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New insights into managing symptoms during statin therapy

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ABSTRACT

Symptoms during statin therapy are common and often attributed to statin intolerance. Recent data suggest few patients are truly intolerant to statins. Muscle symptoms are similar in statin and control groups in blinded treatment periods of clinical trials. The "nocebo" effect may occur during open-label statin treatment, when previously asymptomatic study participants report symptoms attributed to statin therapy, or during placebo-controlled trials. Most patients reporting statin intolerance can tolerate blinded moderate intensity statin therapy. In clinical practice the large majority of patients are willing to retry a statin, and of those who do, >80–90% successfully remain on statin therapy long-term. Emerging evidence from brain imaging studies and contemporary approaches to pain management suggests that building trust and managing patient expectations can minimize the "nocebo" effect in statin-treated patients.

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Symptoms during statin therapy are commonly reported by patients and are often attributed to intolerance to statins. This often leads to discontinuation or down-titration of statins, resulting in increases in cardiovascular events and mortality.[1–3] In an effort to improve adherence to statins, several expert panels have issued statements on the assessment, management. and etiology of statin-associated muscle symptoms.[4–6]

The large body of evidence reviewed in these statements and summarized below shows that few patients are truly intolerant to statins. Emerging evidence from brain imaging studies and contemporary approaches to pain management suggests that managing patient expectations can minimize the "nocebo" effect in statin-treated patients.

Symptoms during statin therapy

Statin-associated muscle symptoms, with no or little elevation in creatine kinase (CK) have a prevalence of 7–29% in observational studies and registries.[3,7–9] Blinded, controlled trials provide more objective evidence of rates of statin adverse effects. Although rare serious muscle adverse effects occur, mild-moderate muscle symptoms and CK elevations are similar in statin and control groups in clinical trials.[10,11] In the Cholesterol Treatment Trialists individual meta-analysis of 26 cardiovascular outcomes trials with >170,000 participants, serious myopathy or rhabdomyolysis were observed at a rate of 1 per 10,000 patients per year treated with low, moderate or high intensity statins.[12] Rates of adverse muscle and other musculoskeletal adverse effects were similar

Abbreviations: ASCOT, Anglo-Scandinavian Outcomes Trial – Lipid-Lowering Arm; ASCVD, atherosclerotic cardiovascular disease; CK, creatinine kinase; LDL-C, low-density lipoprotein cholesterol; PCSK9 mAbs, proprotein convertase subtilisin/kexin type 9 inhibiting monoclonal antibodies.

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in the statin and placebo or control groups, and in moderate compared to high intensity statins. These trials include the earliest statin trials, where few if any participants had previously been exposed to statins and so could not be excluded on the basis of previous statin intolerance. Although patients with serious comorbidities were excluded from most trials,[13] 4 trials did include patients with serious comorbidities. Of note, similar rates of musculoskeletal adverse effects occurred in the statin and placebo groups in 2 trials performed in patients with New York Heart Association Class 2 through 4 heart failure, and in 2 trials performed in patients receiving maintenance hemodialysis.

Nocebo effect in trials

The placebo effect is a beneficial effect on health resulting from positive expectations for a treatment. Conversely, the nocebo effect is a harmful effect on health resulting from negative expectations for a treatment. Clear demonstrations of the nocebo (and placebo) effects of statin therapy come from 3 randomized trials, ASCOT, ODYSSEY ALTERNATIVE and GAUSS-3. During the double-blind, placebo controlled treatment period of a primary prevention statin trial, ASCOT, similar rates of muscle symptoms were observed with atorvastatin 10 mg and placebo groups.[14] During the un-blinded follow-up, all patients were offered open-label atorvastatin 10 mg. Those receiving open-label atorvastatin 10 mg reported 40% more muscle symptoms definitely or probably related to the atorvastatin, compared to those who were not taking atorvastatin, a demonstration of the nocebo effect (Fig. 1).

