Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials
Machado M, Einarson TR

CRD summary
The review found that there were no substantial clinical differences in outcomes with serotonin-norepinephrine reuptake inhibitors compared to selective serotonin reuptake inhibitors in adults with major depressive disorder. The authors' conclusions were based on the evidence presented, but some methodological flaws made the reliability of the results unclear.

Authors' objectives
To compare the clinical outcomes of adults with major depressive disorder treated with serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs).

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to July 2007 for studies published in English, French, Spanish, Portuguese or Italian. Search terms were reported. References of retrieved articles and reviews of the topic were checked for additional studies.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared treatment with SSRIs and SNRIs (with at least one active drug in each of these pharmacological classes) over eight to 12 weeks in patients over 18 years of age with major depressive disorder diagnosed by any standard scale. Patients were required to be treatment-naive or to have had a washout period of one to two weeks. Patients were excluded if they were taking other drugs such as lithium or thyroid hormone that could interfere with the interpretation of study data and who had other concomitant psychiatric endocrine or metabolic disease.

The mean age of patients who received SNRIs was 41.9 years (standard deviation 11.9) and 41.6 years (standard deviation 12.1) for patients who took SSRIs; mean age of all patients ranged from 37 to 71 years. Most (68%) of the participants were women. The four SSRIs used in the review were escitalopram (10 to 20mg/day), fluoxetine (20 to 60mg/day), paroxetine (20 to 40mg/day) and sertraline (50 to 150mg/day). SNRIs used were venlafaxine (37.5 to 225mg/day) and duloxetine (40 to 120mg/day). The primary outcome of remission rate was defined as scores up to 7 or 8 on the Hamilton Rating Scale for Depression and 10 or 12 on the Montgomery-Asberg Depression Rating Scale.

Two independent reviewers performed study selection; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Downs-Black 27-item checklist. Quality items assessed included methods of sample selection, randomisation and blinding, data presentation, statistical analysis and statistical power. Any disagreements between the reviewers were resolved by discussion.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (OR) and mean differences, with 95% confidence intervals, on rates of total remission and dropouts due to lack of efficacy or adverse drug reactions. Data were categorised on the basis of whether intention-to-treat or per-protocol analyses were used. Any disagreements between the reviewers were resolved by discussion.

Methods of synthesis
Pooled odds ratios and 95% CIs were calculated using a random-effects model. Statistical heterogeneity was evaluated with $\chi^2$. Differences in success rates of SSRIs and SNRIs were computed. The reviewers assessed publication bias using funnel plots and by calculating the Begg-Mazumdar statistic. Where publication bias was identified, Duval and
Tweedie’s trim-and-fill method was used to verify its impact. Post hoc sensitivity analyses excluded escitalopram from the results.

**Results of the review**

Fifteen RCTs (n=3,094 participants) were included in the review. Study quality was judged to be of very good; all trials received quality scores of more than 80%.

Using intention-to-treat analyses, remission rates were 48.5% for SNRIs and 41.9% for SSRIs. Per protocol rates of remission were 66.6% for SNRIs and 53.9% for SSRIs. There were statistically significant benefits observed in total remission with treatment with SNRIs compared to SSRIs for both intention-to-treat data (OR 1.27, 95% CI 1.06 to 1.52; n=3,094) and per protocol data (OR 1.56, 95% CI 1.19 to 2.04; n=2,377).

There were significantly fewer drop-outs observed for the SSRI group compared to SNRIs (difference 0.026, 95% CI -0.004 to 0.056). There were higher rates of drop-outs due to adverse drug reactions in the SNRI group compared to SSRIs, but this difference was not statistically significant.

No statistically significant heterogeneity was reported. There was some evidence of publication bias shown in the funnel plot and the Begg-Mazumdar statistic was marginally statistically significant (p=0.059). The reviewers stated that examination revealed that four studies were missing that potentially caused the observed publication bias. Using intention-to-treat analyses, the adjusted odds ratio for rates of remission was 1.11 (95% CI 0.91 to 1.35), which indicated no difference in remission rates between SSRIs and SNRIs.

**Authors’ conclusions**

Although remission rates were higher for patients with major depressive disorder who were treated with SNRIs compared to SSRIs, the observed differences in remission rates were not considered to be clinically significant.

**CRD commentary**

The review addressed a defined question. Inclusion criteria were clearly stipulated. The review was restricted to studies published in certain languages, so there was a risk of language bias. The review was restricted to fully published studies; some evidence of publication bias was reported in the review. Steps were taken by the reviewers to minimise errors and biases in the processes of study selection, assessment of methodological quality and data extraction. The authors did not present the results of the quality assessment for the individual studies in the review. The reviewers appeared to inappropriately pool data to calculate summary odds ratios from two depression scales with different remission parameters.

The review was generally well conducted, although the identified publication bias raised questions of whether excluding unpublished studies was justified. In general the authors’ conclusions were based on the evidence presented, but their reliability was difficult to judge given the presence of publication bias, a lack of information on the quality of the individual studies and the potentially inappropriate pooling.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future research should evaluate the efficacy of other antidepressants (particularly milnacipran, mirtazapine and bupropion) with individual drug analysis. Future research was required on the clinical effects of antidepressants in other diseases (such as general anxiety disorder).

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