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STATIN DRUGS (R. CESKA, SECTION EDITOR)

# Statins in a Distorted Mirror of Media

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**Abstract**

**Purpose of Review** Statins have proven efficacy with a favorable safety profile yet, despite being widely affordable, remain profoundly underutilized. Statins have acquired a bad reputation, which is likely contributing to high rates of nonadherence and discontinuation. The degree to which negative media perceptions contribute to underutilization is unclear.

**Recent Findings** The media has a key role in informing discussion on the public agenda but also on how issues are framed. In this context, the majority of studies evaluating news coverage suggest that the content on statins is predominantly negative and focused on potential harm. Studies utilizing quasi-experimental and interrupted time series design have shown periods of negative news stories on statins in multiple countries are associated with (a) less statin commencement in eligible patients, (b) high rates of discontinuation, and (c) poor long-term adherence.

**Summary** This review highlights the deleterious impact of negative media coverage on statin utilization through misattribution of muscle complaints and the nocebo effect. Academia must work with the media to harmonize the public health messaging; however, individual physicians have a critical role in mitigating a harmful narrative of misinformation and actively discredit malinformation.

**Keywords** Statins · Statin intolerance · Media · Misinformation

## Introduction

A wealth of evidence from randomized clinical trials has shown that statins reduce the incidence of major vascular events across a continuum of risk [1–4]. Meta-analyses of these data also demonstrate that statins have a favorable safety profile with reports of severe adverse events occurring in very few individuals [5]. Yet despite their position as the cornerstone of preventative cardiology, statins are profoundly underutilized with as few as 50% of eligible individuals receiving them in the USA [6]. In an environment where population-level cardiovascular outcomes appear to be deteriorating [7], such forfeiture of valuable risk reduction represents a failure of scientific translation. But why is a therapy, which costs less than $1 per day, has a proven mortality benefit and a reassuring safety profile, so frequently declined or discontinued by patients? The answer is that statins have developed a bad reputation with the public, a problem we all must address.

## The Beginnings of a Bad Reputation

Key events in the statin story can be told in halves: the first half resulting in a product removal and the second half marked by expansion of eligibility. Despite a protracted preclinical development phase of the first HMG-CoA reductase inhibitor (compactin) in the 1970s, lovastatin's initial compassionate access use in young patients with familial hypercholesterolemia quickly translated to mainstream regulatory approval in the late 1980s. At a time when the "cholesterol hypothesis" was yet to receive widespread endorsement, successive reporting of positive outcome trials in the 1990s not only established the efficacy of statins but also affirmed the role of LDL-cholesterol in the atherosclerotic causal pathway [8].

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While there had been isolated reports of toxicity, particularly in the setting of predictable CYP3A4 enzymatic-based medication interactions, there had been little mention in the literature of systematic safety or tolerability concerns until cerivastatin was removed from the market in 2001 [9]. Undoubtedly, this raised the specter of statin safety among clinicians and patients alike. Although the rates were significantly less than 0.01%, rhabdomyolysis was prominently listed on FDA labels and patient information sheets of all statin medications.

With an abundance of caution, patients were counseled to report muscle aches as a potential early warning sign of rhabdomyolysis and to seek medical attention. Insidiously, muscle aches became conflated with myopathy and rhabdomyolysis on a spectrum of pathological, statin-related myopathic adverse drug reactions. Armed with the information about the potential for muscle aches, patients would be prescribed a statin and frequently return with muscle symptoms. The statin would be ceased and the symptoms would eventually abate not only reinforcing the patient's misled belief of causation, but the notion of intolerance had been enabled and promoted. Statins were now considered potentially dangerous.

The second half of the statin story is marked by expansion of eligibility. Following evidence of consistent relative risk reductions, patients at sufficiently high absolute risk of developing incident cardiovascular disease were progressively included in professional society guidelines for statin eligibility. The extension of recommendations to another 20–30% of the population was viewed by some as over-medicalization of "healthy" people and by others as an attempt by the pharmaceutical industry to sell more drug. What was intended as guidance for shared decision making around intended benefit and risk reduction therapy had given way to a dichotomous narrative that statins were bad (or good) and that the pharmaceutical industry was evil.

