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Introducing the 'Drucebo' effect in statin therapy: a systematic review of studies comparing reported rates of statin-associated muscle symptoms, under blinded and open-label conditions

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Abstract

Background The 'placebo effect' and 'nocebo effect' are phenomena whereby beneficial (placebo) or adverse (nocebo) effects result from the expectation that an inert substance will relieve or cause a particular symptom. These terms are often inappropriately applied to effects experienced on drug therapy. Quantifying the magnitude of placebo and nocebo effects in clinical trials is problematic because it requires a 'no treatment' arm. To overcome the difficulties associated with measuring the nocebo effect, and the fact that its definition refers to inert compounds, rather than drugs, we introduce the concept of 'drucebo' (a combination of DRUg and plaCEBO or noCEBO) to relate to beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug. As an initial application of the concept, we have estimated the contribution of the drucebo effect to statin discontinuation and statin-induced muscle symptoms by performing a systematic review of randomized controlled trial of statin therapy.

Methods This preferred reporting items for systematic reviews and meta-analysis-compliant systematic review was prospectively registered in PROSPERO (CRD42017082700). We searched PubMed and Cochrane Central from inception until 3 January 2018 using a search strategy designed to detect studies including the concepts (Statins AND Placebo AND muscle pain). We included studies that allowed us to quantify the drucebo effect for adverse muscle symptoms of statins by (i) comparing reported rates of muscle symptoms in blinded and unblinded phases of randomized controlled trials and (ii) comparing rates of muscle symptoms at baseline and during blinded therapy in trials that included patients with objectively confirmed statin intolerance at baseline. Extraction was performed by two researchers with disagreements settled by a third reviewer.

Results Five studies allowed the estimation of the drucebo effect. All trials demonstrated an excess of side effects under open-label conditions. The contribution of the drucebo effect to statin-associated muscle pain ranged between 38% and 78%. The heterogeneity of study methods, outcomes, and reporting did not allow for quantitative synthesis (meta-analysis) of the results.

Conclusions The drucebo effect may be useful in evaluating the safety and efficacy of medicines. Diagnosis of the drucebo effect in patients presenting with statin intolerance will allow restoration of life-prolonging lipid-lowering therapy. Our study was limited by heterogeneity of included studies and lack of access to individual patient data. Further studies are necessary to better understand risk factors for and clinical management of the drucebo effect.

Keywords Statins; Nocebo; Placebo; Drucebo

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Introduction

The Latin word 'placebo' translates as 'I will please', whereas 'nocebo' means 'I will harm'.[1] The 'placebo effect' and 'nocebo effect' are the phenomena whereby beneficial (placebo) or adverse (nocebo) effects result from the expectation that an inert substance will relieve or cause a particular symptom (Table 1). Benefits (placebo) and harms (nocebo) associated with inert therapies are usually subjective[2] and are associated with complex neurobiological and psychological mechanisms.[3] The concept of 'placebo effect' is also commonly used in the context of therapeutic drugs, relating to an effect of a drug (rather than an inert substance) resulting from expectation of such an effect. The concept of 'nocebo' effect is increasingly being used in the same context and means the appearance of the drug-related symptoms while treating with the given drug, which are not associated with the medicine but with expectations (fear) and knowledge of these possible adverse effects.

Reduction of endogenous cholesterol synthesis by competitive inhibitors of HMG-CoA-reductase (statins) is safe and effective in the primary and secondary prevention of cardiovascular (CV) disease (CVD).[4] While statin therapy is generally well-tolerated, it has been associated with some adverse effects,[5] including muscle-related symptoms (statin-associated muscle symptoms, SAMS).[6] In fact, causality has been confirmed only for three statin-related adverse effects —SAMS, new onset diabetes, and temporary elevations of alanine aminotransferase activity.[7] Statin-associated adverse effects are sometimes sufficiently severe to lead to treatment discontinuation.[8–10] The phenomenon of 'statin intolerance' and associated dose reduction or cessation has been shown to be associated with increased risk of myocardial infarction and coronary heart disease[11] and a composite outcome of myocardial infarction, stroke, or death.[12] Given the millions of statin users, worldwide, even a small prevalence of statin discontinuation would render a huge number of patients at risk of CV events.

