Time × Group × Baseline | 0.037 | 0.035 | 0.289 |
| Time2 × Group × Baseline | -0.025 | 0.017 | 0.135 |

**Panic disorder (>1 panic attack / 2 weeks)**

Note: for panic disorder, time was grand-mean centered rather than centered at trial endpoint, due to convergence issues.

**Supplemental table 5y. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Deviance** |
| 1. | Full model | 17 | 37876.1 | 37997.6 | 37842.1 |
| 2. | As model 1, but without Time2 × Group × Baseline | 16 | 37876.4 | 37990.8 | 37844.4 |
| 3. | As model 2, but without Time2 × Group | 15 | 37875.2 | 37982.5 | 37845.2 |
| 4. | As model 3, but without Time × Group × Baseline | 14 | 37874.6 | 37974.7 | 37846.6 |
| 5. | As model 4, but without Group × Baseline | 13 | 37875.2 | 37968.2 | 37849.2 |
| **6.** | As model 5, but without Time2 × Baseline | 12 | **37876.5** | 37962.3 | 37852.5 |
| 7. | As model 6, but without Time2 | 11 | 37883 | 37962 | 37861 |

**Supplemental table 5z. Best-fitting model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.480 | 0.073 | <0.001 |
| Time | -0.664 | 0.030 | <0.001 |
| Time2 | 0.035 | 0.011 | 0.003 |
| Group | -0.464 | 0.068 | <0.001 |
| Baseline | 0.889 | 0.032 | <0.001 |
| Time × Group | -0.361 | 0.039 | <0.001 |
| Time × Baseline | 0.110 | 0.018 | <0.001 |

**Supplemental table 5aa. Full model parameters**

|  |  |  |  |
| --- | --- | --- | --- |
|  | B | SE | p-value |
| Intercept | 0.491 | 0.073 | <0.001 |
| Time | -0.662 | 0.030 | <0.001 |
| Time2 | 0.028 | 0.016 | 0.071 |
| Group | -0.495 | 0.071 | <0.001 |
| Baseline | 0.831 | 0.045 | <0.001 |
| Time × Group | -0.355 | 0.040 | <0.001 |
| Time2 × Group | 0.029 | 0.023 | 0.211 |
| Time × Baseline | 0.089 | 0.024 | <0.001 |
| Time2 × Baseline | -0.005 | 0.011 | 0.676 |
| Group × Baseline | 0.146 | 0.065 | 0.025 |
| Time × Group × Baseline | 0.036 | 0.035 | 0.299 |
| Time2 × Group × Baseline | -0.026 | 0.017 | 0.128 |

**Supplemental table 6: Predicted change in score or number of panic attacks/2 weeks and drug-placebo difference at trial endpoint (best-fitting model)**

**Supplemental table 6a. GAD (HAM-A ≥ 10)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted change (95% CI)** | | **Drug-placebo difference (95% CI)** |
|  |  | **Placebo** | **Antidepressant** |  |
| 10 | 79 | 2.6 (1.4 – 3.9) | 4.0 (2.9 – 5.1) | 1.4 (0.3 – 2.5) |
| 15 | 259 | 5.3 (4.4 – 6.3) | 7.4 (6.6 – 8.3) | 2.1 (1.2 – 2.9) |
| 20 | 1388 | 8.1 (7.3 – 8.8) | 10.8 (10.1 – 11.4) | 2.7 (2.1 – 3.3) |
| 25 | 998 | 10.8 (10.2 – 11.4) | 14.1 (13.6 – 14.7) | 3.4 (2.8 – 3.9) |
| 30 | 442 | 13.5 (12.8 – 14.2) | 17.5 (16.9 – 18.2) | 4.0 (3.4 – 4.6) |
| 35 | 187 | 16.3 (15.3 – 17.2) | 20.9 (20.1 – 21.7) | 4.6 (3.8 – 5.4) |
| 40 | 48 | 19.0 (17.7 – 20.2) | 24.3 (23.2 – 25.3) | 5.3 (4.2 – 6.3) |
| 45 | 10 | 21.7 (20.2 – 23.3) | 27.6 (26.3 – 29.0) | 5.9 (4.6 – 7.3) |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 10 includes participants with baseline scores between 10 and 14 (inclusive)).

