Statins and the gut: separating drug action from drug attribution

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Statins are among the most extensively studied medicines in clinical practice [1]. However, adverse effects can limit the dose that patients are able or willing to take, or lead to discontinuation of treatment, in which circumstances patients may be considered statin intolerant [2]. This creates a familiar challenge in clinical pharmacology: distinguishing an adverse event occurring during treatment from one occurring because of treatment. We introduced the term 'drucebo effect' to describe symptoms experienced during active treatment that result from expectations surrounding treatment rather than its pharmacological action [3]. This distinction subsequently underpinned the patient-centred nocebo/drucebo framework developed by the International Lipid Expert Panel (ILEP) for assessment and management of statin-associated symptoms [4].

Against this background, the drug-target Mendelian randomisation (MR) study by Yang *et al.* raises an intriguing possibility: perturbation of lipid-lowering drug targets may influence gastrointestinal disease, sometimes in directions apparently inconsistent with adverse effects attributed to these medicines [5].

Importantly, the investigators considered several lipid-lowering targets rather than HMGCR alone. Genetic proxies for HMGCR, PCSK9, NPC1L1 and PPARG produced different patterns of association across gastrointestinal outcomes [5]. The most striking findings involved HMGCR, with genetically proxied inhibition associated with lower risks of functional constipation, functional dyspepsia, nausea and vomiting, and disorders of the gallbladder, biliary tract and pancreas, but a negligible effect for functional abdominal pain [5]. The absence of a consistent pattern across targets potentially argues against a simple LDL-C-mediated explanation, although differences in instrument strength, statistical power and pleiotropy provide alternative explanations.

The investigators also explored potential mediators of the HMGCR associations and identified the GWAS phenotype "mood swings" as a possible mediator of the associations with functional dyspepsia and gallbladder, biliary and pancreatic disorders [5]. This led the authors to propose a possible role for the gut-brain axis. Although intriguing, the mediated proportions were small and this mechanistic interpretation requires caution.

From genetic targets to medicines

The heterogeneity between targets highlights an important limitation of translating drug-target MR directly into clinical pharmacology. A genetic proxy for lifelong perturbation of HMGCR is not equivalent to

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taking a statin, just as genetically proxied PCSK9 inhibition is not equivalent to receiving a PCSK9 monoclonal antibody.

The intestine may be particularly relevant to this distinction. Although statin pharmacology is generally viewed through its hepatic effects, HMGCR is biologically active within intestinal epithelial cells [6]. Orally administered statins encounter the intestinal lumen and enterocytes before portal and systemic circulation, while intestinal transport contributes substantially to the disposition of several statins [6, 7]. These observations make local effects biologically plausible, although they do not establish that intestinal exposure during conventional treatment produces clinically important local HMGCR inhibition.

Comparison with other lipid-lowering therapies is illuminating. Ezetimibe is orally administered and intestinal pharmacology is integral to its therapeutic action: inhibition of NPC1L1 at the intestinal brush border reduces cholesterol absorption [8]. By contrast, monoclonal antibody PCSK9 inhibitors such as evolocumab and alirocumab are administered parenterally and inhibit circulating PCSK9, thereby reducing LDL-receptor degradation and increasing hepatic LDL clearance [8]. They therefore avoid the direct luminal drug exposure inherent to orally administered therapies. Thus, genetic associations involving HMGCR, NPC1L1 and PCSK9 cannot automatically be assumed to predict equivalent gastrointestinal effects of the corresponding medicines.

Bempedoic acid provides another useful comparator, although ACLY was not examined in the present study. Bempedoic acid is administered orally but requires conversion to its active CoA derivative before inhibiting ATP-citrate lyase, with its pharmacology favouring hepatic rather than extrahepatic inhibition of cholesterol synthesis [9]. Gastrointestinal exposure to the prodrug should therefore not be equated with local inhibition of cholesterol synthesis. Equally, exposure of gastrointestinal tissues to inactivated bempedoic acid could conceivably produce other biological effects, so absence of local ACLY inhibition should not be assumed to mean absence of intestinal pharmacology [9].