Statin-associated muscle symptoms provide an interesting context for the study of adverse effects resulting from the expectation that such effects will occur. The measurement of the severity of muscle pain is subjective, and muscle pain of unrelated origin may be misattributed to statin therapy. Patients may expect harm with treatment with a drug because of the adverse effects listed in patient (or study participant) information leaflets.[13] However, expectations of harm from statins may be greater than for other drugs because of the widespread reporting of adverse effects of statins

Table 1 Definitions of terms

Term	Definition	Method of estimation/quantification
Placebo effect	Benefit experienced by patient taking an *inert substance* as a result of expectation of benefit	Continuous outcome: (Symptom improvement in non-active treatment group) – (Symptom improvement in no-treatment group) Categorical Outcome: $HR/OR/RR(benefit)_{non\text{-}active\ treatment}$ – $HR/OR/RR\ (benefit)_{no\ treatment}$
Nocebo effect	Harm experienced by patient taking an *inert substance* as a result of expectation of harm	Continuous outcome: (Adverse effects in non-active treatment group) – (Adverse effects in no-treatment group) Categorical outcome: $HR/OR/RR(harm)_{non\text{-}active\ treatment}$ – $HR/OR/RR(harm)_{no\ treatment}$
Positive drucebo effect	Benefit experienced by patient taking a *drug* that is not attributable to the pharmacological action of the drug	Continuous outcome: (Symptom improvement in drug treatment group under open-label conditions) – (Symptom improvement in drug treatment group under blinded conditions)

(*Continues*)

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Table 1 (continued)

Term	Definition	Method of estimation/quantification
Negative drucebo effect	Harm experienced by patient taking a *drug* that is not attributable to the pharmacological action of the drug	Categorical outcome: $HR/OR/RR(benefit)_{drug\ (open\ label)} - HR/OR/RR\ (benefit)_{drug\ (blind)}$ Continuous outcome: (Adverse effects in drug treatment group under open-label conditions) – (Adverse effects in drug treatment group under blinded conditions) Categorical outcome: $HR/OR/RR(harm)_{drug\ (open\ label)} - HR/OR/RR\ (harm)_{drug\ (blind)}$

(particularly relating to muscle pain, cogitative dysfunction, and new onset diabetes) in the lay press, in what has been described as a cult of 'statin fear'.[14]

A systematic and rigorous approach to measuring symptom severity and understanding causality is required in order to confirm that adverse effects are truly a result of statins and therefore to prevent the unnecessary cessation of a beneficial therapy. Definitions of SAMS have been proposed by the American College of Cardiology and the American Heart Association,[15] a Canadian Working Group[16] and the National Lipid Association who proposed a score, which has been recently updated, to ascertain the likelihood that muscle symptoms were caused by statin therapy, based upon the regional distribution of the pain, the temporal pattern, symptom resolution with dechallenge, and symptom recurrence with recurrence of statin therapy.[8,17] An international panel of experts (International Lipid Expert Panel) have developed a unified definition of statin intolerance that includes requirements for the inability to tolerate at least two different statins at low dose, intolerance associated with biomarker abnormalities, which improves upon dose decrease or discontinuation, and the exclusion of predisposing factors such as drug–drug interactions.[18,19]

Reported incidence of muscle symptoms attributable to statins are consistently lower in randomized placebo-controlled trials (3–5%) than in observational studies (15–20%) and data collected in non-blinded means. Summarizing data from observational studies, Tobert and Newman estimated that 5% of patients were reported to be intolerant of statins owing to muscle symptoms, although such effects are rarely accompanied by changes in biomarkers such as creatine kinase, which would be expected to be associated with muscle damage.[2] Hence, however rigorously pain is measured, there exists a large element of subjectivity in its quantification. In the context of an observational study where the allocated treatment and its side effects are known to the participant, this subjectivity may lead to increased reporting of adverse effects. However, the differences between randomized controlled trials (RCTs) and observational studies could be explained in part by different patient characteristics because of more rigorous inclusion/exclusion criteria in RCTs.

