Statin adverse effects: study suggests people are more likely to experience muscle aches and pains if they are expecting them

Rates of adverse effects of atorvastatin were recorded in the double-blind and open label phases of a large randomised controlled trial (RCT) conducted in the UK, Ireland and the Nordic countries. During the double-blind phase, the annual rate of muscle-related problems was similar in the atorvastatin and placebo groups and the difference was not statistically significant. By contrast, in the open-label phase, the annual rate of muscle-related problems was 40% higher among atorvastatin-users than non-users, although lower overall. This suggests that a ‘nocebo’ effect (the reverse of a placebo effect) was at work; that is, people were more likely to experience these muscle-related problems if they were expecting them. Careful explanation to patients of possible side effects, in a balanced way that does not negatively frame the information, is essential. Decision aids, such as the ones produced by NICE, can help people come to informed decisions about the pros and cons of treatment.

Overview and current advice

The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends that people should be offered treatment with a statin (usually atorvastatin) for primary or secondary prevention of cardiovascular disease. However, statins have gained a reputation for causing adverse effects, especially muscle and joint pains. This is supported by observational studies and clinical experience but is in contrast to data from randomised controlled trials (RCTs), which found that statins are generally well tolerated by most people who take them.

The appraisal committee for the NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia considered the prevalence of statin intolerance. It was informed that there are no clear diagnostic criteria for statin intolerance and that although up to approximately 23% of people with primary hypercholesterolemia are currently reported to be intolerant to statins, the true rate was likely to be between 0.5% and 3.0% of the population. A large observational study, which was discussed in a NICE medicines evidence commentary on statins: many people who stop treatment due to side effects may be able to restart treatment, suggested that many people who have discontinued statins because of an adverse event, especially muscle pain, may be able to restart the same or a different statin.

The GAUSS-3 study, which compared evolocumab with ezetimibe in people with muscle symptoms confirmed by statin re-challenge, illustrated the difficulties of identifying people with true statin
intolerance. This 2-stage RCT recruited 511 adults with uncontrolled LDL-C who had a history of intolerance to 2 or more statins. In a double-blind crossover phase less than half (43%) of participants with previous statin intolerance experienced muscle-related adverse effects with atorvastatin 20 mg but not with placebo; more than a quarter (27%) of participants experienced them with placebo but not with atorvastatin.

**New evidence**

An analysis of the double-blind and open-label phases of atorvastatin therapy in the Anglo-Scandinavian cardiac outcomes trial (ASCOT) has explored the issue of statin-related adverse effects. The ASCOT study ran from 1998 and recruited men and women from the UK, Ireland and the Nordic countries aged between 40 and 79 years who had 3 or more risk factors for cardiovascular disease but no history of myocardial infarction or currently treated angina. Participants were randomised to compare an amlodipine-based or atenolol-based blood-pressure-lowering regimen (the blood-pressure-lowering arm, ASCOT-BPLA). Participants in ASCOT-BPLA were also eligible for inclusion in the lipid-lowering arm of ASCOT (ASCOT-LLA) if they had a total cholesterol level 6.5 mmol/l or less and were not taking a statin or a fibrate. They were randomised to receive atorvastatin 10 mg daily or placebo; there was no run-in period or test for statin tolerability and (common for the late 1990s) few, if any participants had had previous exposure to statins. Participants were randomised in a 2x2 factorial design to one of the 4 possible combinations of atenolol-based or amlodipine-based blood pressure regimen, atorvastatin or placebo. ASCOT-BPLA was open-label but ASCOT-LLA was double-blind.

In late 2002 ASCOT-LLA was stopped because efficacy of atorvastatin had been shown, but ASCOT-BPLA continued until June 2005. Blinding of allocated ASCOT-LLA treatment was broken in 2002 and participants were offered open-label atorvastatin until the end of ASCOT-BPLA.

Of the 99.4% of participants in ASCOT-LLA for whom a verifiable date for the end of the blinded period was available, 5,101 received atorvastatin 10 mg daily and 5,079 received placebo during the double-blind phase. After excluding participants who had died (n=268) or were lost to follow-up (n=13), 9,899 people entered the open-label phase. About a third (32%) of people randomised to atorvastatin elected to discontinue it once blinding was broken, and 62% of people previously randomised to placebo elected to start taking atorvastatin. Thus, 6,409 participants took atorvastatin in the open-label phase and 3,490 did not. People who had reported muscle-related adverse effects during the double-blind phase were less likely to use a statin in the open-label phase.

People exposed to atorvastatin and placebo in the double-blind phase were similar in terms of male to female ratios, age (≤60 years or >60 years), white ethnicity, being a current smoker, alcohol consumption, body mass index (BMI) and other characteristics. This was also generally the case in the open-label phase, although in this phase atorvastatin users were less likely to be female or non-smokers than non-users, and more likely to have diabetes at baseline. People who had reported muscle-related adverse effects during the double-blind phase were also less likely to take atorvastatin in the open-label phase.

