

## Is Abnormal Bleeding Caused by Antidepressants?

Meijer WE, Heerdink ER, Nolen WA, et al. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. *Arch Intern Med* 2004;164:2367–70.

### Study Overview

**Objective.** To estimate the risk of abnormal bleeding associated with the use of antidepressants and to establish the relationship between serotonin reuptake inhibition and the risk of bleeding.

**Design.** Nested case-control study of a cohort of more than 64,000 new antidepressant users.

**Setting and participants.** Patients aged 18 years or older with an incident prescription for an antidepressant from 1992 through 2000 were included in the cohort. Data were collected from the PHARMO database, which contained prescription medication histories for 850,000 patients in the Netherlands. Antidepressants were classified according to their degree of inhibition (ie, high, intermediate, or low) of serotonin reuptake. Cases were defined as all patients hospitalized with a primary diagnosis of abnormal bleeding while taking any antidepressant. For each case, up to 5 nonhospitalized controls were randomly selected during the case's follow-up. Controls were matched for age ( $\pm 5$  years), sex, and initiation date of antidepressant therapy.

**Main results.** The initial cohort included 64,647 individuals, with an average follow-up duration of 229 days. During follow-up, 196 individuals were hospitalized with a primary diagnosis of abnormal bleeding (incidence, 4.9 per 1000 person-years). The risk of hospitalization for bleeding increased among 103 study subjects (53.1%) who were using antidepressants with a high affinity for the serotonin transporter compared with patients using low-affinity antidepressants (odds ratio, 2.6 [95% confidence interval {CI}, 1.4–4.8]). Antidepressants with an intermediate affinity showed an odds ratio of 1.9 (95% CI, 1.1–3.5).

**Conclusion.** In a large population of new antidepressant users, there was a significant association between degree of serotonin reuptake inhibition by antidepressants and risk of hospital admission for abnormal bleeding. An increased risk of abnormal bleeding was strongly associated with the degree of serotonin reuptake inhibition.

### Commentary

Over 12 million prescriptions for selective serotonin reuptake inhibitors (SSRIs) are written each year. In the early 1990s, case reports and observational studies began to show a relationship between SSRI use and abnormal bleeding. It is believed that serotonin plays a role in platelet aggregation, and because SSRIs affect serotonin levels, it is postulated that they may be associated with an increased risk of bleeding.

Meijer et al identified all persons (cases) who were hospitalized for a bleeding event and matched them to 5 controls similar in age and sex. They then adjusted for potential confounding by including current and prior use of other medications that may affect the risk of bleeding. These authors found that the odds of being hospitalized for a bleeding event was 2.6 times higher for those who were on highly specific SSRIs compared with those on low-degree SSRIs. These results were similar to results of a large retrospective cohort study that found the risk of bleeding was higher among elderly patients taking SSRIs [1].

Meijer and colleagues noted a potential limitation to their study: bias by misclassification, as they used hospital records to diagnose the outcome of interest. Another potential limitation is that the risk of bleeding may have been underestimated because the authors did not capture users of antidepressants who had bleeding events that were not severe enough to be admitted to the hospital.

### Applications for Clinical Practice

Providers need to be aware of the risks for abnormal bleeding, especially in combination with other medications that can increase bleeding risk. Further pharmacoepidemiologic studies are warranted given the large number of people using antidepressants.

—Review by Christianne L. Roumie, MD, MPH

### References

1. van Walraven C, Mamdani MM, Wells PS, Williams JJ. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001;323:655–8.