Nefarious Nausea: A Systematic Review and Meta-analysis of the Risks of Nausea in the Treatment of Major Depressive, Obsessive-Compulsive, and Anxiety Disorders with Selective Serotonin Re-uptake Inhibitors (SSRI)

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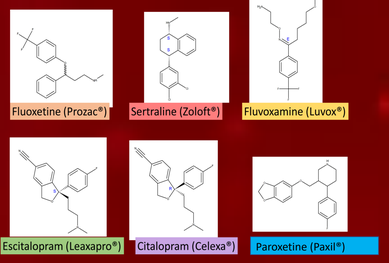
INTRODUCTION:

Selective serotonin re-uptake inhibitors (SSRI's) form a fundamental pharmacologic modality for the treatment of major depressive (MDD), anxiety (AD), and obsessive-compulsive (OCD) disorders. There are six medications which belong to the SSRI class: fluoxetine, paroxetine, fluvoxamine, sertraline, escitalopram, and citalopram.



Previous meta-analyses have provided significant evidence to support the effectiveness and tolerability of SSRI's in the treatment of multiple neuropsychiatric conditions (Cipriani et al. 2018; Bighelli et al. 2018; Soomro et al 2008). However, recent meta-analyses have highlighted discrepancies in the literature, suggesting SSRI's may not be favorable as once perceived (Munkholm et al. 2019; Jacobsen et al. 2017). As such, re-evaluations of efficacy and tolerability data have been warranted.

From these re-evaluations has arisen a subset-of-narrow focused meta-analyses that study a side-effect in comprehensive detail. Nausea is one of the most common and pervasive side-effects elicited by SSRI. SSRI induced nausea has not been studied in the same comprehensive detail as other side-effects, such as insomnia, headache, and weight gain.

Thus, this analysis seeks to perform a comprehensive assessment of the risks of nausea induced by SSRI's relative to placebo across MDD, AD, and OCD diagnoses. This analysis will also provide an updated quality assessment of tolerability literature.

METHODOLOGY:

STATISTICAL ANALYSIS:

Review Manager (Revman) version 5.3 was used to perform all effect size analyses (The Cochrane Collaboration 2014). The operating meta-analytic model was the Dersimonian & Laird random-effects model (Dersimonian & Laird 1986). Relative risk (RR) measures were used to quantify the risk of developing nausea in SSRI relative to placebo. Funnel plots and Egger's regressions were generated to observe small-study effects. Tests of subgroup differences were used to quantify differences between SSRI, conditions, or concomitances in trials. Three sensitivity analyses were performed to explore heterogeneity. The three sensitivity analyses were: isolation of unpublished literature, isolation of panic disorder studies, and analysis of fixed versus flexible dosing.

SYSTEMATIC REVIEW AND QUALITY OF EVIDENCE METHODS:

All studies which passed multi-stage exclusion analysis were systematically reviewed according to the Cochrane Handbook on Systematic Reviews (Higgins & Green 2011). Therefore, the biases assessed for all clinical trials were: two forms of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

Quality of Evidence assessments were generated according to the GRADE approach (GRADE criterion is not provided).

RESULTS:

Figure 1: Flow Diagram from Study Search to Final PI Assessment

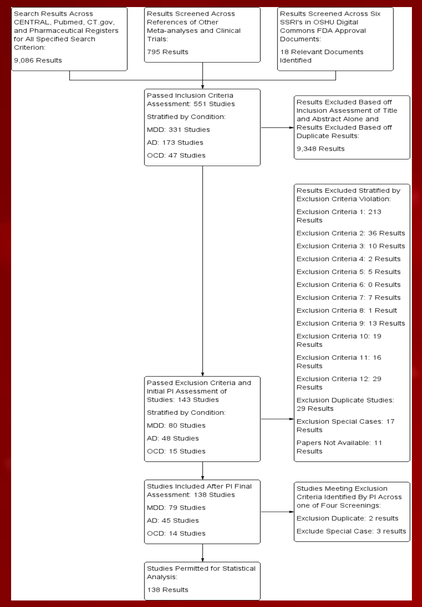


Figure 1 displays the flow of study selection from initial search to final PI assessment. A total of 551 studies passed initial inclusion criteria. A total of 138 studies composed the analytic sample with a participant size of n = 35,952 participants, and an unpublished trial quantity of 24 studies.

