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The nocebo effect in the context of statin intolerance

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Abstract: The nocebo effect, the inverse of the placebo effect, is a well-established phenomenon that is under-appreciated in cardiovascular medicine. It refers to adverse events, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention or a nonmedical situation. These expectations can be driven by many factors including the informed consent form in a clinical trial, warnings about adverse effects communicated by clinicians when prescribing a drug, and information in the media about the dangers of certain treatments. The nocebo effect is the best explanation for the high rate of muscle and other symptoms attributed to statins in observational studies and clinical practice, but not in randomized controlled trials, where muscle symptoms, and rates of discontinuation due to any adverse event, are generally similar in the statin and placebo groups. Statin-intolerant patients usually tolerate statins under double-blind conditions, indicating that the intolerance has little if any pharmacological basis. Known techniques for minimizing the nocebo effect can be applied to the prevention and management of statin intolerance.
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Characteristics of the nocebo effect

In 1985, Cairns et al[1] found that aspirin 325 mg qid significantly reduced total and cardiac mortality in a randomized placebo-controlled trial in patients with unstable angina, whereas the uricosuric agent sulfinpyrazone was ineffective. The investigators subsequently noted[2] that the frequency of minor gastrointestinal (GI) adverse events (AEs) in the study population (all patients regardless of treatment allocation) was much greater in 2 centers they denoted A and B, than in center C, as summarized in Table 1. Even more striking, discontinuations of blinded study medication due to minor GI AEs were 6 fold greater in centers A and B, compared with center C.

All participating hospitals were university affiliated and in Ontario. Study procedures were carried out in the same way by all 3 centers using a common procedures manual, including a uniform query for AEs. However, because of local ethical review committee requirements, the consent form differed among centers with regard to adverse effects. In centers A and B, the relevant section read "Side effects are not anticipated beyond occasional GI irritation and, rarely, skin rash." In center C, the consent form read "Sulfinpyrazone and aspirin are generally well tolerated … Occasionally a patient taking sulfinpyrazone or aspirin may develop a tendency to bleed but the risk of serious hemorrhage is extremely unlikely." Thus, study participants in centers A and B were informed of the potential for GI irritation, but at center C, they were not. The investigators concluded that this was the probable source of the differences in GI AEs.

To the best of our knowledge, this report[2] is the first convincing evidence of the nocebo (*Latin: I will harm*) effect in cardiovascular medicine. The nocebo effect (or phenomenon) is the inverse of the placebo effect; it refers to

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Table 1 Adverse events (AEs) in 555 patients with unstable angina allocated to aspirin, sulfinpyrazone, aspirin + sulfinpyrazone, or placebo[2]. All randomized patients included, irrespective of treatment group allocation

Centers (hospitals)	A (4)	B (3)	C (1)	χ^2	*P*
N	313	86	156		
GI AEs in consent form	Yes	Yes	No		
Minor GI AEs	143 (46%)	32 (37%)	25 (16%)	39.8	<.001
Major GI AEs*	8 (2.6%)	1 (1.2%)	6 (3.8%)	1.6	NS
DC due to minor AE†	61 (19%)	15 (17%)	5 (3%)	22.8	<.001
DC due to major AE	27 (9%)	7 (8%)	11 (7%)	3.1	NS

DC, discontinued; GI, gastrointestinal; NS, not significant.
*For example, GI bleeding, peptic ulcer.
†All due to GI AEs.

AEs, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention, or a nonmedical situation. These expectations can be driven by many factors beyond the informed consent form in a randomized controlled trial (RCT), including warnings about adverse effects communicated by clinicians when prescribing a drug,[3,4] information on the Internet and in social media,[5] health scares propagated by broadcast and print media,[6] and simply observing the symptoms and behavior of others.[7,8] Just as an ineffective treatment can be subjectively effective in an uncontrolled setting due to the placebo effect, an innocuous treatment can be subjectively toxic due to the nocebo effect.[6,9] The placebo and nocebo effects reflect normal human neuropsychology and not drug efficacy or toxicity.

The differences reported by Myers et al[2] were not randomized comparisons, but there have since been many studies randomizing subjects to receive different information with follow-up for subsequent AEs. One of the few reports[10] involving a cardiovascular treatment stemmed from the perception at the time of the study that beta blockers commonly cause erectile dysfunction. A total of 96 male patients with hypertension or angina pectoris and normal sexual function completed a multidimensional quality of life questionnaire designed to assess the presence of erectile dysfunction (International Index of Erectile Function). They were then all treated with atenolol 50 mg daily, randomized into 3 groups of 32 receiving different information about the drug. The first group did not know what drug they were taking, the second knew but were not informed about the potential adverse effects, and the third knew they were taking atenolol and were further informed that atenolol could cause erectile dysfunction. The language used was "… it may cause erectile dysfunction but this is uncommon."

