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CURRENT OPINION

Do Statins Have Antidepressant Effects?

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Abstract Statins are used widely in primary and secondary prevention of cardiovascular disease; a treatment effect that has long been thought to be due to their cholesterol-lowering properties. However, statins also have a wide range of anti-inflammatory effects independent of their lipid-lowering mechanisms. In depression, low-grade inflammation is a replicated finding, and several studies have shown antidepressant properties of diverse anti-inflammatory drugs. Large observational studies have suggested reduced risks of depression amongst those taking statins, an effect that is thought to be explained by the anti-inflammatory properties of this class of drugs. Also, preliminary randomized controlled trials (RCTs) have indicated that statins may have adjunctive antidepressant effects when used as add-on treatment to selective serotonin reuptake inhibitors (SSRIs). However, the RCTs were small and limited by low generalizability, and some early observational studies have pointed towards potential neuropsychiatric adverse effects of statin treatment. Nevertheless, based on the good tolerability and general safety of the statins, researchers are currently investigating the potential antidepressant properties of these agents. The present review aims to give an overview on the potential antidepressant effects of statins based on their anti-inflammatory properties, covering topics such as safety versus treatment effects, potential mechanisms of action and the possibility of targeted treatment (precision medicine).

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Key Points

Clinical and epidemiological studies have shown better antidepressant treatment effects of SSRIs and statins compared with SSRIs and placebo in people with depression.

However, the clinical studies were small and future randomized clinical trials need to investigate larger populations, compare specific statins and explore whether pro-inflammatory markers may help predict better treatment response.

There is no clinical trial evidence supporting the fact that statins may have preventive effects against the development of depression in healthy individuals.

1 Introduction

Depression is a major cause of disability worldwide, but despite state-of-the-art treatment including augmentation strategies, remission rates following antidepressant medications are low [1, 2]. Therefore, alternative treatment approaches have been intensely investigated. Based on the potential association between depression and inflammation [3, 4], studies of the potential antidepressant effects of anti-inflammatory drugs is one of the avenues that have been pursued [5, 6]. Due to the anti-inflammatory properties of statins [7, 8], the antidepressant effects of this class of drugs have also been investigated at epidemiological [9–11], preclinical [12, 13] and clinical [14] levels. Here, we provide a review of the background and current evidence for the potential antidepressant effects of statins.

2 Depression and Inflammation

A substantial body of research supports the existence of an intimate connection and interaction between the central nervous system and the immune system [15, 16]. The role of inflammatory processes in the development of depression is the topic that has probably received most attention [17, 18]. The main associations can be summarized as follows:

- Somatic illnesses with inflammatory etiologies have been shown to increase the risk of depression [19–23].
- Pro-inflammatory markers have been found at increased levels among depressed individuals compared with healthy controls, independent of somatic illness, particularly C-reactive protein (CRP) [18, 22, 24], interleukin-6 (IL-6) [3, 18, 24, 25], tumour necrosis factor alpha (TNF-α) [3, 25] and interleukin-1 receptor antagonist (IL-1ra) [18, 24]. In addition to increased levels during depressive episodes [3, 18], studies have associated increments of pro-inflammatory markers with subsequent development of depression [26–28], indicating a bidirectional relationship.
- Treatment with pro-inflammatory agents, such as interferon alpha (IFN-α) for malignant melanoma, induces depressive symptoms in up to 80% of patients [29, 30] and treatment with antidepressants prior to IFN-α treatment results in lower depression scores [31].
- Finally, infusion of cytokines or endotoxins in volunteers is one of the most robust human models of depression [32].

Indeed, inflammation is thought to be one of the operative pathways between depression and increased rates of somatic comorbidity, such as osteoporosis and cardiovascular diseases (CVD) [33, 34]. In addition, recent studies have shown that inflammatory processes may be related to specific depressive symptoms, namely the classical neurovegetative/somatic symptoms such as disturbed sleep, loss of energy and appetite changes [35, 36].

