Use of Selective Serotonin Reuptake Inhibitors and Risk of Upper Gastrointestinal Bleeding: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: **Selective serotonin reuptake inhibitors (SSRIs) are used to treat various psychiatric disorders. However, there are concerns that SSRIs increase the risk for upper gastrointestinal bleeding (UGIB).**

METHODS: **We performed a systematic review and meta-analysis of controlled observational studies to determine whether SSRI use affects the risk for UGIB. Our analysis included all observational studies that compared UGIB development among patients receiving SSRIs vs no treatment. We calculated pooled odds ratios using random- and fixed-effects models.**

RESULTS: **A total of 22 studies (6 cohort and 16 case-control studies) involving more than 1,073,000 individuals were included in our meta-analysis. In comparing SSRI users with patients who had not taken SSRIs, the odds for developing UGIB were 1.55-fold higher (odds ratio, 1.55; 95% confidence interval, 1.35–1.78). In subgroup analyses, the association was greatest for patients who received concurrent therapy with nonsteroidal anti-inflammatory or antiplatelet drugs; we found no significant increase in the risk of developing UGIB among patients receiving concurrent acid-suppressing drugs.**

CONCLUSIONS: **SSRI use was associated with an almost 2-fold increase in the risk of developing UGIB, especially among patients at high risk for GI bleeding (concurrent use of nonsteroidal anti-inflammatory or antiplatelet drugs). This risk might be reduced significantly by concomitant use of acid-suppressing drugs.**

Keywords: Hemorrhage; Antidepressant; 5HT; Stomach.

Selective serotonin reuptake inhibitors (SSRIs) commonly are prescribed for the treatment of diverse psychiatric disorders, including major depressive disorder, general anxiety disorder, and other conditions.[1] These drugs generally are considered safe, and serious adverse effects are rare.[2] However, there have been concerns that SSRI therapy is associated with an increased risk of upper gastrointestinal bleeding (UGIB). The precise mechanism of potential risk is unknown, but several biological mechanism have been proposed to explain a possible relationship between SSRI use and the risk of UGIB, including inhibition of serotonin uptake into platelets or an increase in gastric acid secretion that could increase UGIB risk.[3,4]

Whether SSRI therapy is associated with an increased risk of UGIB is still much debated. A number of epidemiologic studies have investigated the possible association between SSRIs and the risk of UGIB development, but results of previous studies have been inconsistent. Some studies reported[5–7] an increased risk of UGIB in SSRI users, whereas other studies[8–10] did not. Given the widespread use of SSRIs, it is important to

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Abbreviations used in this paper: CI, confidence interval; NNH, number needed to harm; NOS, Newcastle–Ottawa Scale; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; UGIB, upper gastrointestinal bleeding.

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determine whether there is a relationship between SSRI use and the risk of UGIB.

Hence, to understand this association better and to evaluate its magnitude and the quality of the supporting evidence, we performed a systematic review with a meta-analysis of existing observational studies that evaluated an association between the use of SSRIs and the risk for UGIB and explored potential sources of heterogeneity among study results.

Methods

This meta-analysis was conducted following guidance provided by the Cochrane Handbook[11] and Kanwal and White,[12] and is reported according to the meta-analysis of Observational Studies in Epidemiology guidelines. All steps in the literature search, study identification, study selection, quality, and data extraction were performed independently by 2 investigators from different subspecialties (H.-Y.J. and Y.-H.Z.). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Search Strategy

We conducted a comprehensive literature search of the Cochrane Library, PubMed, and EMBASE databases. The search was performed using the terms "selective serotonin inhibitors OR antidepressant OR SSRIs OR paroxetine OR fluvoxamine OR sertraline OR fluoxetine OR citalopram OR escitalopram OR duloxetine OR dapoxetine OR venlafaxine," "gi OR gastrointestinal OR upper gastrointestinal OR gastrointestinal tract," "bleed OR bleeding OR hemorrhage" from January 1990 to March 2014 in English language publications (including abstracts). Reference lists of retrieved articles were hand-searched for further relevant articles. When incomplete information was available, attempts were made to contact the study investigators for additional information.

Study Selection

We included observational studies that met all of the following inclusion criteria: (1) the study was a case-control or cohort study; (2) non-SSRI users were used as the reference group for comparison; (3) the association between the use of SSRIs and the risk of UGIB was investigated; and (4) adequate data were provided to extract the risk estimates. We excluded studies that only reported outcomes of patients with UGIB.

Data Extraction and Quality Assessment

Data extraction was conducted independently by H.-Y.J. and H.Z.C., and discrepancies were resolved by W.Y., Z.-H.Y., M.D., and X.-J.H. before the final analysis. The following data were collected from each study: study design, study time period/year of publication, country of origin of the population studied, total number of subjects in each group, information source for exposure ascertainment, and statistic adjustment. Because of the different mechanistic etiologies between variceal and nonvariceal UGIB, the definition of UGIB used in the source studies also was recorded. If the included studies did not clarify the definition of UGIB, we classified them in the group "include variceal UGIB." We assessed the methodologic quality of the included studies based on the Newcastle–Ottawa Scale (NOS),[13] which was developed for assessing the quality of nonrandomized studies in meta-analyses. In this scale, observational studies were scored across 3 categories: selection (4 questions) and comparability (2 questions) of study group, and ascertainment of the outcome of interest (3 questions), with all questions having a score of 1, except for comparability of study groups, for which separate points were awarded for controlling age and/or sex (maximum, 2 points). A score of $\geq$7 points was suggestive of a high-quality study.

Outcomes Assessed

The primary analysis focused on assessing the risk of UGIB among users of SSRIs. Based on a priori hypotheses to explain potential heterogeneity in the direction and magnitude of effect among different studies, we performed subgroup analyses based on study design (case-control or cohort), concurrent drug use, type of SSRIs, duration of exposure, definition of UGIB, the methodologic quality of the study (high or low), study location (Asia, Western, or North America), and study setting (hospital-based or population-based).

Statistical Analysis

Statistical analysis was conducted using STATA 10.0 software (StataCorp LP, College Station, TX). The Cochran Q chi-square test and the I^2 statistic were used to assess heterogeneity among studies.[14] An I^2 value of $>$50% or a P value of $<$.05 for the Q-statistic was taken to indicate significant heterogeneity.[15] In the presence of heterogeneity, we used a random-effects model because its assumptions account for the presence of variability among studies. When possible, we extracted adjusted effect estimates (odds ratios [ORs], relative risks, hazard risks) between outcome measures and the use of SSRIs with standard error, otherwise we calculated the unadjusted risk ratio using the raw data. All risk estimates included in the pooled analyses were from the most fully adjusted multivariable model. The association between SSRI use and UGIB risk was estimated using the ORs and corresponding 95% confidence intervals (CIs) generated from comparisons between cases and controls. Because the outcomes were relatively uncommon, ORs were