Penson, PE and Banach, M

Nocebo/drucebo effect in statin-intolerant patients: an attempt at recommendations.

Cardiopulse (Invited Manuscript)

Nocebo/drucebo effect in statin intolerant patients - an attempt at recommendations

Peter E. Penson[1-2*] and Maciej Banach[3,4]

[1]School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [2]Liverpool Centre for Cardiovascular Science, Liverpool, UK. [3] Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland;, [4]Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland.

*Corresponding Author:

Dr P.E. Penson, MPharm, PhD, FHEA, FESC, School of Pharmacy and Biomolecular Sciences

Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

Email: P.Penson@LJMU.AC.UK

Telephone +44 151 231 2071

In the field of cardiovascular disease (CVD) prevention, much recent attention has naturally focused on the remarkable opportunities afforded by novel lipid-lowering drugs, including monoclonal antibody inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9)[1], and inclisiran[2]. Equally important, are efforts to optimise the use of existing therapies. Statins are commonly available, cheap, safe and effective drugs, which reduce the risk of CV events by approximately 25% per year, for each mmol/L reduction in LDL-C[3]. Whilst acknowledging that statins might cause adverse effects (including muscle symptoms, new-onset diabetes, and elevation of liver enzymes) in small numbers of treated individuals, it is increasingly clear that statin therapy is strongly associated with the 'nocebo effect', whereby adverse effects result from the expectation that an inert substance will relieve or cause a particular symptom. In the case of statin therapy, the 'expectation' of harm is fuelled by often hostile and unfounded reports on the internet, social media, and in the lay press[4]. The extent of adverse effects is overestimated owing to the misattribution of unrelated symptoms (such as musculoskeletal injury)[5]. The resultant poor rates of compliance with statin therapy inevitably results in unnecessary cardiovascular events[4].

Whilst it has long been recognised that reported rates of adverse effects of statin therapy are greater in open label than randomised trials (a fact strongly suggestive of the nocebo effect), the absolute proportion of adverse effects caused by nocebo has been hard to quantify[5]. Two recent trials have shed light on the issue (**Table 1**), and important forthcoming guidelines from the International Lipid Expert Panel (ILEP) for the first time aim to offer practical guidelines to help patients and prescribers overcome the nocebo problem.

Both recent studies employed so called 'n-of-one trials' in which each participant is exposed to interventions and comparators in a randomised fashion, effectively serving as their own control. The Self-Assessment Method for Statin Side-effects Or Nocebo (SAMSON) Trial recruited 60 patients who had recently discontinued statin therapy because of side-effects.

Participants had their symptoms measured over a 12-month period during which they randomly alternated between receiving statins, placebo, or no treatment[6]. The reported intensity of symptoms did not differ between the periods of statin use and placebo. However when patients were taking statin or placebo, they reported a greater intensity of symptoms than during the periods of no treatment. Patients were shown their scores at the end of the trial period, and the results were used to inform patient-centered decision making. Six months after the trial was completed, over half of the participants had restarted statin therapy, or planned to do so.

The inclusion of a period without treatment in SAMSON was very important. The term 'nocebo' properly refers to effects elicited by an inert substance (i.e., placebo), and can be problematic when applied to drugs. The magnitude of the nocebo effect can only be properly estimated when a 'no-treatment' group is included in a study – as it was in SAMSON, but this is rare. Therefore, in 2018, ILEP introduced the concept of 'drucebo' (DRUg + noCEBO) to overcome this difficulty, and to allow existing clinical trial data to be used to calculate the proportion of adverse effects attributable to expectation, rather than pharmacological effects[5]. In the case of muscle pain on statin therapy, we found that this proportion may be as high as 78%[5].

A similar study, statinWISE enrolled 200 patients who had stopped, or were considering stopping statin therapy, and randomised them to six two-month periods of atorvastatin 20 mg daily, or placebo. Similarly to SAMSON, there was no difference between the severity of adverse effects on statin therapy or placebo. Two thirds of participants were able to resume statin therapy[7]. The dramatic results of statinWISE and SAMSON demonstrate the importance of identifying and managing the nocebo/drucebo effect to avoid exposing patients to cardiovascular risk by unnecessarily ceasing lipid-lowering therapy. With respect to LDL-C 'lower is better for longer'[8] and periods of non-treatment result in higher LDL-C and greater

risk of cardiovascular events . The forthcoming ILEP guidelines are therefore important and urgently needed.

Whilst the 'n-of-1' approach used in trials provides an extremely useful demonstration of the power of the nocebo/drucebo effect, it may be difficult to implement in the clinical practice. Placebo tablets may not be available, and randomization and blinding may not be practical in routine patient carw. In any event, allocating patients to periods of placebo or no treatment is undesirable as it unnecessarily exposes them to LDL-C and cardiovascular risk.

The forthcoming ILEP recommendations will focus on identifying patients with serious adverse effects, and the use of objective, step by step approaches to identify patients with symptoms likely to result from the nocebo/drucebo effect, in whom we will recommend a range of approaches, including MEDS and SLAP, what was previously briefly presented at European Society of Cardiology (ESC) Congress 2019 as the ILEP guidance on statin intolerance[9].