Follow-up was at 6 weeks and 3 months after randomisation, and then every 6 months until the closure of ASCOT-BPLA. All adverse effects reported by participants at these follow-up visits were recorded. Median follow-up in the double-blind phase was 3.3 years and in the open-label phase it was 2.3 years. In the analysis reported here, all adverse effects were adjudicated by observers blind to treatment, trial phase, baseline characteristics or non-study statin use, looking for reports of muscle-related adverse effects, erectile dysfunction, sleep disturbance or cognitive impairment.

During the double-blind phase, the annual rate of muscle-related adverse effects was similar and not statistically significantly different in the atorvastatin and placebo groups: 2.03% and 2.00%,
respectively (hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.88 to 1.21, \( p=0.72 \)). This was also the case for erectile dysfunction (1.86% compared with 2.14%; HR 0.88, 95% CI 0.75 to 1.04, \( p=0.13 \)) and cognitive impairment (0.20% compared with 0.22%; HR 0.94, 95% CI 0.57 to 1.54, \( p=0.81 \)), although that was reported rarely. Sleep disturbance was reported statistically significantly less often among atorvastatin-users than participants randomised to placebo (1.00% compared with 1.46%, respectively; HR 0.69, 95% CI 0.56 to 0.85, \( p=0.0005 \)).

By contrast, in the open-label phase, the annual rate of muscle-related adverse effects was statistically significantly higher among atorvastatin users than non-users, although in both groups the rate was lower than during the double-blind phase: 1.26% compared with 1.00%; HR 1.41, 95% CI 1.10 to 1.79, \( p=0.006 \). Rates of erectile dysfunction (0.68% compared with 0.80%, \( p=0.44 \)) and sleep disturbance (0.56% compared with 0.66%) were also lower than in the double-blind phase, and there was no longer a statistically significant difference between groups for sleep disturbance (HR 0.87, 95% CI 0.63 to 1.20, \( p=0.40 \)). Rates of cognitive impairment were broadly similar to the double-blind phase and again reported rarely (0.17% compared with 0.29%, \( p=0.06 \)).

**Commentary**

**Commentary provided by NICE**

This study adds useful information to the evidence around statin tolerability. RCT data have consistently shown statins to be generally well tolerated by most people who take them, but observational studies and clinical experience have consistently found much higher rates of adverse effects among statin users, especially muscle and joint pains. How can this be? Statin studies have sometimes been justifiably criticised for having run-in periods, which led to people who could not tolerate the study drug being de-selected. This analysis is therefore interesting in several ways: the double-blind phase had no run-in period or test for statin tolerability and few, if any, participants had had previous exposure to statins, so in that respect it was in a population reasonably representative of people starting statins in usual care. (It should be noted, though, that the population was predominantly male, of white ethnicity and aged over 60 years.) People who had reported muscle-related adverse effects during the double-blind phase were less likely to use a statin in the open-label phase, and about a third of people randomised to atorvastatin elected to discontinue it once blinding was broken. It is not reported how many of those had experienced muscle-related problems, but together this suggests that if there was a bias in statin tolerability in the open-label phase, it was towards ‘statin-tolerant’ people taking atorvastatin. The difference in comparative rates of muscle-related adverse effects (but not other, less well publicised, adverse effects) is therefore all the more striking.

In a 2014 article about statin benefits and risks, the MHRA noted that data from clinical practice can help identify side effects occurring when drugs are used in usual care rather than the more constrained circumstances of clinical trials. However, clinical practice data are subject to other limitations, including the stimulated reporting of side effects for example due to media interest and possible contribution of concomitant medications, the underlying disease, and patient characteristics and lifestyle. Reports of statin-associated muscle problems might result from patients’ perceptions about statins in light of negative press reports of statin use or even poor understanding of warnings about statin-associated side effects. The term ‘nocebo’ (‘I shall harm’) was coined by Kennedy in 1961 to denote the counterpart to the use of placebo (‘I shall please’). An [NHS Choices article](https://www.nhs.uk/conditions/statins/statin-dosing-and-takes/statin-benefits-and-risks/) quotes Ben Goldacre’s example of the nocebo effect: ‘If you want to see the nocebo effect in action, when sitting on a sofa with friends suddenly ask: “does this thing have fleas in it?”’.

It is important to be clear that muscle-related problems in statin users are not deliberately ‘made up’, to be dismissed as imaginary, any more than are the benefits from the placebo response. Although a very reductionist view of human physiology and patient experience would fail to appreciate these more complex, emergent dimensions, they are important in understanding the patient’s experience of statin
side effects – just as the experience of acute and chronic pain is more than arises from basic pathophysiology. In addition, all human beings seek explanations for experiences, and ‘search satisficing’ describes the common tendency to latch on to the most psychologically accessible and obvious explanation, even if this is not the correct or only one. Thus muscle aches and pains actually arising from another cause might be falsely attributed to statin therapy, and perhaps noticed more than they otherwise would be. This might also explain why the rate of muscle-related adverse effects among non-users in the open-label phase was lower than in the double-blind phase: people knew they were not taking a statin and so were less on the look-out for adverse effects they associated with these drugs.

Careful explanation of possible side effects, in a balanced way that does not negatively frame the information, is essential. Decision aids, such as the ones produced by NICE, can help people come to informed decisions about the pros and cons of treatment.

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**References**


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