Estimating treatment effects in observational studies

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Randomized controlled trials are required to determine the effectiveness and safety of medical therapies for clinical use. However, observational studies are used frequently to evaluate treatment effects in a number of situations, such as postmarketing safety evaluations of medications or in situations where clinical trials are not feasible.[1] Unlike randomized controlled trials, where randomization promotes an equal balance of known and unknown confounders between treatment groups, treatment groups in observational studies often differ in the prevalence of key prognostic variables associated with both treatment and outcome.[1] While statistical approaches, such as multivariable adjustment, propensity-based matching, and propensity score risk adjustment, can be used to adjust for the influence of known confounders in observational studies, adjusting for unmeasured confounders is more obviously challenging. In the case of propensity-based approaches, the analyses specifically take account of the factors that predict whether a patient receives the treatment or not (e.g., age, disease severity). Instrumental variable analysis has been suggested as a statistical technique to account for unmeasured confounders in some situations.[1] Even for measured confounders, variables may not be adequately adjusted for in the analyses, resulting in residual confounding.

Selective serotonin reuptake inhibitors (SSRIs) are first-line agents for the management of depression, due to their well-established efficacy, tolerability, and relative safety in overdose.[2] The relatively small sample sizes of clinical trials evaluating SSRIs for treatment of depression has mitigated the ability to detect increases in the risk of infrequent adverse events.[3] From observational studies, an association between SSRI use and major bleeding has emerged, proposed to be related to SSRI-mediated reductions in the concentration of intraplatelet serotonin, which may inhibit platelet aggregation.[4] To date, the most convincing association between SSRIs and major bleeding has been reported for gastrointestinal bleeding, while data for intracranial hemorrhage (ICH) have been more inconsistent.[5]

In this issue of *Neurology*®, Hackam and Mrkobrada[5] performed a systematic review and meta-analysis of 16 observational studies (n = 506,411) to determine the association between SSRI exposure and risk of ICH. The authors include observational studies with a control group (cohort, case-control, and case-crossover designs) that reported the association between SSRI prescribing and ICH. The authors reported a significant association between SSRI exposure and all ICH (rate ratio [RR] 1.51, 95% confidence interval [CI] 1.26–1.81; I^2 = 49%) and intracerebral hemorrhage (RR 1.42, 95% CI 1.23–1.65; I^2 = 29%). Oddly, SSRI exposure was associated with a trend toward a reduced risk of subarachnoid hemorrhage (RR 0.62, 95% CI 0.38–1.01; I^2 = 0%). In absolute risk terms, the authors estimate 1 additional intracerebral hemorrhage event per 10,000 patients treated with SSRIs for 1 year.

The authors should be congratulated for their thorough review of the evidence and succinct summary of findings. Strengths of this study include the comprehensive search strategy, the inclusion of a number of subgroup and sensitivity analyses, use of multivariate estimates from the included studies, and assessment for evidence of publication bias. While an individual-patient meta-analysis is more ideal to address this question, difficulties in obtaining the individual patient data mean it is often unfeasible. The validity of their findings, therefore, is dependent on the methodologic quality of the individual studies included, and whether approaches to statistical analyses minimized the influence of confounding. A central question is: Do patients who receive SSRIs differ from patients who do not receive SSRIs in factors that may confound the association with ICH, and were these variables included in multivariable analyses of individual studies? ICH and depression have shared risk factors, such as small vessel disease, diabetes mellitus, smoking, and alcohol consumption,[6–8] which were not included in many multivariable anal-

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yses of individual studies. Cerebral microbleeds may also be a risk factor for depression.[9] Therefore, the magnitude of association could be further mitigated after accounting for the effects of all important confounders. In addition, only 1 study employed propensity-based analyses and none utilized instrumental variable analyses.

Despite these considerations, the meta-analysis by Hackam and Mrkobrada represents best current evidence of an association between SSRI use and risk of ICH. How should the results of this study influence clinical management of patients? A key consideration is that the absolute risk increase associated with SSRIs is very small for the average patient. Therefore, for patients with a clear indication for SSRI use, the absolute increase in risk of ICH should not deter clinicians from prescribing these agents. However, these findings emphasize the importance of appropriate patient selection and avoidance of inappropriate prescribing, which assumes particular importance in patients at increased risk of ICH (e.g., recent history of ICH). Biologically, use of SSRIs with a high affinity for the serotonin receptor may be associated with a higher risk of bleeding compared to lower affinity agents, if an association is mediated through an antiplatelet effect. For patients at high risk of bleeding, use of newer antidepressants with a low affinity for the serotonin receptor (e.g., mirtazapine) has been suggested by some investigators.[10] An additional consideration is that the risk of ICH associated with SSRI use appears to be predominant in the initial period, and lower among patients who are taking medications for longer than 3 months.

Finally, one needs to consider the morbidity and mortality associated with untreated depression and the entire side-effect spectrum of alternative antidepressant drug classes. For example, the largest study included in this meta-analysis did not find a difference in all-cause mortality or all-stroke between SSRIs, tricyclic antidepressants, and other drug classes.[11]

SSRIs may be associated with an increased risk of ICH but the absolute risk in populations is low. These findings add to the totality of evidence for efficacy and safety of antidepressants overall and within drug classes, used to inform evidence-based prescribing.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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