3 Statins and Their Potential Anti-Inflammatory Effects

Statins have been on the market since the 1980s and are used for primary and secondary prevention of CVD [37–39]. Statins inhibit the enzyme HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis in the liver [40]. Guidelines recommend treatment for individuals who do not reach normal lipid levels through diet and lifestyle changes [39, 41], with a number of different statins being available including combination preparations; in 2003 preparations.

In 2003, atorvastatin became the best-selling pharmaceutical in history [42].

Statins have long been thought to mainly elicit their CVD preventive effects via lowering of cholesterol levels, since high cholesterol has been associated with an increased risk of CVD and death [43, 44]. However, recent evidence suggests that the anti-inflammatory properties of statins also play an important role, since the CVD preventive effects of statins appear to be more pronounced in individuals with elevated CRP [45–49]. Indeed, in some trials, CRP seemed to be a better biomarker for CVD prevention than low-density lipoprotein cholesterol (LDL-C) [46, 50, 51].

Studies showing anti-inflammatory properties of statins have pointed to a variety of potential underlying mechanisms such as a decrease in CRP levels [7, 45, 46], inhibition of monocyte expression of pro-inflammatory cytokines [52], antioxidant activities [53] and inhibition of lymphocytes by blocking leukocyte function antigen-1 (LFA-1) [54]. These anti-inflammatory effects have been found to be independent of the lipid-lowering properties [7, 53, 54], suggesting direct anti-inflammatory properties. For a more detailed overview of the anti-inflammatory effects of statins in relation to CVD, see the review by Devaraj and colleagues [55].

4 Safety of Statin Treatment

The vast majority of clinical trials indicate that statins are generally safe drugs [56, 57]. The most well-known side effect is muscle pain, or myopathy, which can be solved by switching to another statin in most cases. The most feared side effect is life-threatening rhabdomyolysis involving muscle breakdown, identified by high serum levels of

myoglobin and creatine kinase, potentially leading to renal failure. However, rhabdomyolysis occurs very rarely and the risk increases with higher dose [57]. Also, a minor increased risk of diabetes mellitus has been suggested [47, 56], which may be most pronounced among patients with other risk factors for diabetes [56]. Finally, statins may lead to a 21% increased rate of haemorrhagic strokes per mmol/L LDL-C reduction [58], but this risk is outweighed by the reduced risk of ischaemic strokes resulting in an overall reduced rate of strokes [58].

The risks associated with statin treatment have been summarized in a recent meta-analysis estimating that treatment of 10,000 patients for 5 years with a standard statin regimen would be expected to cause five cases of myopathy, 50–100 new cases of diabetes and five to ten haemorrhagic strokes [57]. Concerning rhabdomyolysis, approximately two to three new cases occur per 100,000 treated individuals [57]. The favourable benefit–risk ratio of statins is supported by the fact that treatment with statins is associated with a lower mortality than placebo [45–48]. However, a recent study estimated that the actual median postponement of death was only few days [59].

5 Statins in the Treatment of Depression

Several drugs that are primarily used due to their anti-inflammatory effects have shown antidepressant effects as well, including aspirin [10, 60], other non-steroidal anti-inflammatory drugs (NSAIDs; especially celecoxib [5, 61]), minocycline [62], monoclonal antibodies [63], pioglitazone, *N*-acetylcysteine and curcumin [6, 64]. This section will review the studies that investigated whether statins have antidepressant treatment effects, both covering randomized controlled trials (RCTs) and observational studies.