At the end of the 90-day treatment period, the same questionnaire was administered again. Erectile dysfunction was reported by 1 patient (3.1%) in the group blinded to treatment, 5 (15.6%) in the group that knew they were taking atenolol but were not informed about side effects, and 10 (31.2%) in the group that was informed about sexual dysfunction potentially attributable to atenolol ($P < .01$ for the informed patient group vs the blinded group). The authors concluded that erectile dysfunction in their study was psychogenic. This conclusion is supported by a review[11] of beta blocker RCTs, which concluded that these drugs rarely cause erectile dysfunction, contrary to widespread belief at the time.

Several reviews[3,7,12,13] have summarized studies reporting the nocebo effect in mostly noncardiovascular contexts. The most common manifestation of the nocebo effect is pain of various kinds, with or without other symptoms. Pain may be heightened because of negative expectations about a treatment or situation,[14] and it can be experienced in the total absence of a noxious stimulus, as in mass psychogenic illness, which is the most dramatic manifestation of the nocebo effect.[15] As shown by functional MRI, negative expectations that heighten pain lead to increased activity of regions involved in pain processing, including the prefrontal cortex, anterior cingulate cortex, and insula.[14] The nocebo phenomenon is thus well established. It hinders effective therapy, especially in the age of the Internet and social media, where misinformation can proliferate.

The nocebo phenomenon in randomized controlled trials vs observational studies

It is widely accepted that a well-performed double-blind RCT provides high-quality evidence because it is the most reliable way to evaluate the benefit, safety, and tolerability of a treatment.[16,17] Double-blind RCTs have the great advantage that bias is controlled (providing the blind remains secure), and the only factor (other than random error) determining the outcome of a properly performed RCT is allocation to the test treatment or the control. Because placebo and nocebo effects depend on expectations, they affect all blinded treatment arms equally.[16,17] The main disadvantage of large RCTs is that they are difficult to carry out, require a long time to complete, and are often very costly.

Observational studies can be useful to detect adverse effects that are too rare to be reliably apparent in RCTs,

Exhibit A40-6

particularly when the background incidence is very low.[18] Before 2010, when simvastatin 80 mg was shown in an RCT to cause myopathy (unexplained muscle pain or weakness with creatine kinase >10X ULN) including rhabdomyolysis much more frequently than simvastatin 20 mg,[19] this rare adverse effect had been recorded in statin RCTs, but the numbers were too small for statistically significant differences, so its detection was essentially observational. In this case, observational data were reliable because the background incidence of idiopathic rhabdomyolysis is extremely low, so that any case occurring during statin therapy without another known cause is likely to be causally related to the statin. Cerivastatin was withdrawn from the market in 2001 because observational data derived from post-marketing surveillance revealed that the risk of rhabdomyolysis was much higher than that with other statins.[20]

Because the comparisons made in observational studies are not randomized, all observational studies, whether controlled or not, are at risk of confounding.[16,18] Evaluation of the contribution of placebo or nocebo effects is rarely possible. Statistical adjustment can reduce the risk of confounding but not eliminate it. There are numerous instances of observational findings later refuted by RCTs. In cardiovascular medicine, among the best known is estrogen therapy to reduce coronary heart disease (CHD) risk in post-menopausal women, which was strongly supported by numerous epidemiologic studies[21,22] and subsequently largely refuted by RCTs.[23–25] Another example relates to supplementation with the antioxidant vitamin E, which was associated with a reduced risk of cardiovascular events in several observational studies.[26] RCTs subsequently found no suggestion of cardiovascular benefit.[26,27] These examples and many others show that observational studies should be interpreted cautiously.[16,18]

Surveys and clinical practice medical records provide uncontrolled observational data. In contrast to double-blind RCTs, which measure only the pharmacologic properties of a drug (beneficial or adverse), these methods provide information on the net effect of the pharmacologic properties of the drug combined with background symptoms and any placebo or nocebo effect, subject to confounding factors such as recall or selection bias, if any. Surveys and medical records can provide information on AEs associated with a treatment but are of limited value for evaluating the causal relationship between the event and the treatment.