Briefly, MEDS is a mnemonic encompassing essential considerations in all patients reporting adverse effects with statin therapy: **Minimising disruption** to lipid-lowering therapy – the cornerstone of management of cardiovascular risk. Providing high-quality, accessible, personalised, continuous **Education** relating to the benefits of statin therapy, and an objective assessment of risks. Patients should receive evidence-based advice about **Diet**, lifestyle changes, and nutraceuticals to reduce cardiovascular risk, and careful attention should be made to the intensity of **Symptoms** and biomarkers. SLAP provides a series of interventions, which can be used in patients with partial intolerance, who may be still able to tolerate statin therapy, but not at guideline-recommended doses. These include: **Switch** statins (a patient may have an adverse reaction to a particular drug, or even formulation). **Lower dose** (and add non-statin therapy, e.g., ezetimibe) or **Alternate day dosing,** which may be employed when adverse

effects appear to be dose dependent. However, care should be taken that such approaches do not reinforce the patients view that symptoms are caused by the statin – as they may be employed when symptoms are at their worst, and spontaneous resolution is likely. Finally, **Polypharmacy** (immediate combination lipid lowering therapy or non-statin therapy), using ezetimibe, PCSK9 inhibitors, bempedoic acid, inclisiran, and other evidence-based therapies (including nutraceutical polypills) may be necessary to reach lipid-targets[10].

The abovementioned recommendations of the ILEP experts will be published in the coming months, and we hope that they will benefit physicians and patients alike and improve access to life-saving lipid-lowering therapies.

Declarations of Interest

Dr Penson owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi; Dr Banach - speakers bureau: Amgen, Esperion, Herbapol, Kogen, KRKA, Novartis, Polpharma, Sanofi-Aventis, Servier, Teva, Viatris and Zentiva; consultant to Akcea, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Polfarmex, Sanofi-Aventis; Grants from Amgen, Viatris, Sanofi and Valeant.

REFERENCES:

1. Banach M, Penson PE. What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcome trials: ODYSSEY and FOURIER? Cardiovasc Res 2019;**115**(3):e26-e31.

2. Dyrbus K, Gasior M, Penson P, Ray KK, Banach M. Inclisiran-New hope in the management of lipid disorders? J Clin Lipidol 2020;**14**(1):16-27.

3. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth

L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;**388**(10059):2532-2561.

4. Nissen SE. Statin Denial: An Internet-Driven Cult With Deadly Consequences. Ann Intern Med 2017;**167**(4):281-282.

5. Penson PE, Mancini GBJ, Toth PP, Martin SS, Watts GF, Sahebkar A, Mikhailidis DP, Banach M, Lipid, Blood Pressure Meta-Analysis Collaboration Group, International Lipid Expert Panel. 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. J Cachexia Sarcopenia Muscle 2018;**9**(6):1023-1033.

6. Wood FA, Howard JP, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, Rajkumar CA, Connolly S, Cegla J, Stride C, Sever P, Norton C, Thom SAM, Shun-Shin MJ, Francis DP. N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. N Engl J Med 2020;**383**(22):2182-2184.

7. Herrett E, Williamson E, Brack K, Beaumont D, Perkins A, Thayne A, Shakur-Still H, Roberts I, Prowse D, Goldacre B, van Staa T, MacDonald TM, Armitage J, Wimborne J, Melrose P, Singh J, Brooks L, Moore M, Hoffman M, Smeeth L, Statin WTG. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. BMJ 2021;**372**:n135.

8. Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer-even at low risk. BMC Med 2020;**18**(1):320.

9. Penson P, Toth P, Mikhailidis D, Ezhov M, Fras Z, Mitchenko O, Pella D, Sahebkar A, Rysz J, Reiner Z, Jozwiak J, Mazidi M, Banach M. Step by step diagnosis and management of statin intolerance: position paper from an international lipid expert panel. European Heart Journal 2019;**40**(Supplement_1):P705.