**Supplemental table 6b. GAD (HAM-A ≥ 15)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted change (95% CI)** | | **Drug-placebo difference (95% CI)** |
|  |  | **Placebo** | **Antidepressant** |  |
| 10 | 0 | 2.9 (1.6 – 4.2) | 4.2 (3.0 – 5.3) | 1.3 (0.1 – 2.4) |
| 15 | 259 | 5.5 (4.5 – 6.6) | 7.5 (6.6 – 8.4) | 1.9 (1.1 – 2.8) |
| 20 | 1388 | 8.2 (7.4 – 8.9) | 10.8 (10.2 – 11.5) | 2.6 (2.0 – 3.3) |
| 25 | 998 | 10.8 (10.2 – 11.5) | 14.2 (13.6 – 14.7) | 3.3 (2.8 – 3.9) |
| 30 | 442 | 13.5 (12.8 – 14.2) | 17.5 (16.9 – 18.1) | 4.0 (3.4 – 4.6) |
| 35 | 187 | 16.1 (15.2 – 17.1) | 20.8 (20.0 – 21.7) | 4.7 (3.9 – 5.5) |
| 40 | 48 | 18.8 (17.5 – 20.1) | 24.2 (23.0 – 25.3) | 5.4 (4.3 – 6.5) |
| 45 | 10 | 21.4 (19.8 – 23.1) | 27.5 (26.1 – 28.9) | 6.1 (4.7 – 7.5) |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 10 includes participants with baseline scores between 10 and 14 (inclusive)).

**Supplemental table 6c. GAD (HAM-A ≥ 20)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted change (95% CI)** | | **Drug-placebo difference (95% CI)** |
|  |  | **Placebo** | **Antidepressant** |  |
| 10 | 0 | 3.3 (1.7 – 4.9) | 4.4 (3.0 – 5.7) | 1.1 (-0.3 – 2.4) |
| 15 | 0 | 5.8 (4.7 – 7.0) | 7.6 (6.6 – 8.7) | 1.8 (0.8 – 2.8) |
| 20 | 1388 | 8.4 (7.5 – 9.2) | 10.9 (10.2 – 11.7) | 2.5 (1.8 – 3.3) |
| 25 | 998 | 10.9 (10.2 – 11.6) | 14.2 (13.6 – 14.8) | 3.3 (2.7 – 3.9) |
| 30 | 442 | 13.4 (12.7 – 14.2) | 17.5 (16.8 – 18.1) | 4.0 (3.4 – 4.7) |
| 35 | 187 | 16.0 (14.9 – 17.0) | 20.7 (19.8 – 21.6) | 4.8 (3.9 – 5.7) |
| 40 | 48 | 18.5 (17.1 – 19.9) | 24.0 (22.8 – 25.2) | 5.5 (4.4 – 6.7) |
| 45 | 10 | 21.0 (19.3 – 22.8) | 27.3 (25.7 – 28.9) | 6.3 (4.8 – 7.8) |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 10 includes participants with baseline scores between 10 and 14 (inclusive)).