The broader principle is important: genetic target perturbation, drug exposure and tissue-specific target engagement are not interchangeable concepts.

Gastrointestinal symptoms and the drucebo effect

The genetic findings become particularly interesting when considered alongside gastrointestinal symptoms attributed to statins. Dyspepsia, constipation, abdominal discomfort and nausea are common in the general population, while observational analyses have not consistently demonstrated increased gastrointestinal risk with statin use [10]. More recently, large placebo-controlled trials have provided little support for many adverse effects historically attributed to statins [11].

This discordance is familiar from statin-associated muscle symptoms. Our original analysis estimated a substantial contribution of the drucebo effect to symptoms attributed to statins under unblinded conditions [3], while the subsequent ILEP position paper emphasised a patient-centred approach to recognising and managing such symptoms [4].

The distinction is important. Drucebo does not imply that a patient's symptom is imaginary; it concerns causation, not the reality of the symptom.

Evidence for the drucebo effect relates predominantly to muscle symptoms and should not simply be extrapolated to gastrointestinal intolerance. Nevertheless, gastrointestinal symptoms provide an attractive setting in which to test the concept. They are common, multifactorial and fluctuate over time. The temporal sequence "statin started, symptom appeared" cannot therefore establish pharmacological causality.

The present genetic findings make this distinction particularly provocative. If HMGCR inhibition genuinely reduces susceptibility to some gastrointestinal phenotypes, a patient might develop gastrointestinal symptoms while taking a statin despite, rather than because of, the biological effects of HMGCR inhibition.

Mood, mediation and mechanism

The proposed mediation through "mood swings" warrants particular caution. The phenotype accounted for only 6.23% of the estimated association between HMGCR and functional dyspepsia and 2.62% of that with gallbladder, biliary and pancreatic disorders [5]. Thus, even if the mediation estimates are taken at face value, the great majority of these associations remains unexplained.

Moreover, "mood swings" is a broad GWAS phenotype rather than a specific psychiatric diagnosis or clearly defined neurobiological pathway. There is evidence for bidirectional relationships between psychological factors and disorders of gut-brain interaction [12], but this does not establish mood as the mechanism connecting HMGCR perturbation with the gastrointestinal findings. The mediation results are therefore better regarded as hypothesis-generating than as evidence for an established gut-brain mechanism.

Psychological factors could nevertheless be highly relevant, but in a different way. Rather than assuming:

- HMGCR inhibition → mood → gastrointestinal disease

- it may be useful to distinguish two potentially independent pathways:
- HMGCR inhibition → tissue-specific biological effects → gastrointestinal physiology
  and
  Expectation → symptom perception and reporting → attribution to treatment.

Mood and treatment expectations might therefore influence how gastrointestinal symptoms are experienced, reported and attributed to a statin without necessarily mediating the biological consequences of HMGCR inhibition. This interpretation connects the observations of Yang *et al.* [5] with the nocebo/drucebo framework [3, 4], while avoiding the assumption that evidence derived from statin-associated muscle symptoms can simply be extrapolated to gastrointestinal symptoms.

Conclusions

These findings do not yet justify repurposing statins for functional gastrointestinal disorders. Instead, they raise testable questions. Do therapeutic statin doses meaningfully inhibit HMGCR within intestinal tissues? Do gastrointestinal effects differ among statins according to absorption, transport and metabolism? Are effects upon the microbiome important [13]? And, crucially, are gastrointestinal symptoms attributed to statins more frequent during blinded statin exposure than during placebo or untreated periods?

Addressing these questions will require integration of genetics with pharmacokinetics, tissue biology and appropriately blinded clinical studies. The underlying distinction is fundamental: genetic target perturbation, drug exposure, pharmacological action, symptom experience and symptom attribution describe different phenomena. Understanding how these intersect may ultimately tell us as much about drug intolerance as it does about the gastrointestinal pharmacology of lipid-lowering therapy.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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