Figure 2: Risk of Bias Graph

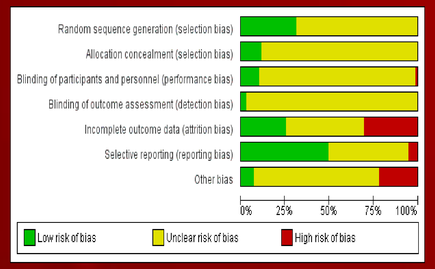


Figure 2 depicts the results of risk of bias assessments for all included studies. A total of 128 studies met classification for high-risk of bias, while 10 studies met classification for low-risk of bias (overall bias of studies). The primary reasons for high-risk of bias classification was four or greater unclear risks across the seven bias categories.

Attrition bias had the greatest concentration of high-risk classifications. This was due to attrition rates of greater than 30% with relative imbalancing in both attrition number and discontinuation reasoning across interventions. Majority of studies were classified as unclear risk of bias for random-sequence generation, allocation concealment, and blinding of outcome assessment, due to limited methodologic extrapolation that prevented an adequate assessment of bias.

Figure 3: *Part A Risk of Nausea Analysis for SSRI's Across All-Conditions*

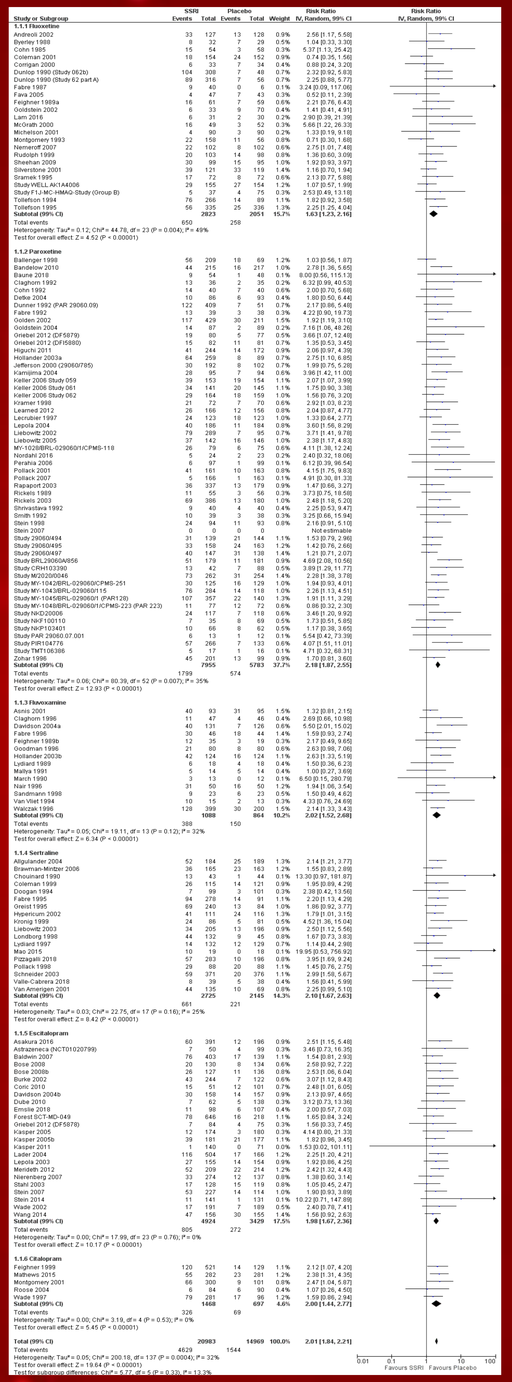


Figure 3 displays the Part A risk of nausea analysis across all diagnostic indications. SSRI's collectively showed a significant association in increased risk of nausea relative to placebo in Part A (RR = 2.01; Z = 19.64, 99%CI = 1.84-2.21). This increased association was observed across all six SSRI subgroups (Figure 3). Test of subgroup differences showed no significant difference in risks of nausea across SSRI's (χ^2 = 5.77; df = 5; p = 0.33; I^2 = 13.3%). Significant heterogeneity was detected for the cumulative SSRI outcome (τ^2 = 0.05; χ^2 = 200.18; df = 137; p = .0004; I^2 = 32%).

Figure 4: *Funnel Plot for Part A All-Conditional Analysis*

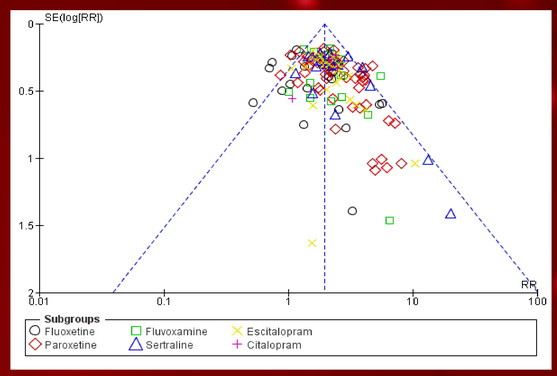


Figure 4 displays the funnel plot for assessment of small-study effects in the Part A all-conditional analysis. The funnel plot is relatively asymmetrical in favor of the right side. A significant Egger's regression confirmed this asymmetry (p>.1). This asymmetry is likely originating from increased heterogeneity and the intrinsic nature of risk estimates.