Statin intolerance in the clinic

Statin intolerance is a recent concept. The first statin, lovastatin, was introduced in 1987,[20] but the first article with "statin intolerance" in the title did not appear until 2005. A Medline search returns 9 such articles before the end of 2010 and 44 from 2011 until March 2016. Before the current decade, statins (other than cerivastatin) were generally regarded as a safe and well-tolerated class of drugs with a favorable benefit risk relationship.[20,28–30]

One in 4 Americans aged older than 40 years, about 25 million people, take a statin.[31] Statin therapy is a long-term endeavor, sometimes lifelong. As with any chronic therapy intended to prevent adverse outcomes rather than treat symptoms, adherence can be problematic.[32] Compounding the problem, a significant minority of patients report AEs during treatment with statins, which may lead to discontinuation. In a retrospective cohort study in eastern Massachusetts, 18,778 (17%) of 107,835 statin-treated patients had a statin-associated AE.[33] Of these, 11,124 (10%) patients discontinued their statin, at least temporarily, and were thus intolerant. From a multinational survey of 810 statin prescribers—mainly cardiologists—Hovingh et al[34] estimated an overall average of 6% as the percentage of patients who are statin intolerant (defined as unable to tolerate the recommended statin dose). The range was wide, even within Western Europe, where the percentage was 2% in Italy, Spain, and Sweden, 4% in Germany, 6% in France, and 11% in the United Kingdom. English-speaking countries (Australia, Canada, the United Kingdom, and the United States) all reported percentages of 8% to 12%, with the 12% US value similar to the 10% reported previously by Zhang et al.[33] Cultural factors, including local language media misinformation that can create the nocebo effect, likely play a role in this distribution. The most common complaints of statin-intolerant patients are related to muscle, occurring in 64% in an international survey,[34] and over 90% in a specialist lipid clinic.[35] In the study by Zhang et al the percentage of patients who discontinued statins because of muscle symptoms is not provided; however, of 18,778 patients with AEs, of whom 11,124 discontinued their statin, 27% had myalgia.[33] Overall, perhaps about half of all statin discontinuations caused by AEs are due to muscle symptoms. Taking 10% as an overall average for the percentage of patients who are statin-intolerant and one half as the proportion in whom the intolerance is caused by muscle symptoms, roughly 5% of all statin-treated patients are intolerant due to muscle symptoms. These symptoms are rarely accompanied by significant elevations in creatine kinase (CK) or other objective changes,[35] and no pathophysiological explanation for muscle symptoms during statin therapy has been found.[36] As discussed in the following section, RCTs demonstrate that muscle and other intolerable symptoms are generally not caused by the statin.

Statin intolerance in randomized controlled trials

In contrast to the substantial AE rate under the uncontrolled open-label conditions of clinical practice, in randomized placebo-controlled trials, the incidence of muscle symptoms[37] and of discontinuations due to any AE[38] are consistently similar in the patient group allocated to the

statin and the group allocated to placebo.[37] Recently, the HOPE 3 investigators reported a small excess of patients with muscle symptoms in patients allocated to rosuvastatin 10 mg daily compared with placebo (5.8% vs 4.7%, respectively, $P = .005$), but no significant difference in the number of patients permanently discontinuing study treatment because of these symptoms (1.3% vs 1.2%, respectively).[39] Meta-analyses of placebo-controlled studies have shown no significant difference between statin and placebo in the rates of muscle symptoms.[40,41] Table 2 summarizes AEs pooled from 17 placebo-controlled trials with atorvastatin (the statin most commonly prescribed) across the 10- to 80-mg dosage range. Table 2 is reproduced from the US LIPITOR (atorvastatin) prescribing information and therefore has been reviewed and approved by the US Food and Drug Administration, which had access to the raw data. The 20-mg and 40-mg doses were used in few studies, so data with these doses are sparse and less reliable. There is no suggestion that atorvastatin increases the incidence of any of these AEs, including muscle symptoms. Indeed, there is a trend to fewer AEs with the maximal 80-mg dose compared with lower doses and placebo. This may reflect the play of chance and the fact that most studies did not include all doses.

Randomized controlled trials in statin-intolerant patients

The first study specifically in statin-intolerant patients was a proof-of-concept N-of-1 placebo-controlled study in 8 patients.[42] No difference between statin and placebo was observed. ODYSSEY ALTERNATIVE[43,44] was an RCT in 361 patients with statin intolerance due to muscle symptoms that included a rechallenge over 24 weeks with atorvastatin 20 mg, with the PCSK9 inhibitor alirocumab and ezetimibe as comparators in a parallel design. In an exploratory analysis, there was no significant difference in withdrawal due to muscle AEs, which were recorded in 16% of patients allocated to alirocumab, 20% to ezetimibe, and 22% to atorvastatin ($P > .20$); 82%, 75%, and 75% of study participants in these 3 groups, respectively, did not have an AE of any type causing discontinuation.