Two randomized trials evaluating PCSK9 mAbs in patients reporting intolerance to 2 or more statins used blinded atorvastatin 20 mg therapy. In the ODYSSEY ALTERNATIVE trial, during the placebo lead-in phase, 8% of subjects discontinued placebo due to intolerable muscle symptoms (Fig. 2).[15] Asymptomatic subjects were then randomized to the PCSK9 mAb alirocumab, ezetimibe, or atorvastatin 20 mg. Notably, similar rates of discontinuation due to intolerable symptoms (about 20%) were observed in the blinded ezetimibe and atorvastatin 20 mg groups. All patients, regardless of symptomatology, were then enrolled in an open-label extension where all received alirocumab. Interestingly, only 2% reported muscle symptoms, compared to the 16% who reported intolerable muscle symptoms from blinded alirocumab therapy.

The GAUSS 3 trial had a cross-over design with 2 double-blind treatment periods. In phase A, statin intolerant subjects were randomized to blinded atorvastatin 20 mg or placebo for 24 weeks, then crossed over to the opposite treatment for another 24 weeks.[16] In phase B, after a 2-week wash-out, subjects were randomized to a PCSK9 mAb, evolocumab, or ezetimibe. In phase A1, 60% of placebo-treated subjects reported intolerable muscle symptoms and discontinued treatment, compared to about 68% of the atorvastatin-treated subjects. In phase A2, 35% of those now receiving placebo discontinued treatment due to symptoms, compared to about 52% receiving atorvastatin 20 mg. These results demonstrate the nocebo effect in the placebo groups, and suggest that about 20% of atorvastatin-treated patients were truly statin intolerant. For completeness, in phase B in the GAUSS 3 trial, 29% of subjects receiving ezetimibe discontinued treatment due to symptoms, compared to 21% of the evolocumab treated subjects. *Based on the results from the 2 PCSK9 mAb trials, an important point can be made to patients reporting symptoms during statin therapy: about 80% or 4 out 5 patients who have reported symptoms in the past can successfully tolerate a moderate intensity statin.*

Observational data on statin rechallenge

The large majority of patients reporting symptoms during statin therapy can tolerate the re-initiation of moderate or high statin therapy.[17] In a retrospective analysis of a large healthcare system, statin discontinuation with documented symptoms occurred in 17% of patients.[3] More than half were rechallenged, with 92% still taking a statin 12 months later, 84% at the initial or higher dose. Similar rates have been found in other studies. In Medicare beneficiaries, 85% of patients remain on the statin prescribed at discharge following a myocardial infarction.[18] In the 6 months after discharge, 15% discontinued the statin. Of these, 54% reinitiated statins, and 66% reinitiated the same statin and intensity. *Re*-initiation of moderate intensity statins was about 20% more successful than when high-intensity statins were reinitiated. Down-titration and reinitiating a different versus the same statin modestly increased the probability of statin persistence. Taken together with the data from the blinded randomized trials, this evidence suggests there is no physiologic basis in the muscle for the large majority of patients reporting muscle symptoms during statin therapy. Nevertheless, nocebo hyperalgesia is perceived as real pain. Misattribution of this perceived pain that results in discontinuation or reduction in statin intensity translates into a loss of statin's cardio-protective and mortality benefits (Fig. 3).

Physiologic basis for nocebo effect

Emerging evidence suggests there is a physiologic basis in the brain for the perception of muscle pain during statin therapy. A recent trial used functional magnetic resonance scanning to localize a putative nocebo pathway in the brain (Fig. 4).[19] In this double-blind trial, 49 subjects were randomized to a “cheap” topical creme or an “expensive” topical creme to be applied to the forearm to determine acceptability as a treatment for atopic dermatitis (Fig. 4A). The cheap, expensive and placebo cremes were identical inert substances. During the training phase,

