Initial depression severity and response to antidepressants v. placebo: patient-level data analysis from 34 randomised controlled trials

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Summary
Several often-cited meta-analyses have reported that the efficacy of antidepressant medications depends on the severity of depression. They found that drug-placebo differences increased as a function of initial severity, which was attributed to decreased responsiveness to placebo among patients with severe depression rather than to increased responsiveness to medication. We retested this using patient-level data and also undertaking a meta-analysis of trial-level data from 34 randomised placebo controlled trials (n = 10,737) from the NEWMEDS registry. Although our trial-level data support previous findings, patient-level data did not show any significant effect of initial depression severity on drug v. placebo difference.

One of the most controversial studies on the treatment of depression, a meta-analysis conducted by Kirsch et al cited 1500 times, found that the efficacy of antidepressant treatment is attributable to decreased responsiveness to placebo among patients who were severely depressed rather than to increased responsiveness to medication. That analysis included data from 35 published and unpublished studies on fluoxetine, venlafaxine, nefazodone and paroxetine conducted between 1987 and 1999. A more recent analysis of the same data-set did not find that initial severity determined drug-placebo differences. Khan et al examined the association of baseline severity and outcome in 45 phase II and III antidepressant clinical trials. They found that in the active treatment group in trials that included patients with severe depression, more severe depression at baseline was associated with decreased responsiveness to placebo among patients with severe depression rather than to increased responsiveness to medication. We conducted both patient-level and meta-analysis of trial-level data.

Method
We used patient- and trial-level data from 34 randomised placebo-controlled trials (n = 10,737) (1987–2007) of citalopram, duloxetine, escitalopram, quetiapine and sertraline from the NEWMEDS registry (see online supplement DS1 for a list of studies). This included all acute placebo-controlled trials of major depressive disorder in adult populations sponsored or owned by Pfizer (12 studies; active: n = 2455, placebo: n = 888), Lilly (11 studies; active: n = 2425, placebo: n = 1134), AstraZeneca (4 studies; active: n = 1021, placebo: n = 524) and Lundbeck (7 studies; active: n = 1509, placebo n = 781) on these five compounds. In three studies the Hamilton Rating Scale for Depression (HRSD) was estimated based on the Montgomery–Åsberg Depression Rating Scale (MADRS) using equipercentile linking, which gives an equivalent score of one measure on the other measure. It was done using data from 16 studies that included both measures.

Results
Patient-level results did not support our hypothesis. The interaction of placebo v. active treatment and baseline severity was not significant (F = 1.19, P = 0.28; B = 0.045 (95% CI −0.035 to 0.125), β = 0.059). Linear and quadratic regression results were the same for both models and were almost the same for active treatment and for placebo (R² = 0.06, s.e. = 8.1; R² = 0.04, 2016). 


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The difference between our results and Kirsch et al’s appear to be the result of differences in methodology – meta-analysis v. patient-level analysis. This is supported by our finding that when examining the same drugs as Kirsch et al using patient-level analysis, we did not find the effect that their study did. However, we note that for the most part our studies did not overlap with those included in the work of Kirsch et al. Caution is advised when examining positive relationships between baseline severity and symptom improvement as these may be the result of regression to the mean.

Table 1  Placebo-active differences in Hamilton Rating Scale for Depression (HRSD) scores and drop-out rates by group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Baseline</th>
<th>Change from baseline</th>
<th>Drug-placebo difference, mean (95% CI), s.e.</th>
<th>Drop-out, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 3258)</td>
<td>23.0 (4.1)</td>
<td>−8.8 (8.1)</td>
<td>−2.05 (−2.38 to −1.72) 0.17</td>
<td>35.6</td>
</tr>
<tr>
<td>Active (n = 7323)</td>
<td>23.1 (4.2)</td>
<td>−10.8 (8.4)</td>
<td></td>
<td>35.0</td>
</tr>
</tbody>
</table>

Baseline severity

| Low (less than 22) | Placebo (n = 1328) | 19.3 (2.7) | −7.1 (7.2) | −2.04 (−2.50 to −1.58) 0.24 | 34.8 |
| Active (n = 3046) | 19.4 (2.8) | −9.1 (7.4) | | 34.5 |
| Medium (22-25) | Placebo (n = 1102) | 23.8 (0.8) | −9.2 (8.0) | −1.82 (−2.40 to −1.24) 0.30 | 31.9 |
| Active (n = 2345) | 23.8 (0.8) | −11.0 (8.1) | | 33.3 |
| High (above 25) | Placebo (n = 828) | 28.0 (2.4) | −10.7 (9.1) | −2.41 (−3.17 to −1.64) 0.39 | 40.0 |
| Active (n = 1932) | 28.1 (2.6) | −13.1 (9.4) | | 35.6 |

The difference between our results and Kirsch et al’s appear to be the result of differences in methodology – meta-analysis v. patient-level analysis. This is supported by our finding that when examining the same drugs as Kirsch et al using patient-level analysis, we did not find the effect that their study did. However, we note that for the most part our studies did not overlap with those included in the work of Kirsch et al. Caution is advised when examining positive relationships between baseline severity and symptom improvement as these may be the result of regression to the mean.

Discussion

Baseline severity was not associated with a more pronounced change from baseline in the active v. placebo-treated patients when using patient-level data, but was evident to some extent when using aggregate trial-level data. The patient-level analysis does not support the findings of the previous meta-analyses4,5 that antidepressants act at the same magnitude irrespective of initial severity while placebo changes as a function of baseline severity. Patient-level data are more sensitive than trial-level data in measuring the effects in question as they allow for adjusting each patient’s change score by their baseline value and other patient-level characteristics.

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References