In the most recent and largest rechallenge RCT in statin-intolerant patients, GAUSS-3,[45,46] 491 patients with well-documented statin intolerance were randomly allocated to atorvastatin 20 mg or placebo for 10 weeks or until they experienced intolerable muscle symptoms. After a 2-week washout period, they were crossed over to the other treatment for an additional 10 weeks or until the onset of intolerable muscle symptoms. This sequence comprised Phase A of the study, the results of which were subject to an exploratory analysis without predefined methods in the statistical analysis plan.[46]

Overall, 133 patients (27.1%) experienced intolerable muscle-related symptoms while taking both treatments or had no symptoms on either treatment. Intolerable symptoms were experienced by 209 patients (42.6%) on atorvastatin but not placebo, and 130 (26.5%) on placebo but not atorvastatin. Taking the results at face value, the excess of 79 of 491 (16%) participants relative to placebo could represent patients whose muscle symptoms were due to the pharmacologic properties of atorvastatin. Symptoms in the remaining 84% can be accounted for by the nocebo effect.

Before settling on this conclusion, it should be noted that the GAUSS-3[46] results contain features that complicate interpretation. Most obviously, in the first period, the Kaplan–Meier cumulative probability curves do not start to separate until at least 50 days after randomization (period length was 70 days). Muscle symptoms causing statin intolerance can occur at any time but typically arise within the

Table 2 Adverse events as listed in the LIPITOR (atorvastatin) US prescribing information

	Any dose	10 mg	20 mg	40 mg	80 mg	Placebo
Adverse reaction*	N = 8755	N = 3908	N = 188	N = 604	N = 4055	N = 7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

Clinical adverse reactions occurring in ≥2% in patients treated with any dose of LIPITOR and at an incidence greater than placebo regardless of causality (% of patients).

*Adverse reaction > 2% in any dose greater than placebo.

Exhibit A40-6

first few weeks of treatment.[36] Of the 262 patients in GAUSS-3 who reported intolerable symptoms during period 1, about 70% had reported these symptoms by 50 days after randomization. This is consistent with the findings of a retrospective cohort study in a US specialist lipid clinic, in which 52% of patients who could not tolerate a statin (due to muscle symptoms in over 90%) reported symptoms within the first month of therapy.[35] Therefore, if atorvastatin could produce reproducible muscle symptoms in these statin-intolerant patients, the excess over placebo in intolerable symptoms should have been substantial in the early weeks after randomization. But the period 1 Kaplan–Meier cumulative probability curves are virtually superimposable up to 50 days.

In GAUSS-3, the muscle symptom end point is purely subjective, and intolerable muscle symptoms on at least 2 statins was an entry criterion. In this situation, maintaining the blind is crucial, as without it virtually all subjects would report muscle symptoms on atorvastatin but not placebo, but in any study, participants may self-unblind if given the opportunity.[47,48] Crossover designs are particularly vulnerable because all subjects have access to the 2 dosage forms and can compare them.[47] In GAUSS-3, participants had the ability to self-unblind either by obtaining a lipid profile outside the study or by removing the overencapsulation from a dose of study medication.[48] Some participants may have felt that a placebo-controlled rechallenge questioned the credibility of their symptoms or exposed them to the potential embarrassment of being found intolerant of placebo, either of which would have created a motive for self-unblinding. In addition, only patients who in phase A had experienced intolerable symptoms on atorvastatin but not placebo could enter phase B of the study, in which they would be randomly allocated to either the PCSK9 inhibitor evolocumab or ezetimibe for 24 weeks, followed by open-label evolocumab in phase C for 2 years. The mean baseline low-density lipoprotein cholesterol in GAUSS-3 was very high—5.5 mmol/L (212 mg/dL), one third had CHD, and all subjects believed they could not tolerate a statin. Some sites may have been able to offer another evolocumab study to participants in GAUSS-3 not proceeding to phases B and C, but participants at other sites who wanted to be sure of access to evolocumab (in phase C) would have had an additional motive to self-unblind. This triad of a crossover design, unusual motivating factors, and a purely subjective end point is not present in most RCTs (for which the overencapsulation method used in GAUSS-3 may suffice). Self-unblinding would most likely commence toward the end of the period 1, when participants who had not yet reported intolerable symptoms might well have started to have doubts about their ability to distinguish atorvastatin from placebo before the period ended. This would create bias that can explain the delayed separation of the Kaplan–Meier curves toward the end of period 1, a phenomenon that is otherwise not easily explained, and the continuing separation in period 2. Therefore, bias caused by self-unblinding explains the results of phase A in GAUSS-3 at least as plausibly as an appreciably greater frequency of intolerable muscle symptoms on a statin compared to placebo, a phenomenon never previously demonstrated. Future rechallenge studies in statin-intolerant patients should use designs that minimize incentives and opportunities to unblind and should avoid overencapsulation by contracting with a statin manufacturer to use established tablet matching techniques that minimize the risk of unblinding.[47] It is easier to make a placebo tablet matching simvastatin, which is tasteless, than atorvastatin, which is bitter.