In RCTs, the incidence of muscle symptoms is similar in participants treated with statins and those assigned to the placebo group.[20,21] A meta-analysis including 83 880 participants in 29 primary and secondary prevention RCTs found no evidence of a difference in reported muscle symptoms between statin and placebo groups.[22] The authors of the meta-analysis raised the possibility of the 'nocebo effect' being responsible for the high rate of reporting of muscle symptoms in non-blinded trials.[22] These findings were confirmed in a more recent meta-analysis.[23]

Evidence relating to the role of the nocebo effect in statin intolerance was recently extensively reviewed by Tobert and Newman.[2] Since then, Gupta *et al.*, in a retrospective analysis of the Anglo-Scandinavian Cardiac Outcomes Trial, found no difference between the incidence of muscle symptoms in patients taking atorvastatin 10 mg compared with placebo [hazard ratio 1.03, 95% confidence interval (CI) 0.88–1.21] in the initial double-blind phase of the trial, whereas in a later-open-label extension, significantly more muscle symptoms were reported in the statin-treated group 1.41 (1.10–1.79).[24] These results were strongly suggestive of the reporting of adverse effects, which were not caused by the pharmacological actions of the drug—and were attributed to the nocebo effect by the authors.[24]

However, it is questionable whether these differences truly represent the nocebo effect. Rojas-Mirquez has highlighted the difficulties with measuring a true nocebo effect. In particular, they observe that 'In the context of a RCT, in order to assess a true placebo or nocebo effect, the non-active drug should ideally be compared to a no-treatment group. True placebo response would be symptom improvements in the non-active treatment arm that go above and beyond spontaneous remission in the no-treatment group. Likewise, true nocebo

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responses are adverse effects that go above and beyond symptoms in the no-treatment group'.[25] While a similar degree of adverse effects in a treatment and placebo group can give reassurance that adverse effects are not drug-related, it cannot estimate the extent to which expectation of an adverse effect is responsible for the patient experiencing the effect. The Nordic Cochrane Centre reviewed studies in all conditions, which compared placebo with no treatment and found no evidence for clinically important effects of placebo.[26]

To overcome the difficulties associated with measuring the nocebo effect, and the fact that its definition refers to inert compounds, rather than drugs, we introduce the concept of 'drucebo' (a combination of DRUg and plaCEBO or noCEBO) to relate to beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug (Table 1). Our portmanteau term may not immediately appeal to classicists, but we anticipate it will prove to be a useful concept with wide applicability across all medical disciplines. We aim to estimate the magnitude of the negative drucebo effect in the specific context of statin therapy by (i) comparing reported rates of muscle symptoms in blinded and unblinded phases of a RCT and (ii) comparing rates of muscle symptoms at baseline and during blinded therapy during a placebo-controlled trial that included patients with statin intolerance at baseline.

Methods

Data sources and searches

We followed the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis statement.[27] The study protocol was prospectively registered in the PROSPERO database (Ref: CRD42017082700). Because this study was planned as a meta-analysis of data available in the public domain, neither ethical approval nor patient informed consent were needed. PubMed (Medline) AND Cochrane Central were searched from inception until 3 January 2018 using the following search terms: ('atorvastatin' OR 'simvastatin' OR 'rosuvastatin' OR 'fluvastatin' OR 'pravastatin' OR 'pitavastatin' OR 'lovastatin' OR 'cerivastatin' OR 'statin therapy' OR statin* OR 'hydroxymethylglutaryl-CoA reductase inhibitors') AND (blinded OR masked OR placebo OR nocebo) AND (muscle OR myopathy OR myalgia OR statin-related/associated side effects statin-related/associated adverse effects OR SAMS). The wild-card term '*' was used to increase the sensitivity of the search strategy.

Study selection

Randomized controlled trials were eligible for inclusion if they compared statin therapy with placebo and either included an open-label phase and a blinded phase or recruited participants with prior statin intolerance due to muscle symptoms, objectively confirmed through cessation and rechallenge with daily statin therapy. No language criteria were applied.

Data extraction

Data were extracted into a pre-prepared form. This was carried out independently by two reviewers (P. E. P. + M. B.). Discrepancies were resolved by consensus, or discussion with a third reviewer (D. P. M.). Extracted information included first author, year of publication, citation, study design; number of participants (divided into experimental groups where appropriate; age, gender, and body mass index of the participants; baseline systolic and diastolic blood pressures; baseline total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and history of SAMS.