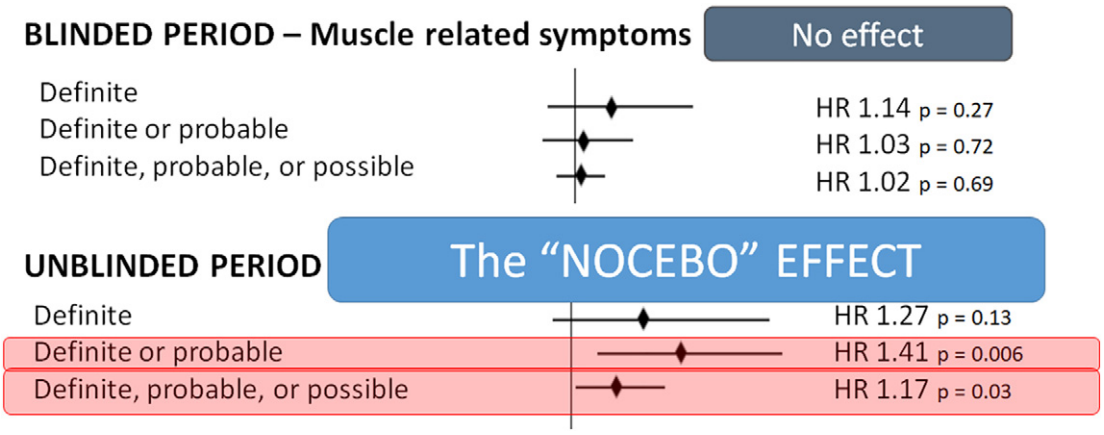

Fig. 1. Muscle symptoms from atorvastatin 10 mg during the ASCOT trial randomized, double-blind, placebo-controlled treatment period and the unblinded follow-up period when patients were offered open-label atorvastatin 10 mg.
(Adapted from Gupta A, et al. Lancet 2017; 389: 2473–2481)

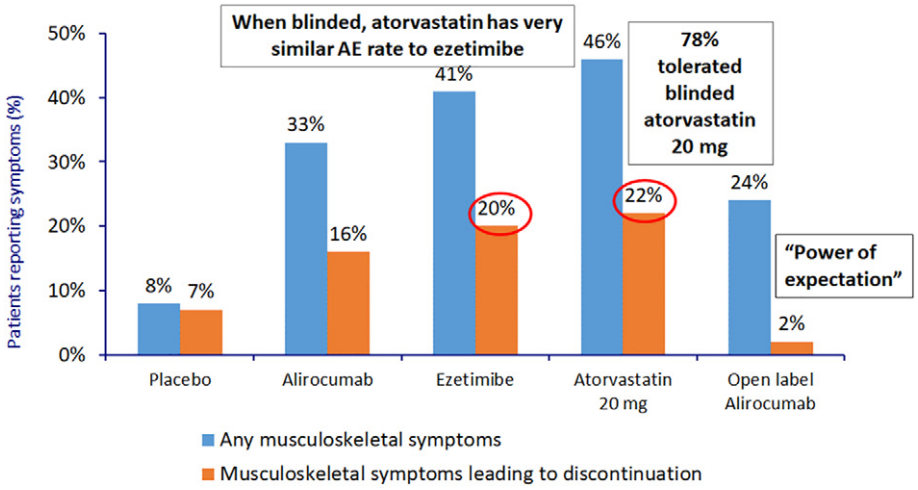

Fig. 2. Placebo and nocebo effects in statin intolerant patients (symptoms on 2 or more statins) during ODYSSEY ALTERNATIVE trial. (Adapted from Moriarty PM, et al. J Clin Lipidol 2015;9:758–769)

negative treatment expectations were induced using placebo cream by increasing the temperature of a skin patch applied to the left forearm. During the randomized treatment phase the temperature was not increased. More pain was perceived in those receiving the expensive cream (Fig. 4B). This represents a phenomenon where there was an expectation that higher price meant greater potency, and therefore more potential for adverse effects such as heat or pain. Functional MRI identified numerous central nervous system pathways that were activated during the perceived painful stimuli. Two areas in the prefrontal cortex facilitated expectation-induced pain modulation, e.g. nocebo hyperalgesia (Fig. 4C). This nocebo pathway appear to be separate from the placebo pathways for pain alleviation, which involve an opioidergic mechanism and recruit the descending pain modulatory system targeting the spinal cord dorsal horn.[19,20]

Psyching up patients for rechallenge

Discontinuing the statin until symptoms resolve, then rechallenging with the statin therapy is critical for long-term atherosclerotic cardiovascular disease (ASCVD) risk reduction (Fig. 3). In community practice, over 70% of patients that have discontinued statin therapy due to symptoms are willing to retry statin therapy.[9]

An approach to managing symptoms perceived statin intolerance can be derived from the evidence-based approaches to pain management used in other diseases and may have applicability to management of symptoms during statin therapy (Table 1).[21–25] Keys to this approach are developing a trust relationship and managing expectations.

