Safety of fluoxetine use in children and adolescents: a disproportionality analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database

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Dear Editor,

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) is currently the only licensed SSRI recommended in combination with cognitive behavioural therapy to treat depression in those under 18 years of age. (1) In 2004, a black box warning communicating the increased risk of suicidal thinking and behaviour compared to placebo in children and adolescents was added to the labelling of all antidepressants. (2) In this letter, we assess the overall safety of fluoxetine by analysing the reports of adverse events in children and adolescents using fluoxetine, submitted to the FDA Adverse Event Reporting System (FAERS) between 01-Jan-2015 to 30-Jun-2019.

We performed a case/non-case analysis on the top 10 most reported adverse events for fluoxetine users under 18 years old. Cases were reports which included at least one of the top 10 adverse events, whereas non-cases were all remaining reports. Reporting odds ratio (ROR), with 95% confidence intervals was calculated for each of the top 10 most frequently reported adverse events, shown in **Figure 1.** We used the PharmaPendium® (3) database (which extracts data directly from FAERS) to export the relevant data into an excel spreadsheet. We then used R 3.6.1 statistical software to calculate ROR, which compared patients within the same age and study date range. Reports in FAERS can be submitted by lawyers, consumers, physicians, pharmacists and other healthcare professionals. We verified the preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1, and retrieved reports as per the preferred term.

Our analysis identified 359 adverse event reports (01-Jan-2015 - 30-Jun-2019), after de-duplication. In order of decreasing frequency of events, the top 10 adverse event reports were: 'foetal exposure during pregnancy' (n=128), 'suicidal ideation' (n=63), 'suicidal attempt' (n=49), 'anxiety' (n=42), 'serotonin syndrome' (n=42), 'vomiting' (n=38), 'intentional self-injury' (n=38), 'atrial septal defect' (n=35), depression (n=34) and 'seizure' (n=31).

Our study identified expected and unexpected findings. Findings were expected if the electronic medicines compendium (emc) (1) lists the specific adverse event as a "common" adverse event. Expected signals were found for 'serotonin syndrome' ROR = 22.06, 95% CI = 15.88-30.64, 'intentional self-injury' ROR = 7.41, 95% CI = 5.34 – 10.3, 'suicidal ideation' ROR = 6.19, 95% CI = 4.8 – 7.99, 'foetal exposure during pregnancy' (ROR = 5.13, CI = 4.29 – 6.14), 'suicide attempt' ROR = 4.5, 95% CI = 3.38 – 5.99, 'depression' ROR = 2.84, 95% CI = 2.02 – 4 and 'anxiety' (ROR = 2.51, 95% CI = 1.85 – 3.42). 'Vomiting' (ROR = 0.68, 95% CI = 0.49-0.93) and 'seizure' (ROR = 0.91, 95% CI = 0.64-1.30) did not show disproportionate signals.

Our study identified the known link between maternal fluoxetine use and 'atrial septal defects' (ASD), ROR = 8.36, 95% CI = 5.93 - 11.79); 27.3% of foetuses exposed to fluoxetine during pregnancy had ASD's. The remaining cases, however, were for 9 to 18-year-olds (still undergoing cardiac development). The emc does not warn for ASD for those exposed to fluoxetine who are under 18 years old. There are zero cases of ASD for those older than 19 years old, indicating a potential link between the developing myocardium and ASD. There is biological plausibility explaining why adolescents are more prone to ASD compared to adults; serotonin regulates key cellular processes in cardiac development, and fluoxetine can inhibit proliferation of the myocardium and cushion mesenchyme cells. (4) Another study compared the safety profile of fluoxetine in combination with olanzapine in adolescents and adults. However, ASD with fluoxetine use was not examined. (5) The higher reporting of ASD among children exposed to fluoxetine in our study is important for advancing paediatric pharmacoepidemiology research. Further confirmation from a large case-control study is needed to validate this adverse effect.

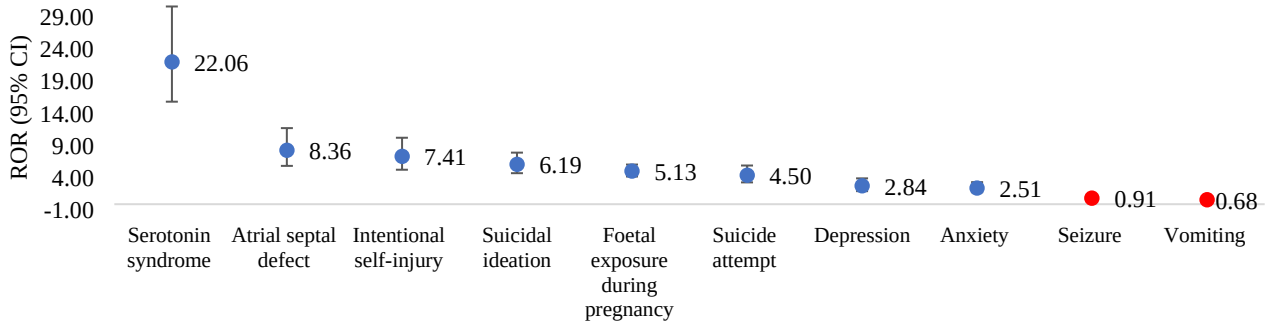

Figure 3. *Reporting odds ratio (ROR) with 95% confidence intervals (95% CI) for the top 10 adverse events reported in the FAERS database between 01-Jan-2015 and 30-Jun-2019 for under 18-year-old fluoxetine users.*

Data Sharing

We agree to share all relevant raw data used to draw conclusions for this study to any researcher wishing to use them for non-commercial purposes.

Compliance with Ethical Standards

The authors have no conflicts of interest, received no funding and received ethical approval from the departmental research officer prior to the start of the research.

References

1. Electronic medicines compendium. Fluoxetine 10mg Film-coated Tablets – Summary of Product Characteristics (SmPc) [internet]. Surrey: emc; 2017 [Updated 2019 Jul 29; Cited 2020 Jan 02].
2. US FDA Adverse Event Reporting System (FAERS) Public Dashboard [internet]. [Cited 2020 Mar 01].
3. PharmaPendium. Amsterdam, Netherlands. Elsevier [updated 2018 Oct 31, cited 2020 Mar 03] Available from: https://www.pharmapendium.com.
4. Yavarone MS, Shuey DL, Tamir H, Sadler TW, Lauder JM. Serotonin and cardiac morphogenesis in the mouse embryo. *Teratology*. 1993 Jun; 47(6):573–84.
5. Liu XI, Schuette P, Burckart GJ, et al. A Comparison of Pediatric and Adult Safety Studies for Antipsychotic and Antidepressant Drugs Submitted to the United States Food and Drug Administration. *Journal of Pediatrics* 2019; 208: 236-242.e233.