Quality assessment

Assessment of risk of bias in the studies included in the analysis was performed systematically using the Cochrane revised quality assessment tool for RCTs (RoB 2.0) based upon the blinded phase of the studies.[28] The Cochrane tool has five criteria for quality assessment: (i) Bias arising from the randomization process; (ii) Bias due to deviations from intended interventions; (iii) Bias due to missing outcome data; (iv) Bias in measurement of the outcome; (v) Bias in selection of the reported result. The risk of bias in each study was judged to be either low risk of bias, some concerns or high risk of bias. Risk of bias assessment was performed independently by two reviewers (P. E. P. and M. B.); disagreements were resolved by a third reviewer (D. P. M.).

Data synthesis and analysis

Owing to the small number of studies found and the heterogeneity of methods used, we did not perform quantitative data synthesis (meta-analysis) but instead produced a narrative synthesis of the results.

Role of the funding source

This work was not externally funded and no funding organization had any involvement.

Results

Search results and trial flow

After automated removal of duplicates by Endnote, 934 publications were identified for screening. After screening of titles and abstracts, 14 papers were selected for full-text screening. Five papers were rejected as duplicate reports, one paper was rejected for not including an appropriate placebo arm, one paper was rejected for not including a statin, one paper was rejected for an inappropriate (weekly) statin dose, and one paper was rejected for not reporting an appropriate endpoint. This left five studies for inclusion (Table 2), and these are described in the succeeding text. The quality assessment of the included studies is presented in Table 3.

Eligible studies

Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm

The lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial was a large double-blind RCT comparing atorvastatin 10 mg and placebo, which was conducted between 1998 and 2002.[29] The trial was stopped early for efficacy, and patients were unblinded and offered the opportunity to be treated with open-label statins. Both statin users and non-users were followed up for adverse effects and CV events, and the two groups were generally well matched with respect to baseline characteristics. This unique set of circumstances allowed the largest investigation (10 180 participants) to date of the difference between adverse effects of statins under blinded and open-label conditions. As already mentioned earlier, the authors found no difference between the incidence of muscle symptoms in patients taking atorvastatin 10 mg compared with placebo—hazard ratio (95% CI) 1.03 (0.88–1.21) in the initial double-blind phase of the trial, whereas in a later-open-label extension, more muscle symptoms were reported in the statin group 1.41 (1.10–1.79).[24] Interestingly, the overall rate of reported muscle symptoms was lower in the open-label extension phase of the study than during the blinded phase. This is possibly because patients who reported muscle-related adverse effects in the first phase were less likely to choose to take an open-label statin than those who did not experience adverse effects. Based upon our definition, we calculated that 38% of SAMS in this study was attributable to the drucebo effect (Tables 1 and 2).

GAUSS-3

The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3 (GAUSS-3) was a two-stage RCT, which included 511 patients with intolerance to two or more statins used in clinical treatment.[30] The trial was designed to compare the effectiveness of two non-statin therapies (evolocumab and ezetimibe) in these patients. Statin intolerance was confirmed by a rigorous process of crossover between blinded placebo and atorvastatin 20 mg for up to 10 weeks to identify individuals who experienced adverse effects while taking atorvastatin but not on placebo.[30] In a thoughtful discussion of the data from this phase of the study, Tobert *et al*. compared the rates of intolerable muscle-related adverse effects reported with blinded placebo and blinded atorvastatin; 133/491 patients reported adverse effect with both treatments or no adverse effects on either treatment, 209/491 reported adverse events on atorvastatin but not placebo, and 130/491 reported adverse effects on placebo but not atorvastatin. On this basis, they calculated that only 16% [(209–130)/491] of adverse effects were attributable to the pharmacological effects of statins, whereas the remaining 84% could be attributable to the nocebo effect.[2] Using our definition, we calculated that 58% of intolerable SAMS might be attributable to the drucebo effect (Table 2).

ODYSSEY ALTERNATIVE

ODYSSEY ALTERNATIVE was another study that recruited statin patients who had demonstrated intolerance to two statins (one of which had to be at the lowest approved daily starting dose) into a RCT comparing alirocumab, ezetimibe, and atorvastatin 20 mg. Statin intolerance was confirmed by a placebo run-in and statin rechallenge arm.[31] Of 361 individuals who undertook the placebo run-in, 25 (6.9%) experienced skeletal muscle symptoms on placebo (nocebo effect), and of 63 participants randomized to atorvastatin, 14 (22%) discontinued therapy because of a skeletal muscle adverse event. This suggests that 78% of individuals who met the criteria of statin intolerance at baseline could tolerate this dose of atorvastatin[31] and that 78% of statin intolerance may be attributed to a drucebo effect (Table 2).

