**NMA on PTSD**

**Appendix 7**

Results of the direct pairwise comparisons for all outcomes

**Pairwise meta-analysis results**

**Summary**

The primary outcome (efficacy as continuous outcome) was reported in 47 studies (3 three-arm and 44 two-arm), including 5493 patients (Figure 1). Acceptability was evaluated in 47 studies (3 three-arm and 44 two-arm) with 5441 patients in total. 27 studies reported efficacy as the total number of patients who responded. All 27 studies included placebo, 1 was a three-arm and 26 were two-arm studies. In total 3645 patients were randomized to 16 different treatments. The proportion of patients who left the study due to adverse events was reported in 37 studies (2 three-arm and 35 two-arm trials); 5071 patients, 19 interventions. The number of studies and the number of participants per comparison with available direct data are given in Tables 1 and 2. Table 3 summarizes the number of studies and number of participants per treatment arm.

**Pairwise meta-analysis results**

Tables 4 and 5 show the available direct estimates for the primary and secondary outcomes. Direct evidence suggests that Phenelzine is better than Placebo in terms of change in symptoms, any-cause dropouts and response rate; it also appears to perform better than Imipramine for the two primary outcomes (change in symptoms and any cause dropouts). Paroxetine is more effective than Placebo in terms of change in symptoms and response rate but is associated with relatively more dropouts due to adverse events. Risperidone and Venlafaxine ER are better than Placebo for the two efficacy outcomes (change in symptoms and response rate), whereas no statistically significant difference was detected between these two treatments and Placebo in terms of dropouts.

Assuming a common heterogeneity parameter across all direct comparisons gave similar point estimates with the primary analysis (that assumed comparison-specific heterogeneities), but resulted in small differences in precision according to the change in heterogeneity. No important heterogeneity ( was found in any outcome.

Table 1. Number of studies per comparison for primary and secondary outcomes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comparisons** | **Primary outcomes** | | **Secondary outcomes** | |
| **Change in symptoms** | **Any-cause dropouts** | **Response rate** | **Dropouts due to adverse events** |
|  |  |  |  |
| **Placebo vs** |  | |  | |
| Nefazodone | 1 | 1 | 1 | 1 |
| Phenelzine | 1 | 1 | 1 | 1 |
| Imipramine | 1 | 1 | 1 | 1 |
| Citalopram | 1 | 1 | - | - |
| Bupropion SR | 1 | 1 | - | - |
| Paroxetine | 4 | 4 | 4 | 4 |
| NK1R antagonist | 2 | 2 | 2 | 1 |
| Topiramate | 3 | 3 | 2 | 3 |
| Divalproex | 2 | 2 | - | 2 |
| Guanfacine | 2 | 2 | - | 1 |
| Brofaromine | 1 | 1 | - | 1 |
| Lamotrigine | - | 1 | 1 | Excluded |
| Risperidone | 4 | 4 | 1 | 4 |
| Sertraline | 8 | 9 | 4 | 5 |
| Olanzapine | 3 | 3 | 3 | 3 |
| Fluoxetine | 5 | 4 | 4 | 3 |
| Amitriptyline | 1 | 1 | 1 | 1 |
| Mirtazapine | 1 | 1 | 1 | 1 |
| Tiagabine | 1 | 1 | 1 | 1 |
| Venlafaxine ER | 2 | 2 | 1 | 2 |
| Prazosin | 3 | 3 | - | 3 |
| **Sertaline vs** | | |  |  |
| Nefazodone | 1 | - | - | 1 |
| Citalopram | 1 | 1 | - | - |
| Venlafaxine ER | 1 | 1 | - | 1 |
| **Phenelzine vs** | | |  |  |
| Imipramine | 1 | 1 | 1 | 1 |
| **Fluvoxamine vs** | | |  |  |
| Reboxetine | 1 | 1 | - | - |
| **Paroxetine**  **vs** |  |  |  |  |
| Desipramine | 1 | 1 | - | - |