## The Media and the Motive: Sympathy and Similarities with Academia

As alluded to, the lay public are often exposed to two dangerously unbalanced claims: firstly, that statins are associated with intolerable and irreversible side effects such as muscle aches and dementia [10]; and secondly, that statin therapy is pushed by drug companies onto patients and the community [11]. Neither of these assertions had an evidence base, yet they are repetitively promulgated across both organized and social media, as well as through websites proclaiming to be health-focused. These stories gain attention and traction as they represent a departure from the prevailing scientific narrative. A medication that has been used for over 30 years by millions of people, which no longer profits any company and is considered to be one of the critical breakthroughs to lower population-level cardiac mortality, does not generate "news" interest unless it is a contrary view. Even more problematic is that there has been essentially no new efficacy data for statins in years. Yet there continued to be reports in the media that stimulated concern. It would be unfair, and incorrect, to condemn all media and journalists since there certainly are well-researched, informed, and balanced contributors [12–14]; however, they were drowned out by commentators that are frequently sensationalized [15], leverage n-of-1 experiences [16], and present emotive and polarizing perspectives without a balanced counterpoint [17].

But why? In some respects, the media industry is under similar pressures to academia. The media and journalists, like academia and scientists, share some common performance indicators; they are both inexorably subject to an external assessment of their "impact" as a measure of their respective worth. Scientists have citations; journalists have readers; academic journals have subscribers and advertising space, so too the media; scientists have grantors and institutions, and journalists have managers and employers. Some of the "tools of the trade" are also shared; scientists include "spin" in their manuscripts and grant proposals to exaggerate the importance of their findings [18]. Journalists leverage controversial or contrarian views to produce alarmist stories, which attract readers and sell papers or subscriptions—"if it bleeds it leads" [19]. The industrial pressures are also comparable; there is less funding, diminishing jobs, and greater expectations in fewer hours' work. But for all of the similarities, there are critical differences that contribute to a tension between the academic and media industries.

While a scientific publication endures laborious peer review and revision (as imperfect a process as it is) prior to consumption by a subscribed and intended audience, an article from the media may be put through editorial channels but is ultimately disseminated to a broader and less defined readership. The impact of the message is not only rapid but also vast and reaches an audience with highly heterogeneous health literacy. Although material that goes directly to patients in clinical research is closely written and approved for readability by ethics committees and patient representatives to ensure baseline comprehension across a range of education levels, can the same be said for media articles that also directly touch the patient? Covering areas where there is genuine scientific uncertainty is even more fraught with danger, particularly given the context that individuals in the community have a unique set of medical characteristics and medication history. Providing a nuanced view that successfully conveys population-level benefit and risk information and how that relates to an individual is challenging even in a 1-on-1 setting, let alone in a coarse public communication. More broadly, inflammatory or incorrect views may be subsequently countered in letters or through follow up media

coverage, yet the first message may be the indelible one. So how much does a news story change statin-related behaviors?

## How Much Influence Does the Media Really Have?

A decision to commence treatment with a statin is a discrete event that occurs within a clinician-patient therapeutic partnership. However, the treatment is lifelong and the willingness to continue is subject to constant reevaluation, which occurs outside a clinic room and under external influence. Friends and family are often referred to for guidance and counsel around health-related decision making, but there has long been recognition that the media plays a critical role in shaping health perceptions and choices. Not only is the media responsible for setting an agenda (health and other areas) but the manner in which this content is framed and reported also influences the way individuals think and talk about these issues [20].

Identifying cause and effect relationships between media content and health-related behavior is challenging; however, there are examples. For instance, in the psychiatric literature, there are multiple case series that clearly demonstrate the links between media coverage of high-profile suicide and subsequent spikes in the rates of community suicide [21–23]. Other studies including a Cochrane review in this area [24] have focused on the effect of the media messaging and its capacity to stimulate population health screening participation. However, the direct impact of media coverage on medication perceptions and behavior is less well described but does include case studies involving antidepressants [25] and thyroxine formulations [26].

Two large studies have employed interrupted time series or quasi-experimental design to study the effect of protracted or negative news coverage on various behaviors around statin therapy. Following an intense period of media interest in a study published in the BMJ in 2013, which reported high rates of side effects in a non-blinded study [27], Matthews et al. attempted to analyze its impact on statin initiation and discontinuation in the period that followed [28••]. Matthews et al. defined a period of exposure based on the appearance of multiple media articles and the heightened presence of "statin risk" in Google search trends from October 2013 to March 2014. Using a general practice database, participants who were newly eligible for ($n = 99{,}002$) or currently taking statins for primary and secondary cardiovascular disease prevention ($n = 687{,}683$) were identified between 2011 and 2015. Odds ratios for statin initiation and cessation in the postexposure period were calculated based on preexposure trends. Changes in statin initiation were not detected; however, the rates of discontinuation post media exposure were significantly higher in both primary (OR 1.11, 95%CI 1.05–1.18) and secondary prevention (OR 1.12, 95%CI 1.04–1.21) patients. In stratified post hoc analyses, these rates were significantly higher for older patients and those who had been on statin therapy the longest. Although this does not provide causal evidence, the supportive negative control and sensitivity analysis does increase the rigor of the findings.