As previously noted (under "Statin intolerance in the clinic" section), the incidence of statin intolerance due to muscle symptoms in statin-treated patients appears to be roughly 5%. If the 16% excess in the statin-intolerant patients studied in GAUSS-3 could be shown to accurately reflect intolerance with a pharmacologic basis, as opposed to self-unblinding, then the incidence of discontinuation of statin therapy due to muscle AEs caused by the statin would be about 1% in unselected patients. A difference between statin and placebo in discontinuations due to AEs has not been observed in earlier clinical trials[38] or the recent HOPE 3 study,[39] as previously noted. A new UK National Institute for Health Research N-of-1 study in 200 patients[49] may shed more light on statin intolerance under double-blind conditions.

Taken together, GAUSS 3, ODYSSEY ALTERNATIVE, and the small N-of-1 study of Joy et al[42] provide evidence that intolerance usually depends on patients knowing they are taking a statin.[37,50,51] Added to the massive amount of information provided by cardiovascular outcome and other statin RCTs, these rechallenge studies provide further evidence that the predominant cause of statin intolerance is the nocebo effect, which is totally dependent on patient awareness of a treatment and its potential adverse effects. Under double-blind conditions, patients do not know what they are taking (as long as the blind is secure), so expectations are the same regardless of treatment allocation; the nocebo effect can increase the frequency of an AE in the study population[2,10] but cannot cause differences between the treatment and control groups.

The nocebo effect and statin intolerance in the clinic

Muscle symptoms are subjective and common in untreated middle-aged or elderly patients. In the Heart Protection Study,[52] which compared simvastatin 40 mg and placebo in over 20,000 patients during a follow-up period of 5 years, participants were directly questioned at every visit about muscle symptoms (in addition to the standard general query for AEs typically used in clinical trials). At each visit, about 6% of patients in both groups reported muscle symptoms, and 32.9% and 33.2% reported these symptoms at least once during the trial in the simvastatin and placebo groups, respectively. The Heart Protection

Study illustrates the high prevalence of muscle symptoms in middle-aged to elderly people who are taking a placebo, are queried at regular intervals about muscle symptoms, and have been informed that a statin can cause muscle injury.

The risk of myopathy and rhabdomyolysis is prominent in statin patient information leaflets, and clinicians warn patients to report muscle symptoms; furthermore, Internet searches bring up mainly disturbing misinformation about statin adverse effects. This is the fate of many advances in medicine, such as vaccination programs and fluoridation of water.[5] Aggravating this problem, there is an inbuilt bias in news outlets and social media; "Statins have very few adverse effects" is not newsworthy, but "Cholesterol drugs taken by millions are dangerous" often is. These influences appear to have set up a powerful belief system. Therefore, some patients will expect muscle and other symptoms[6,9] and may associate background symptoms with their statin use—the nocebo effect. Furthermore, normal healthy people can experience pain in the absence of any painful stimulus, as previously noted.

In recent years, various objections have been raised to the reassuring adverse effect profile demonstrated in statin RCTs, which include over 170,000 patients followed for several years.[30] Some have argued that the statin trials do not reflect clinical practice and therefore fail to reliably assess adverse effects.[53–56] For example, the NLA Task Force on Statin Safety has written[55] "One of the major limitations of using randomized controlled trials (RCTs) for the evaluation of safety is that the populations studied are very restricted in their study entry characteristics and often patients with multiple comorbidities and previous statin intolerance are excluded. Thus there is limited generalizability of patients in RCTs compared with the general clinical population, which tends to have more comorbidity and frailty."

We disagree. We have previously challenged the argument that any exclusion of patients with statin intolerance casts doubt on the tolerability data in RCTs.[38] Also, while it is true that individual statin RCTs, in common with RCTs in general, had inclusion and exclusion criteria, over 170,000 patients[30] have participated in the statin RCTs and among them are large numbers with multiple comorbidities. Table 3 summarizes discontinuation rates due to any AE in 8 large cardiovascular outcome trials with statins comprising over 45,000 participants, many female or elderly, with complex medical histories including one or more of CHD, stroke, diabetes, chronic kidney disease, and heart failure. Taking the participants in the cardiovascular outcome RCTs with statins as a whole, the entry characteristics were very broad. Consequently, there is no good reason not to generalize these RCT results to clinical practice.