Taylor *et al*. analysis

Taylor *et al*. recruited patients with a history of muscle complaints into a study designed to investigate the role of coenzyme Q10 (CoQ10) on the frequency of statin myopathy.[32] Statin myopathy was confirmed in the study by a randomized double-blind crossover treatment with placebo or simvastatin 20 mg. Treatment was for 8 weeks or until intolerable muscle symptoms occurred, or symptoms persisted for a week. Crossover occurred after a 4-week washout period. In this population, statin myopathy was confirmed in only 43/110 patients, indicating that for remaining 57% of patients, all symptoms could have been attributable to the drucebo effect (Table 2).

Joy *et al*. analysis

A small series of N-of-1 trials (defined by the authors as single patient, randomized, multiple crossover, blinded comparison of active treatment vs. placebo with eight patients) was

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Table 2 Characteristics of included studies

Reference	[24]	[34]	[32]	[30]	[33]
1st author	Gupta	Joy	Moriarty	Nissen	Taylor
Year of publication	2017	2014	2015	2016	2015
Trial name	ASCOT	NA	Odyssey Alternative	GAUSS-3	NA
Study design	Randomized, double-blind, placebo-controlled trial followed by open-label statin therapy	N-of-1 trial with three double-blind, crossover comparisons separated by 3-week washout periods	Randomized, double-blind, placebo-controlled trial with placebo and statin rechallenge run-in	Two-stage randomized clinical trial. Initial phase used a 24-week crossover procedure with atorvastatin or placebo	Randomized double-blind crossover study of statin and placebo
Participants	10 180	8	361	511	120
Inclusion Criteria.	Men and women aged 40–79 years with >3 risk factors for CVD	Patients aged 18 years or older with prior statin-related myalgia with or without mild elevation of CK levels	Patients aged 18 years or older with moderate to high cardiovascular risk with statin intolerance (unable to tolerate >/=2 statins, including one at the lowest approved starting dose) due to muscle symptoms	Patients aged 18–80 years with uncontrolled low density lipoprotein cholesterol (LDL-C) levels and history of intolerance to two or more statins enrolled	Patients aged 18 years or older with confirmed statin myalgia
Age of participants	36% ≤ 60 years (blinded phase)	66 ± 8	63.4 ± 8.9 (atorvastatin group)	60.7 ± 10.2 (first phase)	58 ± 11 (confirmed myalgia)
Mean ± SD unless otherwise stated	34% ≤ 60 years (blinded phase)			58.8 ± 10.5 (second phase)	61 ± 9 (not confirmed myalgia)
Statin used	Atorvastatin 10 mg daily	Atorvastatin, 10 mg daily, Rosuvastatin, 10 mg weekly Rosuvastatin, 5 mg daily Rosuvastatin, 10 mg daily Rosuvastatin, 20 mg daily Pravastatin, 10 mg daily	Atorvastatin 20 mg daily	Atorvastatin 20 mg daily	Simvastatin 20 mg daily
Endpoints	Annual rate of adjudicated definite or probable muscle adverse effects	Visual analogue score for myalgia, resumption of statin treatment	Incidence of and discontinuation due to skeletal muscle-related adverse events	Incidence of skeletal muscle-related adverse events	Incidence of muscle pain
Frequency of intolerance/severity of SAMS under open-label conditions ($SAMS_{open}$)	HR 1.41 [1.10–1.79] vs. placebo	8 (100%)	63 (100%)	492 (100%)	120 (100%)
Explanation of how the above was calculated	HR reported in paper	Statin discontinuation due to SAMS on open-label therapy was inclusion criterion for the study	Intolerance to at least 2 statins owing to SAMS on open-label therapy was inclusion criterion for the study. 63/361 participants were randomized to statin therapy so are considered.	Intolerance to at least 2 statins owing to SAMS on open-label therapy was inclusion criterion to the first phase of the study	History of SAMS was inclusion criteria of the study

(*Continues*)

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Table 2 (continued)