The first RCT on the antidepressant effects of statins was published in 2013 [65], where 68 patients with major depressive disorder were randomized to 6 weeks treatment with fluoxetine (up to 40 mg/day) plus lovastatin (30 mg/day) or fluoxetine plus placebo. The fluoxetine + lovastatin group showed a significantly larger decrease on the Hamilton Depression Rating Scale (HDRS) compared with fluoxetine + placebo (mean decrease 12.8 versus 8.2, $p < 0.001$). Subsequently, Haghighi and colleagues showed that citalopram (40 mg/day) plus atorvastatin (20 mg/day; $n = 30$) was associated with greater HDRS response compared with citalopram + placebo ($n = 30$) after 12 weeks (mean decrease 13.7 versus 9.3, $p < 0.001$) [66]. Gougol and colleagues compared 22 individuals randomized to fluoxetine (20 mg/day rising to 40 mg/day) plus simvastatin (20 mg/day) with 22 individuals on fluoxetine + placebo over 6 weeks [67]. Individuals on fluoxetine + simvastatin improved significantly more (mean HDRS decrease 18.5 versus 13.7, $p = 0.02$). A recent meta-analysis pooled the above-mentioned trials and found that the combination of a selective serotonin reuptake inhibitor (SSRI) and a statin was associated with significantly higher reductions in HDRS scores compared with SSRIs and placebo [standard mean difference (SMD) of −0.73; 95% CI −1.04 to −0.42; $p < 0.001$), indicative of a clinically relevant effect without heterogeneity between studies ($I^2 = 0\%$; $p = 0.99$) [14]. However, the authors emphasized that the trials were small and of a pilot nature and all were conducted in Iran, limiting generalizability [14]. Larger and more definitive trials are needed.

In terms of head-to-head comparisons of statins, a study among 46 individuals who had undergone a coronary artery bypass graft and had mild to moderate depression found that those randomized to simvastatin (20 mg/day) for 6 weeks showed greater improvement in depression scores than those randomized to atorvastatin (20 mg/day) [68].

Furthermore, two large RCTs are ongoing. First, Kim et al. included 446 individuals with acute coronary syndrome (ACS) and comorbid depressive disorder and followed them for 1 year [69]. The initial findings suggest that treatment with escitalopram and a statin showed higher response compared with individuals on escitalopram only [69]. Secondly, the Youth Depression Alleviation–Augmentation with an anti-inflammatory agent (YoDA-A) study compares treatment with rosuvastatin (10 mg/day) or aspirin (100 mg/day) with placebo, in addition to treatment as usual [70]. Participants are aged 15–25 years, have moderate to severe depression and will be treated for 12 weeks.

Epidemiological data support the association of a reduced risk for depression in individuals treated with an SSRI and a statin compared with those treated with a SSRI alone [10, 11]. This is despite the fact that statin prescription is associated with cardiovascular comorbidity and known risk factors for depression [71]. In a recent study of 872,216 SSRI users, among whom 113,108 (13.0%) used statins concomitantly [11], combined treatment with an SSRI and a statin was associated with a 36% decreased risk for hospitalization with depression (hazard rate ratio of 0.64; 95% CI 0.55–0.75) compared with treatment with an SSRI only.

In addition to the potential add-on effects, studies have investigated whether statins alone have a primary preventive effect against the development of depression—with somewhat mixed findings. A meta-analysis from 2014 included seven observational studies and found that statin users were 32% less likely to develop depression compared with non-users [9]. Furthermore, a Swedish study found that statin use was associated with a 5% decreased risk of a

subsequent depression diagnosis [72]. In addition, studies have indicated that statin use was associated with lower risk of depression among individuals with hyperlipidemia [73] and after stroke [74]. Moreover, a meta-analysis from 2012 found in sub-analyses that statins were associated with improvement in mood scores [75]. Finally, some data suggest that statins might be protective against cognitive decline and dementia, although these data are mixed [76–78]. However, observational studies are limited by a substantial risk for confounding by indication, which might bias against statins, and healthy user bias, which might bias in favour of statins. It has therefore been argued that larger high-quality observational studies are needed to confirm the above-mentioned findings [9]. Indeed, an epidemiological study using propensity score matching to reduce the extent of confounding did not find an association between statin use and a lower risk of mental disorders [79]. This is consistent with preliminary findings from a large ongoing propensity score matched study from our group (unpublished personal data). Other studies have indicated that statin use may be associated with cognitive decline and an increase in depressive symptoms among individuals aged ≥65 years [80] and that long-term statin treatment might actually result in depressive symptoms and depression [81]. The authors have argued that an inverse association may exist between LDL-C and depressive symptoms [81]; that is, there may be a higher risk for depressive symptoms when LDL-C levels become too low. A similar association has also earlier been suggested for suicidal ideation [82], although recent reports do not support this contention [83]. Finally, the evidence from case reports regarding the possible associations between statin use and a wide variety of neuropsychiatric adverse events indicates that these events are rare and most likely in patients with other risk factors [84].

