ADVERSE EVENTS ASSOCIATED WITH ANTIDEPRESSANTS: A SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS

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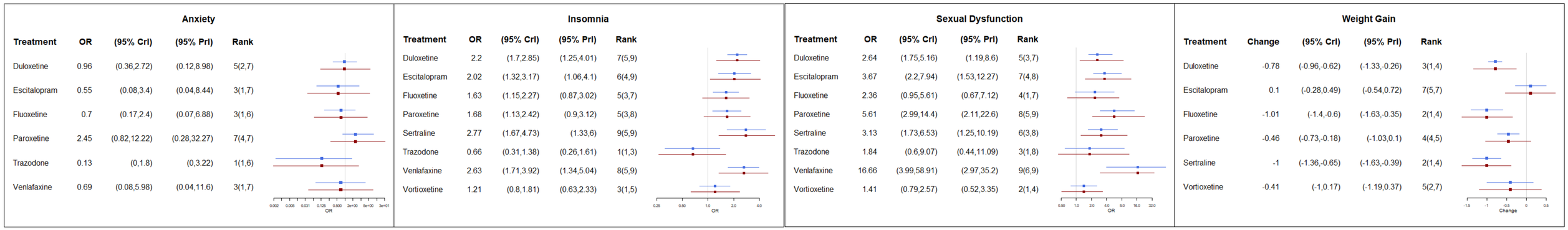
Introduction

Many antidepressants have similar efficacy but can vary with their rates of adverse events, which are a common cause of treatment discontinuation. Hence contemporary comparative evidence on rates of adverse events can be a key factor influencing the choice of antidepressant. The aim of this study was to identify existing trials reporting on key adverse events and synthesise this evidence via network meta analyses (NMA).

Methods

A *de novo* systematic review was conducted of placebo-controlled RCTs reporting at least one of the following adverse events: sexual dysfunction, weight change (in kg), insomnia, anxiety, and anhedonia. Eight antidepressants were considered: duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, trazodone, venlafaxine, and vortioxetine. Intermediate-release formulations were excluded as their results may not be representative of current depression management. The search was conducted in February 2021 in four databases (Medline, Embase, PsycINFO, CENTRAL) for trials of adults with major depressive disorder published since 2018, with earlier studies sourced from existing reviews [1-5]. Results were synthesised via Bayesian random effects NMAs (one network per outcome). Modelling followed published best-practice [6].

Figure 1: Results from the four network meta-analyses. Results are odds ratios relative to placebo, with the exception of weight gain, which is absolute change relative to placebo.



Results

Database searching identified 555 articles, with an additional 55 from existing reviews. Of these 610 references, 67 full texts were examined for eligibility, and 47 were included in the clinical review. Of these, 41 provided evidence that could be used in the NMA. For sexual dysfunction 15 studies were included (although definitions varied), with 21 studies reporting on absolute weight change (a further 8 studies noted there was no significant change without providing data), 36 studies for insomnia, and 10 studies for anxiety. There was no evidence identified for anhedonia.

Results from the NMAs are provided in Figure 1. Rates of anxiety were lowest with trazodone (odds ratio [OR] 0.13, 95% credible interval <0.01 to 1.80), and highest with paroxetine (OR 2.45, 0.82 to 12.22). For insomnia, the only treatment with a lower risk than placebo was trazodone (OR 0.66, 0.31 to 1.38). All of the antidepressants had higher rates of sexual dysfunction than placebo. Rates were lowest for vortioxetine and trazodone (ORs 1.41 and 1.84 respectively) and highest for venlafaxine (OR 16.66, 3.99 to 58.91). Weight change was largest for fluoxetine and sertraline (kg change -1.01 and -1.00 respectively). Both trazodone and venlafaxine were reported to not be significantly different to placebo.

Discussion

Rates of all four adverse events varied by antidepressant. Trazodone had the lowest rates for both anxiety and insomnia and, along with vortioxetine, had the lowest rates of sexual dysfunction. Trazodone also had similar outcomes to placebo for weight change. The largest odds ratios were observed for paroxetine (anxiety), sertraline (insomnia), and venlafaxine (sexual dysfunction). These results suggest that trazodone may be an appropriate treatment choice when the goal is to provide an efficacious treatment which has low rates of these adverse events.

No evidence was identified for anhedonia, future work could consider searching for other study designs.

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