In any double-blind RCT, the difference between the active and placebo treatments in discontinuation rates due to any AE is a good measure of tolerability. The discontinuation rates in the broad array of patient types summarized in Table 3 were consistently similar in participants allocated to statin and placebo, and withdrawal due to any AE in the 8 studies pooled was 8.0% (1814/22,714) and 8.1% (1843/22,715) in patients allocated to statin and placebo, respectively. Thus, there was no intolerance in these studies, not because of the characteristics of the participants, whose comorbidities were at least that of patients in most clinical practices, but because statins are well tolerated when treatment is blinded.

The authors[53–56] dismissing statin RCTs appear not to have considered the possibility that the nocebo effect could lead to high rates of subjective AEs attributed to statins in uncontrolled observational studies, in contrast to RCTs, which consistently show little difference between statin and placebo. This is not surprising because there are few reports of the nocebo effect in cardiovascular medicine. A Medline search on March 19, 2016 using the terms "nocebo" and "cardiovascular" in any field revealed only 6 publications. Substituting "pain" for "cardiovascular" returned 151 publications. As far as we are aware, the first explicit mention of the nocebo effect in the context of statins was in a review of AEs in statin RCTs by Finegold et al.[57]

Although most cases of statin intolerance can be adequately explained by the nocebo effect, it remains a clinical problem. Virtually all patients and some clinicians are convinced that the intolerance has a pharmacologic basis. In a typical scenario, a clinician prescribes a statin, the patient returns complaining of muscle symptoms with no obvious cause, the clinician or patient stops the statin, and the symptoms resolve. This sequence of events convinces the patient that the symptoms are caused by the statin, especially if symptoms recur during rechallenge. But this scenario is readily explained by the nocebo effect, and there is no reason for the clinician to invoke drug toxicity that somehow fails to appear in RCTs.[37,38] However, this does not make the symptoms any less relevant.

Although the nocebo effect reflects normal human neuropsychology, very few patients will accept that their symptoms are psychogenic; any such suggestion is stigmatizing for many people and should generally be avoided. This is seen most clearly when the nocebo phenomenon is manifested in a group setting as mass psychogenic illness; those affected often vigorously reject any psychological explanation.[15] On the other hand, knowing that purely subjective symptoms during statin therapy are unlikely to be caused by the statin helps the clinician to preempt statin intolerance and to deal with it if it does occur, as discussed in the following section.

Devoting effort to restarting treatment with a statin is important because the only class of lipid-lowering agent capable of matching the efficacy of high-intensity statin therapy is the PCSK9 inhibitors, but as of April 2016, these lack cardiovascular outcome and long-term safety data. In addition, atorvastatin 80 mg, the maximum dose of the most commonly prescribed generic statin and capable of producing a mean reduction in low-density lipoprotein

Exhibit A40-6

Table 3 Discontinuation due to any adverse event (AE) in randomized double-blind placebo-controlled cardiovascular outcome trials of statins in patients with advanced disease

Trial*	N	Drug, dose (mg)	Duration (y)†	Patient type	Age (y)†	% Female	Discontinuation due to AEs (%)	
							Statin	Placebo
4S	4444	S 20-40	5.4	CHD	59	19	5.7	5.7
HPS	20,536	S 40	4.9	Mixed‡	64	25	4.8	5.1
ALERT	2102	F 40-80	5.1	Renal transplant	50	34	14.8	16.3
4D	1255	A 20	4.0	Diabetes on dialysis	66	46	11.8	8.2
SPARCL	4731	A 80	4.9	Stroke/TIA§	63	40	17.5	14.5
CORONA	5011	R 10	2.7	Heart failure	73	24	9.6	12.1
GISSI-HF	4574	R 10	3.9	Heart failure	68	23	4.6	4.0
AURORA	2776	R 10	3.8	Hemodialysis	64	38	14.9¶	16.8¶
Total	**45,429**						**8.0**	**8.1**

A, atorvastatin; CHD, coronary heart disease; F, fluvastatin; HPS, Heart Protection Study; R, rosuvastatin; S, simvastatin; TIA, transient ischemic attack.

*Trials are listed in order of publication date of the main results.

†Mean or median.

‡65% CHD, 16% cerebrovascular disease, and 29% diabetes.

§69% stroke and 31% TIA.

¶Included end point events.