**Supplemental table 6d. Panic disorder (>0 panic attacks / 2 weeks)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted no. panic attacks / 2 weeks**  **(95% CI)** | | **Drug-placebo difference (95% CI)** |
|  |  | **Placebo** | **Antidepressant** |  |
| 2 | 636 | 0.39 (0.31 – 0.46) | 0.16 (0.12 – 0.19) | 0.23 (0.16 – 0.30) |
| 4 | 396 | 0.45 (0.36 – 0.54) | 0.18 (0.15 – 0.22) | 0.27 (0.19 – 0.35) |
| 6 | 258 | 0.53 (0.43 – 0.63) | 0.21 (0.17 – 0.26) | 0.32 (0.22 – 0.41) |
| 8 | 175 | 0.62 (0.50 – 0.74) | 0.25 (0.20 – 0.30) | 0.37 (0.26 – 0.48) |
| 10 | 240 | 0.73 (0.59 – 0.86) | 0.29 (0.24 – 0.35) | 0.43 (0.31 – 0.56) |
| 15 | 123 | 1.08 (0.88 – 1.28) | 0.44 (0.35 – 0.52) | 0.64 (0.45 – 0.83) |
| 20 | 133 | 1.60 (1.29 – 1.92) | 0.65 (0.52 – 0.78) | 0.96 (0.67 – 1.24) |
| 30 | 58 | 3.54 (2.72 – 4.36) | 1.43 (1.10 – 1.76) | 2.11 (1.42 – 2.79) |
| 40 | 44 | 7.81 (5.60 – 10.03) | 3.16 (2.28 – 4.05) | 4.65 (2.96 – 6.34) |
| 60 | 37 | 38.05 (22.47 – 53.62) | 15.40 (9.16 – 21.65) | 22.64 (12.00 – 33.29) |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 2 includes participants with baseline scores of 2 or 3).

**Supplemental table 6e. Panic disorder (>1 panic attacks / 2 weeks)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted no. panic attacks / 2 weeks**  **(95% CI)** | | **Drug-placebo difference** |
|  |  | **Placebo** | **Antidepressant** |  |
| 2 | 636 | 0.40 (0.32 – 0.48) | 0.16 (0.13 – 0.20) | 0.24 (0.17 – 0.31) |
| 4 | 396 | 0.47 (0.38 – 0.56) | 0.19 (0.15 – 0.23) | 0.28 (0.20 – 0.36) |
| 6 | 258 | 0.55 (0.44 – 0.65) | 0.22 (0.18 – 0.27) | 0.33 (0.23 – 0.42) |
| 8 | 175 | 0.64 (0.52 – 0.76) | 0.26 (0.21 – 0.31) | 0.38 (0.27 – 0.49) |
| 10 | 240 | 0.75 (0.61 – 0.89) | 0.30 (0.24 – 0.36) | 0.44 (0.31 – 0.57) |
| 15 | 123 | 1.10 (0.89 – 1.31) | 0.45 (0.36 – 0.53) | 0.66 (0.46 – 0.85) |
| 20 | 133 | 1.63 (1.31 – 1.95) | 0.66 (0.53 – 0.79) | 0.97 (0.68 – 1.26) |
| 30 | 58 | 3.55 (2.72 – 4.38) | 1.44 (1.11 – 1.77) | 2.11 (1.42 – 2.80) |
| 40 | 44 | 7.74 (5.54 – 9.94) | 3.14 (2.26 – 4.02) | 4.60 (2.92 – 6.28) |
| 60 | 37 | 36.78 (21.72 – 51.85) | 14.92 (8.87 – 20.96) | 21.87 (11.57 – 32.16) |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 2 includes participants with baseline scores of 2 or 3).

**Supplemental table 6f. SAD (LSAS ≥ 50 and LSAS ≥ 60), OCD (Y-BOCS ≥ 16), and PTSD (CAPS ≥ 50) (best-fitting models)**

|  |  |  |
| --- | --- | --- |
| **Disorder** | **Minimum score** | **Drug-placebo difference** |
| SAD | LSAS ≥ 50 | 16.8 (13.3 – 20.2) |
|  | LSAS ≥ 60 | 16.8 (13.0 – 20.6) |
| OCD | Y-BOCS ≥ 16 | 3.4 (2.4 – 4.4) |
| PTSD | CAPS ≥ 50 | 10.3 (7.0 – 13.6) |