Table 2. Number of participants per comparison for primary and secondary outcomes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comparisons** | **Primary outcomes** | | **Secondary outcomes** | |
| **Change in symptoms** | **Any-cause dropouts** | **Response rate** | **Dropouts due to adverse events** |
|  |  |  |  |
| **Placebo vs** |  | |  | |
| Nefazodone | 41 | 42 | 42 | 42 |
| Phenelzine | 37 | 37 | 37 | 37 |
| Imipramine | 41 | 41 | 41 | 41 |
| Citalopram | 35 | 35 | - | - |
| Bupropion SR | 28 | 30 | - | - |
| Paroxetine | 1101 | 1260 | 1260 | 1260 |
| NK1R antagonist | 159 | 176 | 176 | 129 |
| Topiramate | 97 | 115 | 75 | 115 |
| Divalproex | 110 | 114 | - | 114 |
| Guanfacine | 87 | 99 | - | 63 |
| Brofaromine | 52 | 68 | - | 114 |
| Lamotrigine | - | 15 | 15 | 15 |
| Risperidone | 343 | 131 | 65 | 131 |
| Sertraline | 1236 | 1346 | 468 | 986 |
| Olanzapine | 62 | 70 | 70 | 70 |
| Fluoxetine | 722 | 536 | 778 | 724 |
| Amitriptyline | 40 | 46 | 46 | 46 |
| Mirtazapine | 26 | 29 | 29 | 29 |
| Tiagabine | 202 | 232 | 232 | 232 |
| Venlafaxine ER | 687 | 687 | 329 | 687 |
| Prazosin | 358 | 411 | - | 411 |
| **Sertaline vs** | | |  |  |
| Nefazodone | 26 | - | - | 37 |
| Citalopram | 48 | 49 | - | - |
| Venlafaxine ER | 352 | 352 | - | 352 |
| **Phenelzine vs** | | |  |  |
| Imipramine | 42 | 42 | 42 | 42 |
| **Fluvoxamine vs** | | |  |  |
| Reboxetine | 28 | 40 | - | - |
| **Paroxetine**  **vs** |  |  |  |  |
| Desipramine | 88 | 88 | - | - |

Table 3. Number of studies and number of participants per treatment for primary and secondary outcomes.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatments** | **Primary outcomes** | | | | **Secondary outcomes** | | | |
| **Change in symptoms** | | **Any-cause dropouts** | | **Response rate** | | **Dropouts due to adverse events** | |
| Number of studies | Number of participants | Number of studies | Number of participants | Number of studies | Number of participants | Number of studies | Number of participants |
| Placebo | 44 | 2245 | 44 | 2280 | 28 | 1501 | 36 | 2115 |
| Nefazodone | 2 | 39 | 1 | 27 | 1 | 27 | 2 | 45 |
| Phenelzine | 1 | 19 | 1 | 19 | 2 | 19 | 1 | 19 |
| Imipramine | 1 | 23 | 1 | 23 | 2 | 23 | 1 | 23 |
| Citalopram | 1 | 25 | 1 | 25 | - | - | - | - |
| Bupropion SR | 1 | 18 | 1 | 20 | - | - | - | - |
| Paroxetine | 5 | 671 | 5 | 765 | 4 | 723 | 4 | 723 |
| NK1R antagonist | 2 | 84 | 2 | 91 | 2 | 91 | 1 | 69 |
| Topiramate | 3 | 47 | 3 | 57 | 2 | 37 | 3 | 57 |
| Divalproex | 2 | 56 | 2 | 60 | - | - | 2 | 60 |
| Guanfacine | 2 | 41 | 2 | 47 | - | - | 1 | 29 |
| Brofaromine | 1 | 26 | 1 | 35 | - | - | 1 | 56 |
| Lamotrigine | - | - | 1 | 11 | 1 | 11 | - | - |
| Risperidone | 4 | 176 | 4 | 70 | 1 | 33 | 4 | 70 |
| Sertraline | 9 | 636 | 9 | 679 | 4 | 238 | 6 | 507 |
| Olanzapine | 3 | 34 | 3 | 38 | 3 | 38 | 3 | 38 |
| Fluoxetine | 5 | 522 | 4 | 386 | 4 | 582 | 3 | 555 |
| Amitriptyline | 1 | 22 | 1 | 25 | 1 | 25 | 1 | 25 |
| Mirtazapine | 1 | 17 | 1 | 20 | 1 | 20 | 1 | 20 |
| Tiagabine | 1 | 105 | 1 | 116 | 1 | 116 | 1 | 116 |
| Venlafaxine ER | 2 | 340 | 2 | 340 | 1 | 161 | 2 | 340 |
| Prazosin | 3 | 179 | 3 | 204 | - | - | 3 | 204 |
| Fluvoxamine | 1 | 17 | 1 | 20 | - | - | - | - |
| Reboxetine | 1 | 11 | 1 | 20 | - | - | - | - |
| Desipramine | 1 | 46 | 1 | 46 | - | - | - | - |