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cholesterol of about 55%, is obtainable for less than $100 per year of treatment in the United States. The US list price of both marketed PCSK9 inhibitors, alirocumab and evolocumab, was over $14,000 per year of treatment at launch in 2015.

Minimizing the nocebo effect during statin therapy

Prevention of statin intolerance is better than cure. The prescribing information for all statins advises warning patients about the risk of myopathy (unexplained muscle pain or weakness with CK >10X ULN), including rhabdomyolysis, and to promptly report unexplained muscle symptoms. Because warning patients about a subjective AE can substantially increase the risk that it will occur,[2,4,6,10,58,59] the frequency of subjective AEs can be strongly influenced by clinician–patient communication.[3,4,9,59] The goal of the nocebo-conscious clinician is to avoid creating negative expectations and to counter any that already exist. Therefore, it is important to emphasize to the patient that myopathy including rhabdomyolysis is rare, occurring in less than 1 in 1000 patients, and to put this very small risk in the context of the proven substantial benefits of statins. Patients starting a statin can be reminded that muscle aches and pains are very common background symptoms in middle-aged and older people. They can also be informed that in the event of any new muscle symptoms with no reason such as vigorous exercise, a simple blood test can determine whether the statin is the likely cause (if CK is >5X ULN) or far more commonly not (if CK is <3X ULN). Clinicians can also advise patients that statins are safe medicines in clinical use for nearly 30 years, and that statins as a common cause of muscle and other symptoms is a recent myth perpetuated on the Internet and elsewhere.

The nocebo minimization approach summarized here is very different from the advice of the National Lipid Association Statin Intolerance Panel, whose recommendations to patients include "About 1 in 10 people who try taking a statin will report some kind of intolerance, most commonly muscle aches in the legs, trunk, or shoulders and upper arms….".[56] This is more explicitly negative than the patient information examples provided at the beginning of this article,[2,10] which produced large nocebo effects. Patients need to know about proven serious adverse effects, as described in the *Patient Counseling* or equivalent section of the prescribing information; what other patients report is not useful.

In patients stopping their statin because of subjective AEs (such as muscle symptoms without a significant elevation of CK), rechallenge is usually successful,[33] although not necessarily with the same statin or at the same dose. Patient expectations are critical.[6] Communicating an optimistic outlook[3,9] can reverse or reduce the effect of previous negative expectations.[5] Patients need to know that intolerance is a soluble problem that responds to therapy adjustments. It is also useful to remind the patient of the proven cardiovascular benefits of statins and to explore any ambivalence about the need to take a statin. Knowing the value of a treatment reduces the nocebo effect.[9] There is some evidence[60] that the nocebo effect is attenuated if a choice of treatments is available, so it may be worth asking a patient agreeing to rechallenge, which option he or she prefers—switching to a different statin,

lowering the dose of the existing statin, or just giving the statin another try at the same dose.

In summary, the nocebo effect is a well-established phenomenon that is under-appreciated in cardiovascular medicine. It is the best explanation to account for the high rate of muscle and other symptoms attributed to statins in observational studies and clinical practice, in contrast to RCTs where muscle symptoms, and rates of discontinuation due to any AE, are consistently similar in the statin and placebo groups. Statin-intolerant patients usually tolerate statins under double-blind conditions, indicating that the intolerance has little if any pharmacologic basis. Known techniques for minimizing the nocebo effect can be applied to the prevention and management of statin intolerance.