Reference	[24]	[34]	[32]	[30]	[33]
Frequency of intolerance/severity SAMS under blinded conditions ($SAMS_{blind}$)	HR 1.03 [0.88–1.21]	3 (37.5%)	14 (22%)	209 (42%)	43 (36%)
Explanation of how the above was calculated	HR reported in paper	After randomized protocol of blinded statin and placebo, 3 participants were still unable to tolerate statin therapy	14 patients discontinued statin therapy during blinded phase because of muscle symptoms	209 patients experienced muscle-related adverse effects with atorvastatin but not placebo	43 patients experienced muscle-related adverse effects with simvastatin but not placebo
Calculation of extent of Drucebo effect ($SAMS_{open}$) – ($SAMS_{blind}$)	1.41 – 1.03 = 0.38	100% – 37.5% = 62.5%	100% – 22% = 78%	100% – 42% = 58%	100% – 43% = 57%
Estimation of extent of drucebo effect	38% of SAMS attributable to Drucebo effect	62.5% of statin discontinuation may be attributable to drucebo effect	78% of statin intolerance may be attributable to drucebo effect	58% of intolerable SAMS may be attributable to drucebo effect	57% of incidence of muscle pain may be attributable to drucebo effect

CVD, cardiovascular disease; HR, hazard ratio; NA, not applicable; SAMS, statin-associated muscle symptoms.

Table 3 Cochrane Revised Risk of Bias assessment (RoB 2.0)

Reference	[24]	[34]	[32]	[30]	[33]
1st author	Gupta	Joy	Moriarty	Nissen	Taylor
Year of publication	2017	2014	2015	2016	2015
Bias arising from the randomization process	Low	High	Low	Low	High
Bias due to deviations from intended interventions	Low	Low	Low	Low	Low
Bias due to missing outcome data	Low	Low	Low	Low	Low
Bias in measurement of the outcome	Low	High	Low	Low	Low
Bias in selection of the reported result	Low	Low	Low	Low	Low

conducted to compare the effect of statin rechallenge with placebo in patients with previously reported muscle pain on statin therapy.[33] The study consisted of three double-blind crossover comparisons of the statin, which was previously not tolerated and placebo. The primary outcome was a visual analogue score designed to quantify myalgia. No significant differences in the score were found between placebo and statin treatment phases for any of the patients. Five patients (62.5%) resumed statin treatment (thus, 62.5% of statin discontinuation may be attributable to a drucebo effect). Adherence to the study protocol was extremely high, and the authors propose their method of blinded crossover comparisons as an effective approach to identifying true statin-related myalgia (Table 2).

Conclusions

Statin therapy under blinded and open-label conditions

Our results suggest a substantial increased incidence of statin-related muscle symptoms under open-label therapy than when study participants are blinded to treatment. Indeed, our estimate of the contribution of the drucebo effect to statin-associated muscle pain and statin discontinuation ranged between 38% and 78%. This finding reflects previous observations of low rates of statin-associated myalgia in RCTs.[34] However, in many RCTs (e.g. the Treating to New Targets trial), an open-label run-in phase was used to eliminate patients with SAMS prior to randomization.[35] The wide range of the drucebo effect (38% and 78%) is likely to reflect differences between the clinical trials employed in our analysis. In particular, the characteristics of participants in the trials may affect their susceptibility to the drucebo effect. Differences in study design (in particular duration of

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follow-up) may also contribute to the differences in results. Further studies with both blinded and open-label phases may allow us to refine our analysis; however, it is unlikely that there exists a 'true' value of the drucebo, applicable in all circumstances. Perhaps the most important observation is that even at the lowest estimate (38%), the drucebo effect contributes substantially to statin discontinuation and adverse effects.

Drucebo effect

The difference in myalgia under blinded and open-label conditions corresponds to our definition of a negative drucebo effect. The concept of 'drucebo' effect differs from the 'nocebo' effect in its practicality and in its relation to drugs rather than inert substances. The contribution of the drucebo effect to reported symptom worsening (or improvement) can be estimated in any study with both blinded and open-label phases. In contrast, accurate quantification of the nocebo effect requires a 'no treatment' group, which is very rarely seen in clinical trials of statins. It should be emphasized that although the drucebo effect is relatively easy to measure, it is not a pure measure of the extent to which expectation of symptoms leads to patients experiencing such symptoms—because blinded patients may have expectations about the effect of the formulation they are taking, and they may guess its identity. Furthermore (and particularly in the case of a relatively common symptom such as muscle pain), misattribution of symptoms with other causes (such as physical injury) as adverse drug effects will contribute to the measured drucebo effect. We have studied an example of a 'negative' drucebo effect; however, it is equally possible that a patient's expectation will lead to a beneficial effect (or that a coincidental improvement in symptoms will be incorrectly attributed to the medicine by the patient).