Table 4. Summary estimates for primary and secondary outcomes derived from standard pairwise meta-analysis (using random effects model and assuming a common heterogeneity). Heterogeneity was estimated using the restricted maximum likelihood (REML). SMDs smaller than 0 or ORs smaller than 1 favor the first treatment. Underlined results indicate statistical significance.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Comparisons**  **Heterogeneity SD** | | **Primary outcomes** | | | | **Secondary outcomes** | | |
| **Change in symptoms (=0.12)** | | **Any-cause dropouts (=0)** | | **Response rate (=0.44)** | **Dropouts due to adverse events (=0)** | |
| **SMD (95% CI)** | | **OR (95% CI)** | | **OR (95% CI)** | **OR (95% CI)** | |
| **Placebo vs** | |  | | | |  | | |
| Nefazodone | | 0.23 (-0.44, 0.90) | | 0.72 (0.20, 2.58) | | 1 (0.21, 4.68) | 0.11 (0.01, 2.04) | |
| Phenelzine | | 1.06 (0.33, 1.79) | | 7.5 (1.72, 32.80) | | 5.63 (1.08, 29.44) | 3.6 (0.34, 38.30) | |
| Imipramine | | 0.24 (-0.42, 0.90) | | 1.83 (0.51, 6.57) | | 4.88 (0.99, 23.96) | 0.95 (0.18, 4.91) | |
| Citalopram | | -0.17 (-0.94, 0.59) | | 1.71 (0.32, 9.11) | | - | - | |
| Bupropion SR | | -0.10 (-0.91, 0.70) | | 0.75 (0.12, 4.77) | | - | - | |
| Paroxetine | | 0.38 (0.21, 0.55) | | 1.04 (0.82, 1.32) | | 2.04 (1.26, 3.30) | 0.63 (0.42, 0.94) | |
| NK1R antagonist | | 0.21 (-0.15, 0.56) | | 0.83 (0.42, 1.64) | | 1.51 (0.61, 3.77) | 0.55 (0.13, 2.31) | |
| Topiramate | | 0.29 (-0.13, 0.71) | | 0.64 (0.28, 1.48) | | 3.46 (1.06, 11.24) | 0.37 (0.11, 1.25) | |
| Divalproex | | -0.14 (-0.55, 0.28) | | 0.91 (0.38, 2.18) | | - | 0.25 (0.04, 1.57) | |
| Guanfacine | | 0.12 (-0.33, 0.57) | | 0.58 (0.20, 1.68) | | - | 0.26 (0.03, 2.67) | |