First, develop the *trust relationship* between clinician and patient. Former statin users are less likely to trust their physician than current statin users.[9] Trust relationships with their physicians are an even greater issue for African American patients.[26] Concrete steps to increase trust include:

- *Talking with the patient*, rather than at them. Trust is enhanced when patients feel they are being listened to respectfully
- *Making frequent eye contact* while they are speaking and you are talking, an increasing challenge in the electronic medical record era.
- *Listening without interrupting* while the patient tells their symptom story. In a study of US family practitioners, the physician interrupted the patient within 11 s on average.[21]
- *Eliciting patient values* is a key component of shared decision-making. Patients have a range of values regarding the importance of prevention in their lives, and concerns regarding safety and impairment of function may weigh more heavily with advancing age. Initial preferences may change after deliberating new information, with informed preferences influencing the decisions made during the shared decision-making process.

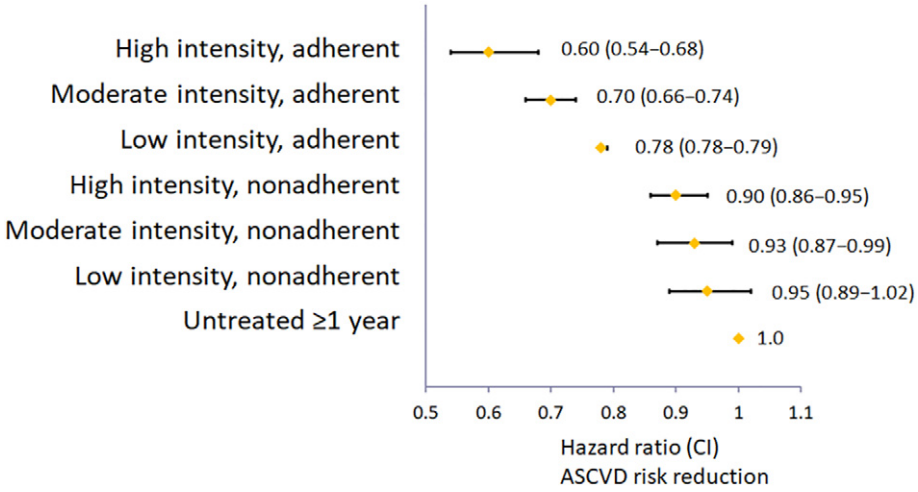

Fig. 3. Statin adherence and intensity are key to long-term ASCVD risk reduction. (Adapted from Khunti K, et al. *JAMA Network Open.* 2018;1(8):e185554)