**Supplemental table 7: Tables of models for the Panic Disorder Severity Scale**

**Supplemental table 7a. Model comparisons**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Model** | **Specifications** | **DF** | **AIC** | **BIC** | **Log-likelihood** |
| 1. | Full model | 21 | 3626.25 | 3743.82 | -1792.13 |
| 2. | As model 1, but without Time2 × Group × Baseline | 20 | 3624.66 | 3736.22 | -1792.33 |
| 3. | As model 2, but without Time2 × Group | 19 | 3622.69 | 3728.66 | -1792.34 |
| **4.** | As model 3, but without Time2 × Baseline | 18 | **3622.00** | 3722.40 | -1793.00 |
| 5. | As model 4, but without Time× Group × Baseline | 17 | 3632.65 | 3727.47 | -1799.32 |
| 6. | As model 5, but without Group × Baseline | 16 | 3634.07 | 3723.31 | -1801.04 |

**Supplemental table 7b. Best-fitting model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.252 | 0.131 | 1576 | 0.054 |
| Time | 0.110 | 0.046 | 1576 | 0.017 |
| Time2 | -0.079 | 0.014 | 1576 | <0.001 |
| Group | 0.569 | 0.109 | 368 | <0.001 |
| Baseline | 0.006 | 0.078 | 368 | 0.936 |
| Time × Group | 0.202 | 0.039 | 1576 | <0.001 |
| Time × Baseline | 0.017 | 0.028 | 1576 | 0.531 |
| Group × Baseline | 0.430 | 0.108 | 368 | <0.001 |
| Time× Group × Baseline | 0.138 | 0.039 | 1576 | <0.001 |

**Supplemental table 7c. Full model parameters (after refitting with REML)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE | DF | p-value |
| Intercept | 0.253 | 0.133 | 1573 | 0.058 |
| Time | 0.101 | 0.058 | 1573 | 0.083 |
| Time2 | -0.083 | 0.020 | 1573 | 0.000 |
| Group | 0.568 | 0.110 | 368 | 0.000 |
| Baseline | 0.016 | 0.078 | 368 | 0.839 |
| Time × Group | 0.223 | 0.085 | 1573 | 0.009 |
| Time2 × Group | 0.008 | 0.029 | 1573 | 0.787 |
| Time × Baseline | -0.048 | 0.059 | 1573 | 0.419 |
| Time2 × Baseline | -0.025 | 0.020 | 1573 | 0.214 |
| Group × Baseline | 0.423 | 0.108 | 368 | 0.000 |
| Time × Group × Baseline | 0.182 | 0.083 | 1573 | 0.029 |
| Time2 × Group × Baseline | 0.017 | 0.028 | 1573 | 0.541 |

**Supplemental table 8: Predicted change on the Panic Disorder Severity Scale and antidepressant-placebo difference**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Baseline score** | **Sample size1** | **Predicted change (95% CI)** | | **Drug-placebo difference (95% CI)** | **SMD** |
|  |  | **Placebo** | **Antidepressant** |  |  |
| 12 | 110 | 7.9 (-3.8 – 19.6) | 7.9 (-3.8 – 19.6) | 0.0 (-1.9 – 2.0) | 0.00 |
| 15 | 93 | 7.9 (-1.6 - 17.5) | 9.9 (0.3 – 19.6) | 2.0 (0.7 – 3.3) | 0.38 |
| 18 | 85 | 8.0 (-1.4 -17.3) | 11.9 (2.5 – 21.3) | 3.9 (2.7 – 5.2) | 0.59 |
| 21 | 65 | 8.0 (-3.1 – 19.0) | 13.9 (2.7 – 25.0) | 5.9 (4.1 – 7.7) | 1.00 |

1 Sample size indicates the number of participants with a baseline score in between the indicated score and the subsequent score (e.g. 12 includes participants with baseline scores of 12, 13, or 14).