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Review

Statins use and risk of depression: A systematic review and meta-analysis

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ABSTRACT

Importance: Statin use has been associated with depression; however studies of the association between statin use and depression have yielded mixed results.
Objective: To determine whether statin use is associated with depression and to evaluate the evidence supporting this association.
Data sources: Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched through December 28, 2012.
Study selection: We included studies that evaluated exposure to statins, reported the development of depression, and relative risks or odds ratios (ORs) or provided data for their estimation. Two reviewers screened 981 abstracts independently using a standardized form, reviewed full text of 59 selected articles, and included 7 studies in this metaanalysis.
Data extraction and synthesis: Study design, statin exposure, development of depression, and study quality were extracted by 2 independent reviewers. A pooled OR with 95% confidence interval (CI) was estimated using the random-effects model and heterogeneity was assessed using Cochran's Q test and the I^2 statistic.
Results: Seven observational studies (4 cohort, 2 nested case-control, and 1 cross-sectional) from 5 countries enrolling 9187 patients were included. Statin users were 32% less likely to develop depression than nonusers (adjusted OR, 0.68; 95% CI, 0.52–0.89). Modest heterogeneity was observed between the studies ($I^2=55\%$, $P=0.01$), which could be accounted for by one study, exclusion of which removed the heterogeneity ($P=0.40$, $I^2=2\%$) and further strengthened the antidepressant effect of statin (adjusted OR, 0.63; 95% CI, 0.43–0.93). Heterogeneity could not be explained by study design or study population. The quality of supporting evidence was fair.
Conclusions and relevance: This systematic review and meta-analysis suggests that statin use is associated with lower risk for depression. However, higher-quality studies are needed to confirm the magnitude of this association.

Contents

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1. Introduction

Statins (hydroxymethylglutaryl co-A reductase inhibitors) play a beneficial role in the primary and secondary prevention of coronary artery disease (CAD), including among patients with average cholesterol level (Benito-León et al., 2010; Carney and Freedland, 2008; Chan et al., 2000). Statins also have reported benefits in various other disorders including Alzheime's disease (Cochran, 1954) and other dementia, stroke, macular degeneration and osteoporosis (Cohen, 1960; Davey Smith and Pekkanen, 1992; DerSimonian and Laird, 1986; Downs et al., 1993, 1998; Engelberg, 1992; Freedman et al., 1995; Goldberg et al., 1998). This suggests that statins may have advantages beyond their effect on CAD and cholesterol. As statin use expands, concerns have been raised about possible negative consequences, including increased risk of non-cardiac death and a possible association of low serum cholesterol with antisocial personality, violent behavior, suicide, and aggressive conduct (Hall et al., 2001; Harrison and Ashton, 1994; Higgins et al., 2003; Hillbrand et al., 1995; Jick et al., 2000; Keech et al., 1994; Lindberg and Hallas, 1998; Marx, 2001). Given these concerns regarding statins and behavioral issues, several studies have attempted to determine a connection between statins and depression. A postulated mechanism for positive association of statins with depression relates to low plasma cholesterol leading to decreased membrane cholesterol in the brain, which could affect central neurotransmitter function and lower serotonergic activity, leading to depression (Harrison and Ashton, 1994). Possible direct effect of statins on brain functions could also be responsible for depression (Harrison and Ashton, 1994). Remission rates for elderly depressed patients treated with antidepressants have been shown to be lower when the same patients are taking cholesterol lowering medications (McAlister et al., 2001). This evidence further supports the positive association between the use of statins and depression.

On the other hand, protective effect of statins against depression has also been reported (Meier et al., 2000; Moher et al., 2009). In addition, several studies report no association between depression and statins (Muldoon, 1994; Muldoon et al., 1990; O'Neil et al., 2012; Oliver, 1992; Otte et al., 2012; Pasco et al., 2010). Thus, the association of statins with depression has remained uncertain. A recent review by While et al. found conflicting evidence for the association of statins with mood, however they could not reach a definite conclusion and they did not perform a meta-analysis (Pedersen et al., 1996).

Therefore, we performed a systematic review and meta-analysis of all studies evaluating the association between statin use and depression, to quantify the magnitude of this association and appraise the quality of the supporting evidence.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) stat0ement guidelines (Sacks et al., 1996).

2.1. Study eligibility

We included comparative studies of any design (randomized control trials, cohort, case control and cross-sectional). Eligible studies had to provide documentation of statin use, measure depression as a predefined outcome of interest, and report risk estimates or frequency data from which one could calculate the risk estimates for depression with statin use. Inclusion was not restricted by language or publication status. When data were reported from overlapping study samples (e.g., multiple publications from the same study), data were included from most recent comprehensive report. Studies reporting depression as a post hoc outcome were excluded because of the risk of potential bias due to non-adjustment for confounders.

2.1.1. Data sources and search

A comprehensive search strategy was designed with the assistance of an expert librarian. Major data bases including Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched on December 28, 2012. The complete search strategy is available in Appendix A. We had searched the references cited in the potentially eligible articles and conference proceedings of major psychiatry, internal medicine, cardiovascular and pharmacology organizations. Full articles of relevant abstracts were searched in the PubMed to further increase the yield of relevant articles.

2.1.2. Study selection

Two reviewers (AKP and BS) screened all titles and abstracts independently using a standardized form. This was followed by full text review of selected articles by the same two reviewers. We assessed interobserver agreement on study selection by Cohen's κ (Sano et al., 2011), and resolved disagreements by consensus in the presence of 3rd reviewer.

2.2. Data extraction

Two reviewers (AKP, BS) extracted data independently from selected studies using a predesigned form. Authors of original studies were contacted to obtain missing data whenever required.