# Antidepressants are associated with hospital admitted intracranial bleeds in people taking other medication associated with bleeding

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**ABSTRACT FROM:** Shin JY, Park MJ, Lee SH, et al. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. BMJ 2015;351:h3517.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Antidepressants might decrease platelet aggregation, while nonsteroidalanti-inflammatory drugs (NSAIDs) may also inhibit platelet function, so both may increase bleeding.1 While antidepressants and NSAIDS are thought to increase gastrointestinal haemorrhage,1 there are contradictory results on the risk of intracranial haemorrhage (ICH) with the coprescription of antidepressants and NSAIDs in case control and population studies.2 3 Antidepressants alone are not thought to increase the risk of intracranial haemorrhage.4

**METHODS OF THE STUDY**

A nationwide cohort study of all healthcare insurance claims covering all the population of Korea was carried out. The study examined healthcare claims for people with depression started on antidepressants (including monoamine oxidase inhibitors, buproprion, hypericin, tianeptin) over a 4-year period (2009–2013). NSAIDs included selective inhibitors of COX-2 but excluded low-dose aspirin. People prescribed an antidepressant or a history of intracranial bleeding in the previous year, taking more than one antidepressant at the index date and loss of data at follow-up were excluded. Propensity scoring was used to match two equal size samples of 2 072 613 patients starting antidepressants in people already taking NSAIDs versus those taking antidepressants but not NSAIDs. Matching was for age, gender, years of observation, comorbidities associated with bleeding, severity of comorbidity and other medication associated with bleeding. In total 1 023 607 (19.8%) eligible patients were excluded from the propensity matched samples. The sample was censored for the primary outcome of interest (hospital admission for ICH within 30 days of being prescribed an antidepressant), date switched to another antidepressant, date of discontinuation of an antidepressant or the last date of the study. The incidence rate per 1000 person years was calculated by dividing the number of ICH events by the total number of person years at risk and multiplying the result by 1000. Cox regression models (controlling for dementia, warfarin, heparin and steroids) were used to estimate HRs for ICH with time varying covariates in each the propensity-based matched cohort.

**WHAT THIS PAPER ADDS**

- The risk of ICH requiring hospitalisation was higher within 30 days when antidepressants were combined with NSAIDs compared to antidepressant use without NSAIDs (HR 1.6, 95% CI 1.32 to 1.85).
- There were no differences in risk of ICH between antidepressant drug classes, comorbidities, additional medication nor types of ICH (subarachnoid haemorrhage, intracerebral haemorrhage, other nontraumatic intracerebral haemorrhage).
- The HR for concomitant use of NSAIDs was higher in males (2.6, 95% CI 1.93 to 3.42) than females (1.2, 95% CI 0.89 to 1.57).

**LIMITATIONS**

- Sample with very high rates of warfarin (57%), low-dose aspirin (13%) and antithrombotic drugs (6%) so results are not generalisable to patients not taking other drugs with the potential to cause bleeding.
- There was incomplete and potentially biased assessment of outcome with no assessment of community ICH and sudden death; patients already taking NSAIDs may be more readily identified to be at risk of bleeding so taken to hospital and scanned.
- No check on whether participants took antidepressants prescribed to them and potential inaccuracy of coding within the claims data.
- Propensity scoring introduces selection bias by excluding 20% of participants available for observation and may unleash hidden bias due to latent unobserved variables. The last problem may be operating with no control for history of depression and ICH more than 1 year before the observation period, both factors that are likely to be considered by doctors in their decision-making. Moreover, the propensity matching resulted in a slight excess in the NSAID and antidepressant group on 16 of 17 the most common medical and drug comorbidities that may be clinically related to each other and therefore introducing further confounding in an observational study already confounded by indication for AD and NSAIDs.

**WHAT NEXT IN RESEARCH**

- Repeat the study with improved modelling in a sample with and without coprescription of warfarin or drugs causing bleeding and with the inclusion of community ICH and sudden death.
- Carry out data mining studies in routine practice and a prospective observational study in established cohorts.

**DO THESE RESULTS CHANGE YOUR PRACTICE AND WHY?**

Yes to a limited extent. Before starting patients with depression who are taking NSAIDS with other drugs with the potential for bleeding,

careful review with physician or general practitioner colleagues of the risk of bleeding in that patient and/or consideration of other nonantidepressant approaches in selected patients at risk of bleeding.

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