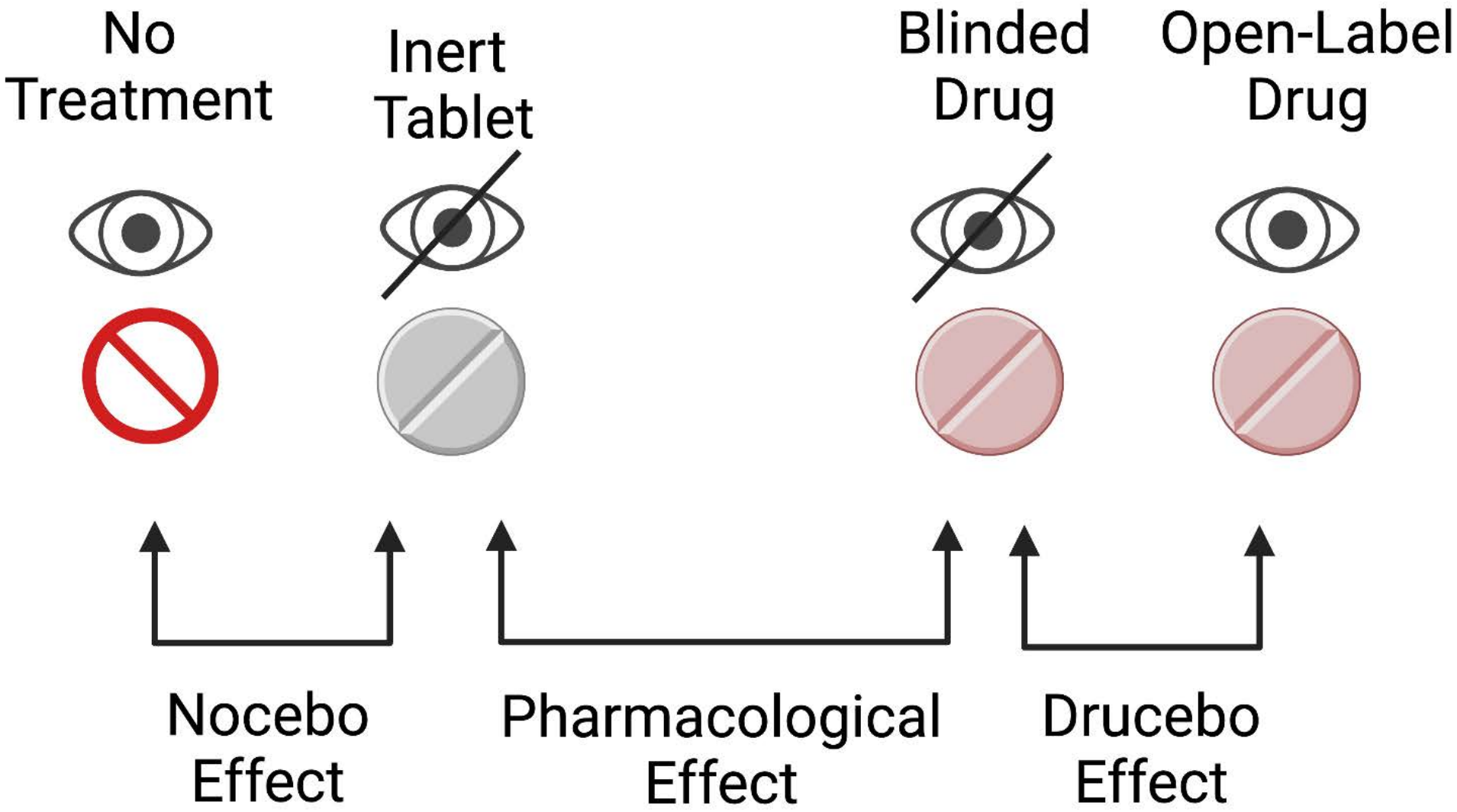
10. Banach M, Penson PE, Vrablik M, Bunc M, Dyrbus K, Fedacko J, Gaita D, Gierlotka M, Jarai Z, Magda SL, Margetic E, Margoczy R, Durak-Nalbantic A, Ostadal P, Pella D, Trbusic M, Udroiu CA, Vlachopoulos C, Vulic D, Fras Z, Dudek D, Reiner Z, Central ACSE, South European Countries P. Optimal use of lipid-lowering therapy after acute coronary syndromes: A Position Paper endorsed by the International Lipid Expert Panel (ILEP). Pharmacol Res 2021;**166**:105499.

Table 1: A summary of major studies investigating the nocebo/drucebo effect with statin therapy. ILEP, International Lipid Expert Panel; LBPMCG, Lipid and Blood Pressure Meta-analysis Collaboration Group; NR, not reported; RCT, randomised controlled trial; SAMS, statin-associated muscle symptoms; SAMSON, Statin Side-effects Or Nocebo Trial.

	Design	**Participants**	**Intervention**	**Comparator**	**Nocebo/Drucebo contribution to SAMS**	**Resumption of therapy**
ILEP & LBPMCG	Meta-analysis	11180	Open-label statin (various)	Blinded statin (various)	Drucebo contributed to between 38% and 78% of muscle pain.	NR
SAMSON	Series of n-of-1 RCTs	60 patients reporting statin side-effects	Atorvastatin 20 mg / day	Placebo and no-treatment	No difference in symptom intensity between statin and placebo.	57% had, or intended to restart statin 6 months after trial
StatinWISE	Series of n-of-1 RCTs	200 with SAMS	Atorvastatin 20 mg / day	Placebo	No difference in symptom intensity between statin and placebo.	66% had or intended to restart statin at trial end.

Figure 1: Nocebo, drucebo, and pharmacological effects explained. The nocebo effect refers to adverse effects experienced when taking an inert substance (i.e. the difference in symptom intensity between no treatment, and an inert tablet), and is analogous to the placebo effect (albeit with adverse rather than desired symptoms). The drucebo effect is

defined as the difference in the frequency or intensity of symptoms between blinded and open-label use of a drug. The difference between symptoms experienced with an inert tablet and an apparently identically drug-containing tablet represents the true pharmacological effect of the drug. Image created using Biorender.com


No Treatment
Inert Tablet
Blinded Drug
Open-Label Drug
Nocebo Effect
Pharmacological Effect
Drucebo Effect