Journal of Clinical Lipidology (2016) 10, 739–747

Journal of Clinical Lipidology

The nocebo effect in the context of statin intolerance

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KEYWORDS:
Statin intolerance;
Nocebo;
Muscle;
Statin adverse effects;
Rechallenge;
PCSK9 inhibitor;
Blinding techniques;
Internet;
Social media;
Iatrogenic

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.

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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1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.05.002

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,