In Denmark, Nielsen et al. followed a cohort of 674,000 patients who initiated statin therapy from 1995 to 2010 and calculated the proportion that had discontinued by December 2011 [29••]. Using a news media database, the authors identified 1931 news stories that were published over that time frame and after reviewing each one, adjudged the stories to be negative, positive, or neutral with respect to statins. For each participant in the sample, a weighted sum of exposure to each of the negative news stories was calculated (based on expected readership, geography of patient) over a 6-month period following their first prescription—the same was done for neutral and positive news stories, thereby generating three covariates for news story exposure. In multivariable modeling, negative news story exposure was independently associated with increased odds of discontinuation, OR 1.09 (95%CI 1.06–1.12), while there was no impact of neutral news story exposure, OR 0.98 (0.96–1.01). Saliently, exposure to positive news stories about statins was associated with less likelihood of discontinuation, OR 0.92 (0.90–0.94), supporting not only the hypothesis that it is the narrative within the story that mediates behavioral change rather than just the media coverage per se but also that the media therefore could be considered an instrument of public health.

Other smaller studies have evaluated more discrete news events—isolated stories or a handful of stories—and shown negative statin coverage to result in greater rates of discontinuation or potential for discontinuation. In Australia, following a controversial segment in the TV program "Catalyst," which espoused a generally negative view of statin therapy, there was a 28.8% (95%CI 15.4–43.7%) increase in statin discontinuation the week it was aired (with 9% decay per week thereafter) [30]. Furthermore there was a 2.6% reduction in statin dispensing despite there being no effect on proton-pump inhibitors as a control comparator. Similar findings were reported in a smaller Danish study, which found higher rates of statin discontinuation, which was not observed for anti-hypertensives following an intense period of predominantly negative media coverage in 2007 [31]. Another smaller study in France suggested that patients exposed to a period of negative messaging in the news-media may have greater likelihood of statin cessation but lacked a control group or a sophisticated interrupted time-series analysis [32].

Again, while none of these studies can infer causality, it does pose the question that if the nature of a news story can positively and negatively impact health behaviors, why then should it not be subject to the same rigor (and consequences)

as organized public health messaging? And importantly, why are clinicians not more involved in driving this narrative?

## The Media: Part of a Milieu of (Mis) Information

While these interrupted time series studies provide some sense of temporal consequence from negative news stories, it is quite likely the magnitude of negative perception is cumulative, more insidious, and less attributable to isolated stories or events. When one considers that news stories about statins are almost twice as likely to be negative than positive [33], it is conceivable that the totality of the lay public's perception over time is going to be negative. However, a media story may only be the beginning—it is likely that the subsequent search for further information is likely to affirm these negative beliefs via less reputable sources. In a study of 250 patients on, or eligible for, statin therapy, almost half (45%) reported being informed of risks through a non-physician source with television, family members, and the internet being the most common [34]. In surveying these patients who seek non-physician information (vs. physician information), respondents were more likely to overestimate their risk of liver damage from statins and underestimate their benefit in reducing heart disease. Of all the candidate sources of information, the internet and social media are the least regulated yet used by a growing majority across multiple age demographics. Coarse evaluation of the material available through a Google search on statins reveals that content on risk dominates; a search on "statin risk" reveals 6,390,000 hits where a search on "statin benefit" reveals 5,530,000 hits. Furthermore, simply typing "statins" into Google provides a number of other "relevant" search items of which 50% are related to risk and none are related to benefits (Table 1). While information concerning medication-related risks is important, in comparison with other cardiac and non-cardiac medications, it is dramatically overrepresented in suggested searches for statins (Table 1). Of concern, while information on "statin benefits" appears to be accessed at a relatively consistent rate per Google search trends, interest in risk-focused statin material appears to be increasing despite there being no additional data to support a change in the risk of statin therapy (Fig. 1). A recent analysis by Khan et al. went one step further and showed the proportion of websites accessible from Google on statin side effects correlated with the national rates of statin intolerance ($R = 0.868$, $p = 0.0001$) [35•]. While these are coarse data, it remains consistent that the volume of amplified risk-focused material is likely to be an important contributor to a vicious cycle of misattribution, misinformation, and the ultimately, the nocebo effect.

