Relative to SSRI users, SSRI–statin users have fewer psychiatric hospital contacts and no increase in suicidal behaviour or all-cause mortality

Chittaranjan Andrade

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India; andradec@gmail.com

ABSTRACT FROM: Kohler O, Gasse C, Petersen L, *et al*. The effect of concomitant treatment with SSRIs and statins: a population-based study. *Am J Psychiatry* 2016;173:807–15.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies have identified inflammatory changes in depression,[1 2] and randomised controlled trials (RCTs) suggest that depression may respond better when anti-inflammatory drugs are used to augment antidepressant drugs.[3] Statins have anti-inflammatory properties. The present study is the first population-level investigation of the benefits and risks of a selective serotonin reuptake inhibitor (SSRI)–statin combination.

METHODS OF THE STUDY

The data for this cohort study were drawn from nationwide Danish electronic national health records from 1997 to 2012. Incident SSRI users (those who received their first prescription for an SSRI) who subsequently received a first prescription for a statin (n=113 108) were compared with incident SSRI users with no statin exposure (n=759 108). There were two efficacy outcomes examined during 642 058 person-years of medication-exposed follow-up: psychiatric hospital contacts and psychiatric hospital contacts for depression. There were two adverse event outcomes: suicide attempt and all-cause mortality.

The data were analysed using Cox regression and competing risk analysis. Analyses were adjusted for a large number of sociodemographic and clinical covariates, including age, medical conditions, anti-inflammatory drug use and use of other general medical and psychotropic medications.

WHAT THIS PAPER ADDS

- Relative to the SSRI group, the SSRI–statin group was older by 10.5 years, had less previous psychiatric contact (15.5% vs 20%), had more medical morbidity (27.2% vs 23.8%) and used more psychotropic (79% vs 66.1%) and cardiovascular (41% vs 28.6%) drugs.
- The commonest SSRIs were citalopram (57.2%), sertraline (17.1%) and escitalopram (11.4%). Simvastatin accounted for 92% of the statin use.
- Relative to the SSRI group, the SSRI–statin group had a lower risk of psychiatric hospital contacts (adjusted HR (aHR), 0.75; 95% CI 0.69 to 0.82) as well as psychiatric hospital contacts for depression (aHR, 0.64; 95% CI 0.55 to 0.75) without impacting the risk of successful or unsuccessful suicide attempt (aHR, 0.85; 95% CI 0.61 to 1.18) or all-cause mortality (aHR, 1.04; 95% CI 0.96 to 1.12).
- The efficacy and adverse event outcomes were similar in analyses restricted to SSRI–simvastatin, SSRI–other statins and citalopram–simvastatin combinations, as well as in various sensitivity analyses and a propensity-matched analysis.
- In an exploratory analysis, the SSRI–lovastatin combination was associated with an increased risk of all-cause mortality (aHR, 3.58; 95% CI 1.15 to 11.10). However, this analysis was based on only four deaths. Additionally, a type I error resulting from data-mining, multiple hypothesis testing cannot be ruled out.

LIMITATIONS

- This study was retrospective; its validity depends on the high, claimed accuracy of the healthcare records from which the data were drawn.
- The study was not an RCT; confounding by indication is possible if clinicians, believing that statins impact negatively on psychiatric outcomes,[4] withheld statin prescription from patients with more severe depression.
- SSRIs are used for many indications, not merely for depression.
- The outcome measures in this study are only proxies for antidepressant benefits.
- At best, therefore, the study suggests that the SSRI–statin combination is a demographic marker of healthcare advantages but does not imply an antidepressant effect for the combination.
- As simvastatin accounted for 92% of the statin use and citalopram for 57% of the SSRI use, the conclusion cannot be generalised with confidence to all SSRI–statin combinations.

WHAT NEXT IN RESEARCH

Adequately powered RCTs are necessary to determine the short-term and long-term benefits and risks of an SSRI–statin combination over SSRI-placebo in statin-naïve depressed patients.[5]

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

Yes and no. These results do not encourage statin use to augment antidepressants due to the limitations listed and because we do not have numbers needed to treat values (that might indicate an effect size) to guide our expectations. However, the results provide modest reassurance that, at a population level, statin use in antidepressant-treated depressed patients is not associated with increased risk of harm.

Competing interests CA publishes an electronic newsletter which attracts donations from Sun Pharmaceuticals to registered charities. Micro Labs publishes a Critical Readings in Psychiatry series, authored by CA, as a free service to psychiatrists in India.

Provenance and peer review Commissioned; internally peer reviewed.

doi:10.1136/eb-2016-102566

Received 6 January 2017; Revised 19 February 2017; Accepted 21 February 2017

REFERENCES

1. **Kiecolt-Glaser JK**, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry* 2015;**172**:1075–91.
2. **Kohler O**, Krogh J, Mors O, *et al*. Inflammation in depression and the potential for anti-inflammatory treatment. *Curr Neuropharmacol* 2016;**14**:732–42.
3. **Kohler O**, Benros ME, Nordentoft M, *et al*. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 2014;**71**:1381–91.
4. **Andrade C.** Primary prevention of cardiovascular events in patients with major mental illness: a possible role for statins. *Bipolar Disord* 2013;**15**:813–23.
5. **Wandel S**, Roychoudhury S. Designing and analysing clinical trials in mental health: an evidence synthesis approach. *Evid Based Ment Health* 2016;**19**:114–17.