Diagnosis of the drucebo effect and management of cardiovascular risk

The contribution of the drucebo effect to any reported beneficial or adverse effects can be easily calculated from suitably designed trials using the formulae defined in this paper. Our findings suggest that the prevalence of the drucebo effect in the population is high and is responsible for a considerable portion of statin-reported muscle pain and intolerance. However, recognizing the drucebo effect in an individual patient requires clinical skill and discernment. It is important that the drucebo effect is identified, because of its potential to lead to cessation of statin therapy thus placing the patient (especially those classified as high-risk for vascular events) at significantly elevated risk of heart disease, stroke, and death.[11,12] Thus, more widespread understanding of the drucebo effect might indeed help to decrease the risk of discontinuation and better adherence to statin therapy and consequently may lead to a reduction in CVD events.

Identification of the drucebo effect in an individual can be approached largely as a diagnosis of exclusion.

- All other conditions that might increase the risk of statin intolerance should be considered and excluded. These include drug–drug interactions, physical exertions, and hypothyroidism.[19]
- Creatine kinase should be measured, because it is a reliable marker of true SAMS.
- The patient should be assessed using the SAMS-CI Score[8,17] to ascertain the likelihood that the muscle pain is truly statin-related.

Patients at high risk of the drucebo effect are likely to benefit from reassurance from their prescriber and regular follow-up. They may benefit from education about the beneficial effects of statins in reducing CVD events and prolonging life. It is important to understand the 'risk factors', which might predispose to the drucebo effect. Taking into account the data from the included studies, these may include polypharmacy, age, sex, concomitant diseases, although insufficient data exist to address this problem at present.

Use of the drucebo effect in evaluating efficacy and safety of medicines

In clinical trial designs, which allow quantification of the drucebo effect, useful information about the safety and efficacy of the treatment can be elicited by measuring adverse effects under blinded and open-label conditions. If the incidence of adverse effects in the treatment group is greater under open-label conditions than when treatment allocation is blinded (negative drucebo effect), this provides some reassurance that the side effects are not caused by a pharmacological action of the drug. Conversely, when reported benefits are greater under open-label conditions than when treatment allocation is blinded (positive drucebo effect), then caution must be employed in the interpretation of the benefit, and an alternative analysis using hard endpoints should be considered. Many RCTs include placebo run-in periods prior to randomization, and the design of such trials has allowed us to conduct this retrospective analysis. Investigators should consider the drucebo effect when designing studies, which compare a treatment and a placebo, in order to improve our understanding of this effect. If feasible and ethically appropriate, studies should commence with run-in periods, in which placebo and drug are crossed over in a randomized order. Investigators should also consider including a baseline assessment of participant expectations of experiencing adverse events or side effects, which could later be compared with incidence of adverse events during the trial.

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Limitations of the current study

Our findings in this study are based on a relatively small number of papers with a wide variety of designs, study populations, and outcome measures. This heterogeneity led us to decide not to perform a quantitative meta-analysis at the level of the studies. However, were it possible to perform an individual participant data meta-analysis, it would be very informative to stratify the analysis according to the relative potencies of the 'challenge' and 'rechallenge' statins. The analyses of studies we included are generally retrospective and were often not pre-specified in the study protocols.

Some of the data we have discussed is based upon small data sets or is from older studies in which low intensity statin therapy is used, which is thus of limited relevance to current therapeutic approaches. National Institute for Health and Care Excellence recommends atorvastatin 20 mg in primary prevention,[36] whereas only two of the five studies we identified used this dose,[30,31] with most participants of the remaining trials taking lower intensity statin therapy. The external validity of our study may also be reduced by the fact that the studies eligible for inclusion in our analysis generally included young participants (with many in their early 60s), and therefore, the results may be less applicable to older statin-users, who may be at particular risk of adverse effects.