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References

1. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. *N Engl J Med*. 1985;313:1369–1375.
2. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther*. 1987;42:250–253.
3. Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int*. 2012;109:459–465.
4. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am J Bioeth*. 2012;12:22–29.
5. Crichton F, Petrie KJ. Accentuate the positive: counteracting psychogenic responses to media health messages in the age of the Internet. *J Psychosom Res*. 2015;79:185–189.
6. Faasse K, Petrie KJ. The nocebo effect: patient expectations and medication side effects. *Postgrad Med J*. 2013;89:540–546.
7. Hahn RA. The nocebo phenomenon: concept, evidence, and implications for public health. *Prev Med*. 1997;26:607–611.
8. Lorber W, Mazzoni G, Kirsch I. Illness by suggestion: expectancy, modeling, and gender in the production of psychosomatic symptoms. *Ann Behav Med*. 2007;33:112–116.
9. Bingel U. Avoiding nocebo effects to optimize treatment outcome. *JAMA*. 2014;312:693–694.
10. Silvestri A, Galetta P, Cerquetani E, et al. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. *Eur Heart J*. 2003;24:1928–1932.
11. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. β-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002;288:351–357.
12. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA*. 2002;287:622–627.
13. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. *Psychosom Med*. 2011;73:598–603.
14. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med*. 2010;16:1277–1283.
15. Wessely S. Responding to mass psychogenic illness. *N Engl J Med*. 2000;342:129–130.
16. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med*. 2000;342:1907–1909.
17. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet*. 2001;357:373–380.
18. MacMahon S, Collins R. Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies. *Lancet*. 2001;357:455–462.
19. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658–1669.
20. Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat Rev Drug Discov*. 2003;2:517–526.
21. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117:1016–1037.
22. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med*. 1996;335:453–461.
23. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280:605–613.
24. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
25. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–1712.
26. Tatsioni A, Bonitsis NG, Ioannidis JP. Persistence of contradicted claims in the literature. *JAMA*. 2007;298:2517–2526.
27. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:23–33.
28. Gotto AM Jr. Safety and statin therapy: reconsidering the risks and benefits. *Arch Intern Med*. 2003;163:657–659.
29. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol*. 2006;97:S52–S60.
30. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
31. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription Cholesterol-Lowering Medication Use in Adults Aged 40 and Over: United States, 2003–2012. NCHS data brief, no 177. Hyattsville, MD: National Center for Health Statistics; 2014.
32. Grundy SM. Statin discontinuation and intolerance: the challenge of lifelong therapy. *Ann Intern Med*. 2013;158:562–563.
33. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med*. 2013;158:526–534.
34. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. *Atherosclerosis*. 2015;245:111–117.
35. Lakey WC, Greyshock NG, Kelley CE, et al. Statin intolerance in a referral lipid clinic. *J Clin Lipidol*. 2016;10:870–879.
36. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis

Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36:1012–1022.
37. Newman CB, Tobert JA. Statin intolerance: Reconciling clinical trials and clinical experience. *JAMA*. 2015;313:1011–1012.
38. Tobert JA, Newman CB. Statin tolerability: in defence of placebo-controlled trials. *Eur J Prev Cardiol*. 2016;23:891–896.
39. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031.
40. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation*. 2006;114:2788–2797.
41. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J*. 2014;168:6–15.
42. Joy TR, Monjed A, Zou GY, Hegele RY, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med*. 2014;160:301–310.
43. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769.
44. Newman CB, Tobert JA. Comment on the article by Moriarty et al. *J Clin Lipidol*. 2016;10:209–210.
45. Nissen SE, Dent-Acosta RE, Rosenson RS, et al. Comparison of PCSK9 inhibitor evolocumab vs ezetimibe in statin-intolerant patients: design of the goal achievement after utilizing an anti-PCSK9 antibody in statin-intolerant subjects 3 (GAUSS-3) trial. *Clin Cardiol*. 2016;39:137–144.
46. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: The GAUSS-3 randomized clinical trial. *JAMA*. 2016;315:1580–1590.
47. Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB. Fundamentals of Clinical Trials. Chapter 7: Blinding. 5th ed International Publishing Switzerland: Springer; 2015.
48. Meinert CL. Clinical Trials: Design, Conduct and Analysis. Chapter 18. Treatment Masking. 2nd ed. New York: Oxford University Press; 2012.
49. Smeeth L. HTA - 14/49/159: Statin Web-based Investigation of Side Effects Trial (Statin WISE Trial). 2016 Available at: http://www.nets.nihr.ac.uk/projects/hta/1449159; 2016 Accessed April 4, 2016.
50. Brown WV, Moriarty PM, McKenney JM. JCL roundtable: PCSK9 inhibitors in clinical practice. *J Clin Lipidol*. 2016;10:5–14.
51. Brown WV. From the Editor: new drugs, old lessons. *J Clin Lipidol*. 2016;10:1–2.
52. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
53. Maningat P, Breslow JL. Needed: pragmatic clinical trials for statin-intolerant patients. *N Engl J Med*. 2011;365:2250–2251.
54. Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: a common dilemma not reflected in clinical trials. *Cleve Clin J Med*. 2011;78:393–403.
55. Jacobson TA. NLA Task Force on Statin Safety–2014 update. *J Clin Lipidol*. 2014;8:S1–S4.
56. Guyton JR, Bays HE, Grundy SM, Jacobson TA, The National Lipid Association Statin Intolerance Panel. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8:S72–S81.
57. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol*. 2014;21:464–474.
58. Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? *J Sex Med*. 2007;4:1708–1712.
59. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA*. 2012;307:567–568.
60. Bartley H, Faasse K, Horne R, Petrie KJ. You can't always get what you want: the influence of choice on nocebo and placebo responding. *Ann Behav Med*. 2016;50:445–451.