| Brofaromine | | 0.47 (-0.12, 1.06) | | 0.96 (0.35, 2.62) | | - | 1.75 (0.72, 4.28) | |
| Lamotrigine | | - | | 8.00 (0.58, 110.27) | | 2.5 (0.17, 36.04) | Excluded | |
| Risperidone | | 0.27 (0.01, 0.54) | | 0.59 (0.25, 1.39) | | 11.63 (1.20, 112.25) | 0.39 (0.11, 1.47) | |
| Sertraline | | 0.23 (0.09, 0.37) | | 0.91 (0.71, 1.15) | | 1.85 (1.03, 3.32) | 0.64 (0.40, 1.00) | |
| Olanzapine | | 0.51 (-0.03, 1.05) | | 0.83 (0.29, 2.37) | | 3.35 (0.98, 11.46) | 0.26 (0.04, 1.65) | |
| Fluoxetine | | 0.30 (0.09, 0.51) | | 1.35 (0.85, 2.14) | | 1.72 (0.96, 3.07) | 0.99 (0.48, 2.03) | |
| Amitriptyline | | 0.34 (-0.32, 1.01) | | 0.66 (0.18, 2.46) | | 1.89 (0.34, 10.48) | 0.15 (0.01, 3.07) | |
| Mirtazapine | | 0.79 (-0.08, 1.66) | | 1.17 (0.22, 6.28) | | 4.28 (0.60, 30.32) | 0.68 (0.03, 18.43) | |
| Tiagabine | | 0.02 (-0.33, 0.37) | | 1.60 (0.94, 2.73) | | 0.97 (0.38, 2.44) | 1 (0.38, 2.62) | |
| Venlafaxine ER | | 0.31 (0.10, 0.53) | | 1.23 (0.90, 1.70) | | 1.93 (0.79, 4.72) | 0.85 (0.50, 1.46) | |
| Prazosin | | -0.06 (-0.32, 0.20) | | 0.95 (0.58, 1.57) | |  | 0.72 (0.24, 2.14) | |
| **Sertaline vs** | | | | | |  |  | |
| Nefazodone | | 0.01 (-0.79, 0.81) | | - | | - | 0.94 (0.12, 7.50) | |
| Citalopram | | -0.65 (-1.27, -0.03) | | 1.33 (0.35, 5.13) | | - | - | |
| Venlafaxine ER | | 0.07 (-0.23, 0.37) | | 1.29 (0.83, 2.02) | | - | 1.39 (0.71, 2.71) | |
| **Phenelzine vs** | | | | | |  |  | |
| Imipramine | | -0.72 (-1.39, -0.05) | | 0.24 (0.06, 0.97) | | 0.87 (0.18, 4.08) | 0.26 (0.03, 2.59) | |
| **Fluvoxamine vs** | | | | | |  |  | |
| Reboxetine | | -0.17 (-0.96, 0.62) | | 0.22 (0.05, 0.98) | | - | - | |
| **Paroxetine**  **vs** | |  | |  | |  |  | |
| Desipramine | | 0.14 (-0.33, 0.62) | | 2.27 (0.96, 5.36) | | - | - | |
|  |  | |  | |  | | |
|  |  | |  | |  | | |