## Misattribution, Misinformation, and the Nocebo Effect

Statins are not free of adverse effects—major increases in liver enzymes, new-onset diabetes, and rhabdomyolysis all occur at a cumulative rate of < 0.1%/year [36]. Despite these side effects, the most common cause of declining a recommended statin or discontinuing a prescription for one is muscle aches [37]. Current estimates suggest that as many as 20% of patients ultimately discontinue or become non-adherent due to muscle-related complaints making statin intolerance a massive problem in clinical cardiology [38]. Randomized clinical trials clearly show that muscle aches are common with almost one third of participants reporting the symptom at some time during follow up [3]. Critically, however, meta-analysis of these data reveal the incidence of muscle aches to be the same in patients receiving statins compared with those receiving placebo [5, 39, 40]. It is therefore entirely reasonable that a significant proportion of statin-eligible individuals over the course of a 3–5 year period (duration of most statin trials) will develop muscle aches and incorrectly attribute these background symptoms to their statin. If incorrectly counseled, as mentioned earlier, patients will draw causal links and develop fear of potential harmful sequelae despite the vast majority having no detectable CK rise or muscle weakness.

While the misattribution is a significant issue, the exaggerated prevalence of muscle aches appears to be largely the result of a somewhat linked nocebo effect. The nocebo effect describes the phenomenon whereby adverse outcomes or symptoms are generated or amplified in the presence of negative expectations. Nocebo effects (and their inverse, placebo effects) have been elegantly demonstrated in the field of pain medicine where a negative expectation of an investigational analgesic compound almost entirely eliminates its analgesic effects [41]. Similar nocebo responses are observed with side effects; when patients are forewarned of their potential development, they are subsequently more likely to report their occurrence. In a study involving the administration of beta blockers, patients warned of the potential to develop erectile dysfunction as a side effect were 10-fold more likely to report the complication than those who were not specifically informed [42].

The narrative that is promulgated by the media and other sources of risk-focused information is likely to drive the nocebo effect in statins, as it has done with vaccination [43]. Presented with an overwhelming message of side effects and reinforced by bold package inserts, patients expect and are then more likely to report or misattribute these symptoms. Several lines of evidence support the existence of a nocebo effect in the reporting of statin-associated muscle aches. In the largest statin-intolerance trial, GAUSS-3, participants were randomized to low dose atorvastatin or placebo for 10 weeks [44]. Following a 2-

**Table 1** Google search terms for medications (top row) with subsequent "suggested relevant searches" auto-populated below. Italicized items represent risk-focused information, which is overrepresented in "statin" Google search suggestions

| Search terms | | | | | | | |
|---|---|---|---|---|---|---|---|
| statins | beta blockers | ACE inhibitors | aspirin | ezetimibe | PSCK9 inhibitor | SSRI | opioids |
| *statins and leg pain* | beta blockers and statins | ACE inhibitors and statins | aspirin and statins | ezetimibe vs statins | PSCK9 inhibitor drugs | SSRI list | *opioid overdose* |
| statins and grapefruit | beta blockers list | ACE inhibitors and diabetes | aspirin uses | ezetimibe and statins | PSCK9 inhibitor vs statins | SSRI drugs | opioid vs opiate |
| statins list | beta blockers names | ACE inhibitors vs. statins | aspirin melting point | ezetimibe class | PSCK9 inhibitor cost | *SSRI side effects* | opioid risk tool |
| *statins and dementia* | beta blockers for blood pressure | *ACE inhibitors side effects* | *aspirin side effects* | ezetimibe cost | *PSCK9 inhibitors side effects* | SSRI vs. SNRI | opioid drugs |
| *statins side effects* | *beta blockers side effects* | ACE inhibitors potassium | aspirin dosage | ezetimibe dose | PSCK9 inhibitor list | SSRI withdrawal | opioid receptors |
| *statins and constipation* | beta blockers and asthma | ACE inhibitors MOA | aspirin MOA | *ezetimibe side effects* | PSCK9 inhibitor MOA | SSRI meds | opioid meaning |
| *statins and memory loss* | beta blockers for anxiety | ACE inhibitors meds | aspirin and statins together | ezetimibe MOA | PSCK9 inhibitor mechanism | SSRI and alcohol | *opioid crisis* |
| statins examples | beta blockers examples | ACE inhibitors vs. ARBs | aspirin trials | ezetimibe uses | PSCK9 inhibitor names | SSRI meaning | *opioid addiction* |
| statins for stroke | beta blockers vs statins | ACE inhibitors action | aspirin drug class | ezetimibe 10 mg | PSCK9 inhibitor wiki | SSRI for anxiety | *opioid epidemic* |