Figure 5: *Part A Risk of Nausea Low-Risk Analysis*

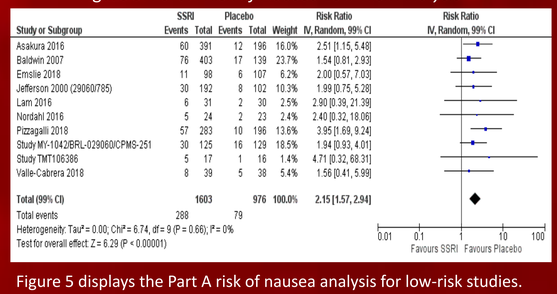


Figure 5 displays the Part A risk of nausea analysis for low-risk studies. SSRI's collectively showed a significant association in increased risk of nausea among Part A low risk studies (RR = 2.15; Z = 6.29, 99%CI = 1.57-2.94). Significant heterogeneity was not detected for the cumulative estimate (τ^2 = 0.00; χ^2 = 6.74; df = 9; p = 0.66; I^2 = 0%).

GRADE quality of evidence assessments for Parts A and B supported a "VERY LOW," quality of evidence for the high-risk analyses. Therefore, the low-risk analysis should be referenced for a more confident estimate.

DISCUSSION:

This meta-analysis has provided significant evidence to suggest that SSRI's greatly increase the risk of nausea relative to placebo. However, none of the SSRI's showed any significant or meaningful differences from each other at α = 0.01. Therefore, while differences in nausea development may exist on an individual basis, there is no significant evidence to suggest any meaningful differences among the SSRI at population levels.

The systematic review portion of this analysis provided an updated assessment of tolerability literature. Majority of studies were classified as high-risk and had a number of limitations. Efforts should be made to improve quality in both clinical trial design and reporting of methodologic characteristics of trials.

In conclusion, this analysis has provided the most comprehensive single side-effect meta-analysis to date.

NOTE TO READERS:

The data presented in this poster is a fraction of the total data analyzed. Only data from the two most relevant hypothesis tests from Part A were provided. This analysis performed a total of 40 hypothesis tests and had a Part B analysis which analyzed secondary treatment arms. The data presented is merely summative of some focal points of the experiment.

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