Table 5. Summary estimates for primary and secondary outcomes derived from standard pairwise meta-analysis (using a random effects model and using different heterogeneity parameters). Heterogeneity was estimated using the method of moments estimator. SMDs smaller than 0 or ORs smaller than 1 favor the first treatment. Underlined results indicate statistical significance.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comparisons** | **Primary outcomes** | | **Secondary outcomes** | |
| **Change in symptoms** | **Any-cause dropouts** | **Response rate** | **Dropouts due to adverse events** |
| **SMD (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| **Placebo vs** |  | |  | |
| Nefazodone | 0.23 (-0.41, 0.86) | 0.72 (0.20, 2.58) | 1.00 (0.26, 3.82) | 0.11 (0.01, 2.04) |
| Phenelzine | 1.06 (0.37, 1.75) | 7.5 (1.72, 32.80) | 5.63 (1.37, 23.17) | 3.60 (0.34, 38.30) |
| Imipramine | 0.24 (-0.38, 0.86) | 1.83 (0.51, 6.57) | 4.88 (1.27, 18.65) | 0.95 (0.18, 4.91) |
| Citalopram | -0.17 (-0.91, 0.56) | 1.71 (0.32, 9.11) | - | - |
| Bupropion SR | -0.10 (-0.88, 0.67) | 0.75 (0.12, 4.77) | - | - |
| Paroxetine | 0.38 (0.20, 0.56) | 1.04 (0.82, 1.32) | 1.98 (1.46, 2.69) | 0.63 (0.42, 0.95) |
| NK1R antagonist | 0.20 (-0.11, 0.51) | 1.31 (0.16, 10.95) | 1.53 (0.59, 4.00) | 0.55 (0.13, 2.31) |
| Topiramate | 0.29 (-0.12, 0.69) | 0.68 (0.20, 2.27) | 3.44 (1.21, 9.78) | 0.37 (0.11, 1.25) |
| Divalproex | -0.19 (-0.75, 0.38) | 0.91 (0.38, 2.18) | - | 0.25 (0.04, 1.57) |
| Guanfacine | 0.12 (-0.30, 0.54) | 0.58 (0.20, 1.68) | - | 0.26 (0.03, 2.68) |
| Brofaromine | 0.47 (-0.08, 1.02) | 0.96 (0.35, 2.62) | - | 1.75 (0.72, 4.28) |
| Lamotrigine | - | 8.00 (0.58, 110.27) | 2.5 (0.19, 32.19) | Excluded |
| Risperidone | 0.26 (0.04, 0.47) | 0.60 (0.22, 1.67) | 11.63 (1.38, 98.18) | 0.40 (0.11, 1.47) |
| Sertraline | 0.25 (0.07, 0.42) | 0.91 (0.71, 1.15) | 1.98 (0.89, 4.45) | 0.64 (0.40, 1.00) |
| Olanzapine | 0.49 (-0.14, 1.13) | 0.83 (0.29, 2.37) | 3.46 (1.11, 10.78) | 0.26 (0.04, 1.65) |
| Fluoxetine | 0.31 (0.07, 0.55) | 1.35 (0.85, 2.14) | 1.77 (0.87, 3.62) | 0.99 (0.48, 2.03) |
| Amitriptyline | 0.34 (-0.29, 0.97) | 0.66 (0.18, 2.46) | 1.90 (0.41, 8.74) | 0.15 (0.01, 3.07) |
| Mirtazapine | 0.79 (-0.05, 1.63) | 1.17 (0.22, 6.28) | 4.28 (0.71, 25.92) | 0.68 (0.03, 18.43) |
| Tiagabine | 0.02 (-0.26, 0.30) | 1.60 (0.94, 2.73) | 0.97 (0.58, 1.62) | 1.00 (0.38, 2.62) |
| Venlafaxine ER | 0.31 (0.16, 0.46) | 1.23 (0.90, 1.70) | 1.93 (1.22, 3.06) | 0.83 (0.41, 1.67) |
| Prazosin | -0.07 (-0.46, 0.32) | 0.95 (0.58, 1.57) | - | 0.71 (0.24, 2.16) |
| **Sertaline vs** | | |  |  |
| Nefazodone | 0.01 (-0.76, 0.78) | - | - | 0.94 (0.12, 7.50) |
| Citalopram | -0.65 (-1.23, -0.07) | 1.33 (0.35, 5.13) | - | - |
| Venlafaxine ER | 0.07 (-0.14, 0.28) | 1.29 (0.83, 2.02) | - | 1.39 (0.71, 2.72) |
| **Phenelzine vs** | | |  |  |
| Imipramine | -0.72 (-1.34, -0.09) | 0.24 (0.06, 0.97) | 0.87 (0.24, 3.15) | 0.26 (0.03, 2.59) |
| **Fluvoxamine vs** | | |  |  |
| Reboxetine | -0.17 (-0.93, 0.59) | 0.22 (0.05, 0.98) | - | - |
| **Paroxetine**  **vs** |  |  |  |  |
| Desipramine | 0.14 (-0.28, 0.56) | 2.27 (0.96, 5.36) | - | - |
|  |  |  |  |  |