The very nature and design of trials may mean that reporting of symptoms differs from clinical practice. Tobert and Newman, commenting upon the Heart Protection Study (a comparison of placebo vs. simvastatin 40 mg in a mixed high-risk population) emphasized that the incidence of muscle symptoms was very high in both the placebo (33.2%) and simvastatin-treated (32.9%) groups[37] in a middle-aged population of individuals who had been warned about statin-associated muscle injury and were repeatedly questioned about muscle symptoms.[2] This is highly suggestive of a negative drucebo effect—although direct comparison of rates of adverse effects in open-label and blinded phases is not possible in this case. Tobert and Newman also discussed the potential problems of patient unblinding in clinical trials, which is a particular problem in crossover trials, in which patients had access to both the placebo and active dosage form.[2] Furthermore, in studies such as GAUSS-3 and ODYSSEY ALTERNATIVE in which patients were required to demonstrate statin intolerance in a placebo-controlled phase of a study before being considered for a trial of a new therapeutic entity, the temptation for participants to be self-unblinded may be strong.[2]

Our findings assume that the placebo used in the studies was inert. Adverse effect detection was only possible during the time course of follow-up of the individual studies. Our results may be complicated by the incidence of pain of other causes (i.e. neither true statin-induced myalgia nor pure nocebo effect). However, this would only be problematic if such pain occurred at different frequencies in the different experimental groups. Furthermore, misattribution of pain caused by mechanical injury to statin is likely to contribute to the drucebo effect.

We propose that the drucebo effect may prove useful in a wide range of clinical disciplines; however, it is by no means clear that appropriately designed trials have been carried out in other disciplines to allow the quantification of the drucebo effect in other settings.

As standard practice for a systematic review, we evaluated each of the studies according to the Cochrane Risk of Bias tool. However, by necessity, all the studies we included had non-blinded phases. Therefore, it was not possible to use the Cochrane tool as intended. The judgments are based only upon the blinded phase of the trials and thus can only be used to give some indication of the quality of the trial.

Summary and recommendations for research and practice

The collated available evidence is suggestive of the existence of a negative drucebo effect with respect to muscle symptoms on statin therapy.[38] Where it can be accommodated without prejudicing the trial, routine inclusion of unblinded phases of clinical trials may be a useful addition to routine practice in clinical trial design in circumstances in which subjective endpoints are employed. Studies are urgently needed to identify 'risk factors' predisposing to the drucebo effect and to determine the prevalence of the drucebo effect across a range of drugs and therapeutic areas. Recent research has shown that genetic differences between individuals can explain differing responses to placebo (the placebome concept).[39] Extension of this work to drucebo effects could provide insights into the identification and management of the drucebo effect in patients. It is possible that the very extensive negative media attention focused on the adverse effects of statins has resulted in a particularly high prevalence of negative drucebo effects in this setting. Clinicians should be aware of the potential of the drucebo effect to promote treatment discontinuation. Taking into account the best quality clinical evidence individual patient characteristics, clinicians should discuss the true likelihood of adverse effects with patients before commencing treatment.

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The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.[40]

Conflict of interest

Dr Penson owns four shares in Astra Zeneca PLC and has received travel/speaker's fees from Amgen Inc. Dr Banach—speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis and Valeant; consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant. Dr Mikhailidis has given talks and attended conferences sponsored by MSD, AstraZeneca, and Libytec. Dr Toth has previously received consulting fees and/or honoraria from AbbVie, Amarin, Amgen, Gemphire, Kowa, Merck, Regeneron, and Sanofi and payment for lectures from Amarin, Amgen, Kowa, Merck, Regeneron, and Sanofi. Dr Martin reports receiving personal fees for serving on scientific advisory boards for Amgen, Sanofi/Regeneron, Quest Diagnostics, and Akcea Therapeutics, as well as grants and research support from the PJ Schafer Cardiovascular Research Fund, the David and June Trone Family Foundation, American Heart Association, Aetna Foundation, Maryland Innovation Initiative, Nokia, Google, and Apple outside the submitted work; in addition, he reports having patent applications pending. Dr Mancini has received consulting fees and/or honoraria from Astra Zeneca, Amgen, Sanofi, Esperion; grants from Amgen, Sanofi. Dr Sahebkar has no declarations.

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