Antidepressants and risk of epilepsy and seizures

Trevor Hill¹, Carol Coupland¹, Richard Morriss¹, Antony Arthur², Michael Moore³, Julia Hippisley-Cox⁴

Introduction
There is conflicting evidence for an association between antidepressant use and the risk of epilepsy and/or seizures. This study aims to clarify the picture by using a large representative cohort from a primary care database.

Methods
- QResearch primary care database.
- 687 different UK practices.
- Cohort of patients aged between 20 and 65 with a first recorded diagnosis of depression between 1/1/2000 and 31/7/2011.
- Patients diagnosed with schizophrenia, bipolar or other psychosis were excluded.
- Patients prescribed antidepressant medication more than 36 months before the date of their depression diagnosis, before the age of 20, or before study entry date were also excluded.
- Information extracted on demographic data, potential confounders and all prescriptions for antidepressant drugs.
- Cox regression used to estimate hazard ratios for the association between antidepressant treatment and epilepsy/seizures during the follow-up period.

Results (1) – Study cohort
The study cohort comprised 238,963 patients, 88% of whom received at least one prescription for an antidepressant during follow-up. The most common class of antidepressant prescribed was selective serotonin reuptake inhibitors (SSRI) comprising 71% of prescriptions, with tricyclic and related antidepressants (TCA) second (14%) and other antidepressants third (12%). Monoamine oxidase inhibitors (MAOI) and combined prescriptions accounted for less than 3% of antidepressant prescriptions.

In the first five years of follow-up there were 878 patients with a first diagnosis of epilepsy/seizures. We found a statistically significant association between all antidepressant drug classes and the risk of epilepsy/seizures. All dosages, apart from low dose SSRI and low doses of other types of antidepressant were significantly associated with an increase in the risk of epilepsy/seizures.

Results (2) – Hazard ratios for the first five years of follow-up
There were significantly increased hazard ratios for 8 of the 11 most commonly prescribed drugs compared to no treatment, with the highest risks associated with trazodone (adjusted HR=5.41, 95% CI 3.05 to 9.61), lofepramine (adjusted HR=3.09, 95% CI 1.73 to 5.50), and venlafaxine (adjusted HR=2.84, 95% CI 1.97 to 4.08). Sertraline, mirtazapine, and escitalopram were not associated with a significant increase in the risk of epilepsy/seizures (at P<0.01).

Results (3) – Numbers needed to harm (NNH)
The table below shows the NNH for those 5-year hazard ratios that were significant (P<0.01). The drug class with the highest NNH is the SSRIs, 312 patients would have to be treated over five years for there to be an extra case of epilepsy/seizures. For combined prescriptions only 166 patients would have to be treated for five years for there to be one extra case. For individual drugs the lowest NNH is for trazodone: only 65 patients would have to be treated for five years for one extra case.

Conclusion
This study highlights the risk of epilepsy/seizures for different classes, doses, and individual antidepressants. All antidepressant drug classes had a significantly increased risk of epilepsy/seizures compared to no treatment. Of the individual antidepressants, trazodone, lofepramine, and venlafaxine had the highest risk. Further confirmation is needed via additional studies.

¹University of Nottingham, ²University of East Anglia, ³University of Southampton