In conclusion, pilot-level RCTs have indicated that statins as add-on to SSRIs have antidepressant effects over 6–12 weeks, supported by a recent observational study. This approach is supported by the fact that there are no clear contraindications for the combination of antidepressants and statins [85]. The primary preventive effect of statins in relation to depression has mainly been addressed in observational studies, with mixed findings.

6 Potential Mechanisms Underlying the Antidepressant Effect of Statins

Several mechanisms may explain the potential antidepressant effects of statins. First, individuals with depression have higher levels of pro-inflammatory markers, such as CRP [3, 18], and statins lower CRP levels independent of their cholesterol-lowering effects [45–48]. Also, the antioxidant activities [53] of statins may contribute to this via suppression of distinct oxidative pathways which are implicated in atherogenesis and inflammation [53].

Second, and in extension of the above, statins have been found to decrease the activity of the enzyme indoleamine-2,3 dioxygenase (IDO) [12]. Inflammation leads to increased IDO levels and hence a greater conversion of tryptophan to neurotoxic compounds. The inhibiting properties of statins on IDO could thus result in higher tryptophan and serotonin levels, which may have antidepressant effects in accordance with the monoamine hypothesis.

Third, since the main effect of statins is a reduction of vascular plaques, it has been proposed that lipid-lowering treatment improves cerebral perfusion and oxygenation, thereby resulting in a lower risk for depression [86]. This vascular effect is likely to be more germane to elderly persons.

Fourth, the lower risk for CVD events due to statin treatment may result in a better quality of life and thus a lower risk of depression [87]. However, only few clinical trials on statins have systematically assessed quality of life and could not show any significant differences between individuals on statins versus placebo, hence this hypothesis is not currently supported by data.

As outlined above, the mechanisms underlying potential antidepressant effects of statins remain unclear. Therefore, future translational studies should aim to elucidate this aspect. A better understanding of the causal mechanism(s) would also allow for more targeted treatment.

7 Which Patient and Which Statin? Towards Personalized Treatment

The clinical trials have not investigated whether specific subgroups of patients with depression may be more likely to benefit from statin treatment, primarily due to small sample sizes. Trials on other anti-inflammatory drugs have indicated that depressed individuals with higher CRP [63] or IL-6 [61] may benefit more from adjunctive anti-inflammatory treatment. Furthermore, studies have indicated that inflammatory processes result in greater severity of neurovegetative depressive symptoms, such as energy, sleep and appetite [35, 36]. Thus, depressed patients with elevated inflammatory markers and/or marked neurovegetative symptoms could benefit from drugs with anti-inflammatory properties (such as statins). Furthermore, in individuals with depression, increased inflammatory markers and neurovegetative symptoms, combining statins with the tricyclic antidepressant nortriptyline should also be tested since a recent study reported that nortriptyline had more pronounced antidepressant effects than escitalopram among individuals with CRP ≥1 mg/L [88].

Another option for targeted treatment concerns the presence/absence of risk factors for CVD or CVD itself. Since there is a high comorbidity between CVD and depression, individuals with depression and comorbid CVD (or vice versa) may receive additional antidepressant benefits with statins. Because people with mental disorders are at far greater risk for CVD, some authors have argued that the Framingham criteria need to be amended to reflect this risk [89]. At the very least, clinicians managing people with mental disorders should consider initiating or referring patients for preventive therapy with statins if high CVD risk is evident. Indeed, clinical data on 446 individuals with acute coronary syndrome and comorbid depression indicate that individuals treated with escitalopram and a statin had better a antidepressant treatment response compared with escitalopram only [69].