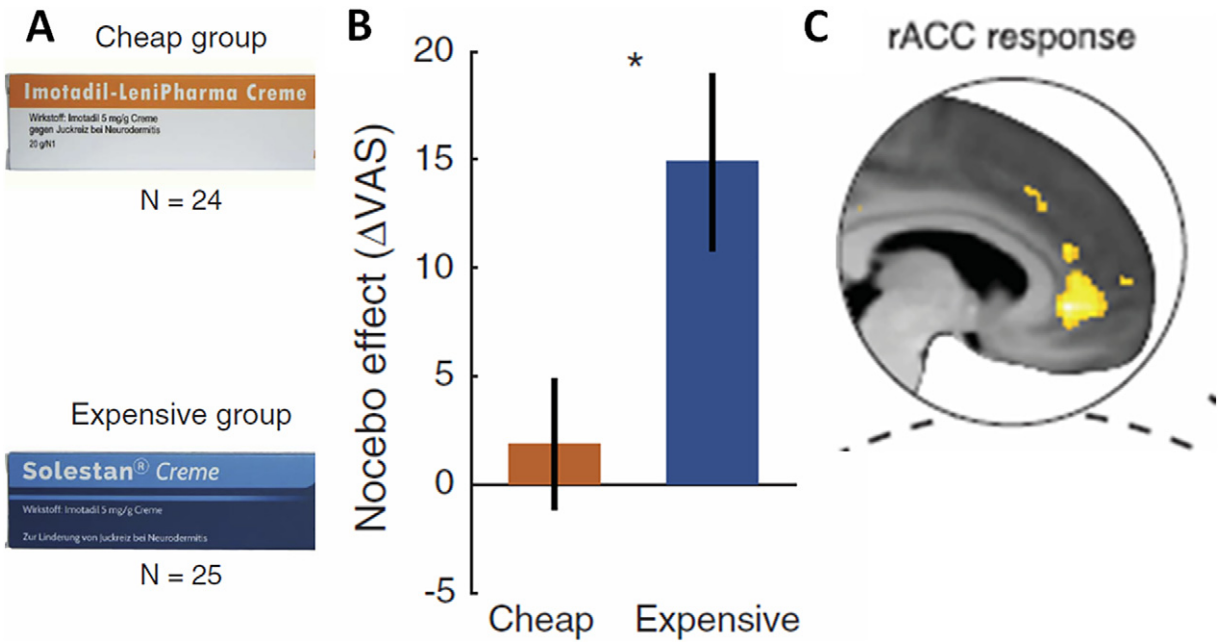

Fig. 4. Putative brain pathway for nocebo effect. (A) Subjects were randomized to "cheap" or "expensive" creams; both were the same inert cremes. (B) where expectations for "expensive" cream resulted in more perceived "nocebo" pain (C) Functional magnetic resonance imaging revealed increased activity in the prefrontal cortex mediated the effect of value on nocebo hyperalgesia.
(Adapted from Tinnerman A, et al. Science, 2017. 358(6359): p. 105–108)

- *Offer choices* regarding reinitiating the statin at the same dose, perhaps at a less frequent interval (every other day, etc.) or a lower dose or another statin. The large majority of patients can successfully return to daily moderate or high intensity statin therapy.

Second, *Manage Expectations*:

- *Engage other brain regions* to prevent/control pain perception. Compared to current statin users, former statin users are more likely to think statins are less effective or unsafe but they are also more worried about their ASCVD risk, supporting the need to inform patients of the extensive data on statin ASCVD risk reduction and safety.[9] Studies also show that over 80–90% of patients successfully rechallenge with a moderate or high intensity statin.
- *Talk about function, not feeling*. Teach patients to avoid pain catastrophizing: Are they still able to do what they want or need to do?

Table 1
Evidence-based approach to managing mild-moderate symptoms during statin therapy and combatting the nocebo effect.

1. Build trust relationship	Talk with patients (not at them) Make eye contact Listen to patient's symptom story without interrupting Elicit patient values regarding prevention and safety Offer choices
2. Manage expectations	Engage other brain regions to control pain - Statins save lives, prevent heart attacks & strokes - Statins very safe in controlled clinical trials >80–90% can successfully resume statin therapy Talk about function not feeling - Avoid pain catastrophizing - Focus on functioning to do what need/want to do
3. Hold statin until symptoms resolve	Evaluate for other causes if symptoms persist >2 months off statin
4. Rechallenge with statin	Same or lower dose/intensity statin, longer dosing interval; plan up-titration as tolerated
5. If symptoms recur, repeat 1–4	

Third, *hold statin therapy* until symptoms resolve. Symptoms persisting >2 months after discontinuing the statin should be evaluated for other causes (hypothyroidism, rheumatologic disease, etc.).[11]

Fourth, once symptoms resolve, *rechallenge* with the statin regimen decided upon during the shared decision-making process. Up-titrate the statin to the guideline recommended intensity as tolerated.

Fifth, if symptoms recur during rechallenge, repeat steps 1–4 until some dose/interval of statin can be tolerated. Most daily doses of statin reduce low-density lipoprotein cholesterol (LDL-C) more than ezetimibe, which lowers LDL-C by about 15% as monotherapy and about 20–25% added to background statin therapy.[11,27,28] Rosuvastatin 5–10 mg twice a week lowers LDL-C by 25% on average.[29]

Conclusions

Statins have a remarkable record of benefit and safety. Although symptoms are common during statin therapy, most patients are not truly statin-intolerant. The statin nocebo effect has been well-documented in randomized, blinded, placebo-and active controlled trials. Most patients reporting statin intolerance can successfully reinitiate statin therapy. Emerging evidence is revealing brain pathways for nocebo hyperalgesia. The nocebo response can be modified by evidence-based approach that increases trust in the shared decision-making relationship and harnesses other brain pathways shown to ameliorate pain responses.

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