Finally, some statins may theoretically have more potent antidepressant effects, since substantial differences exist between specific statins. Some evidence has pointed towards differences in blood-brain barrier (BBB) permeability, with simvastatin crossing the BBB more easily than other statins due to its greater lipophilic properties [90]. It is also possible that the mechanism of action of statins is via reduction of peripheral levels of cytokines. Concordant with this, higher CRP levels may predict better treatment effects from adjunctive anti-inflammatory agents [63], and rosuvastatin has been shown to decrease CRP levels [47]. However, clinical trials have found antidepressant treatment effects for lovastatin [65], atorvastatin [66] and simvastatin [67], pointing towards a class effect, whereas rosuvastatin has not been investigated regarding potential antidepressant add-on effects. On the other hand, different effects based on BBB permeability are supported by a head-to-head comparison trial finding that simvastatin had a higher antidepressant effect than atorvastatin [68]. Hence, it would be worth investigating whether high BBB permeability, for instance during inflammation, or a high CRP level is associated with better antidepressant treatment effects of specific statins.

Particular hope is currently on genetic markers to supplement clinical measures to improve diagnostics, prevention and treatment of mental disorders [91]. The pharmacogenetics of statins have been mainly investigated with regard to pharmacokinetics, thus affecting metabolism and dosage, statin efficacy regarding LDL-C and CVD reduction, and toxicity (e.g. statin-induced myopathy) [92, 93]. A genetic test has been recently launched based on testing the gene variants of *SLCO1B1* [93], influencing statin transport into liver cells, which has been associated with an increased risk of myopathy. Genetic statin response prediction regarding LDL-C and CVD risk reduction has not yet been established [93]. A recent study in individuals aged >60 years treated for >5 years with statins found that a weighted genetic risk score based on four single nucleotide polymorphisms (SNPs) was associated with lower LDL-C plasma levels of 14–28% [94]. However, another study found only a small and clinically not relevant effect size of <2% for decreased LDL-C lowering for an unweighted genetic risk score based on three SNPs, two of them different from those included in the previous score, in younger study populations using statins [95]. In another study investigating whether genetic variants affecting LDL-C levels may affect statins' anti-inflammatory effect, Chu and colleagues found that the genes *ABCG2*, *LPA* and *APOE* associated with LDL-C reduction were not associated with CRP reduction by rosuvastatin [96]. This indicates that pathways mediating the anti-inflammatory and lipid-lowering properties of statins differ, concordant with the notion that reduction in cholesterol is not thought to be the pathway to antidepressant effects. The study, however, identified genes specific for the CRP reduction associated with rosuvastatin (i.e. *CRP* and *PTPN2*). Thus, currently no genetic information beyond statin-induced myopathy is available for clinical implementation and guidance in CVD. While the findings of the genetic impacts on statin-induced myopathy and CRP reduction may inform statin use in depression, further pharmacogenetic studies of statins in relation to treatment of depression are required.

8 Conclusion

Several studies have shown that statins have anti-inflammatory properties independent of their lipid-lowering effects. These anti-inflammatory effects may represent the basis for the potential antidepressant properties of statins. The most consistent finding from RCTs and observational data is that statins have antidepressant effects when used as add-on to SSRIs. Their potential in primary prevention of depression is less clear and should be subjected to further study.

As the initial results are promising (and since statins are generally well tolerated), the antidepressant effect of statins should be investigated by definitive RCTs with larger study populations and longer follow-up. These trials should focus on identification of potential subgroups of patients with depression that may be particularly likely to benefit from statin treatment. For example, it should be clarified whether inflammatory markers, genetic profiles, specific depressive symptomatology or somatic/CVD comorbidity predict treatment response. This would pave the way for personalized use of statins in the treatment of depression. In addition, it should be investigated whether long-term statin treatment, i.e. over several years, can prevent development of depression, for instance among individuals with a family history of CVD and/or depression.

Compliance with ethical standards

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