week washout period, participants were then crossed over to the other treatment arm for a further 10 weeks. The rates of intolerable muscle symptoms were compared in each participant and across treatment groups. In total, 27.1% of participants reported symptoms on both treatments or on neither treatment; 42.6% reported symptoms on statin but not placebo and 26.5% on placebo but not atorvastatin. The summary therefore being that despite all 491 participants on trial entry having a label of "statin intolerance", only 16% of patients developed symptoms that were actually attributable to the statin.

In an elegant post hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial, Gupta et al. compared the rates of muscle aches during different phases of the Lipid-Lowering Arm [45]. During the blinded phase, 10,180 patients were randomized 1:1 to atorvastatin 10 mg or placebo for a median follow-up of 3.3 years, and during the subsequent non-blinded, nonrandomized phase, 9899 patients were evaluated for a further median of 2.3 years. While the rates of muscle aches were similar between groups in the blinded phase (HR 1.03 [95%CI 0.88–1.21]), as observed in prior blinded RCTs, the rates were far higher in the atorvastatin arm of the non-blinded phase (HR 1.41 [95%CI 1.10–1.79]). These results support the widely held view that observational studies that report statin side effects are likely to be greatly exaggerated through ascertainment bias and nocebo effect; the magnitude of which may be even greater than observed in this study when one considers it was performed in 2005, predating a large volume of negative statin-related media.

## Physicians Have a Role to Play

Physicians have a critical role to play in the cycle of health-related information access, not only through curating and disseminating reliable content but also by opening up communication channels with patients to address misinformation. It is clear that patients of today wish, and are able, to access a vast array of information with up to 70% going online to a forum or a health related website within a week of an outpatient appointment [46] and over 50% after an admission for an acute coronary syndrome [47]. Of concern, as few as a third of patients who seek additional information ultimately discuss this content, thereby leaving the majority of patients at risk of remaining ill-informed. Clearly, the manner in which physicians are handling this discussion needs attention as the literature suggests that patients who do raise content from other sources during a consultation frequently feel dismissed or patronized [48] and leave these encounters feeling disempowered [49]. Rather than dismissing the fact that

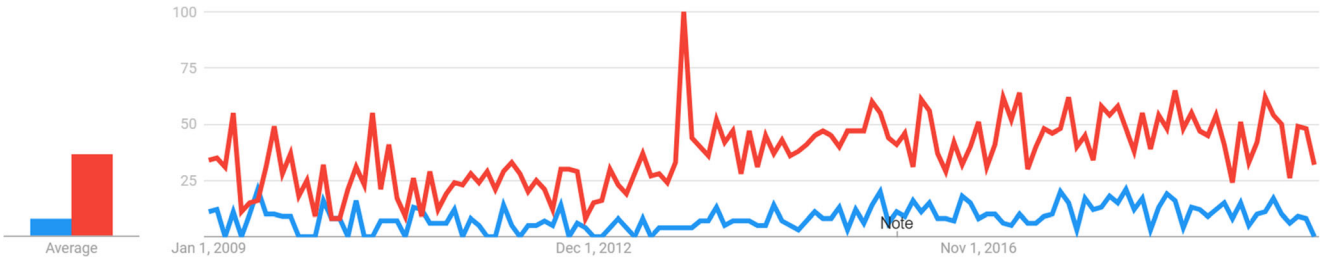


**Fig. 1** Google trend interest analysis for "statin benefit" (blue) compared with "statin risk" (red). Numbers represent search interest relative to the highest point on the chart for global searches with a value of 100 representing the peak popularity for the term

these sources exist, or worse—shooting the messenger (the patient), clinicians instead should be proactive at directing patients to reputable sources and when misinformation has been acquired, time must be invested in providing a balanced and individualized view of the data for that patient. It will not be easy, however, as beyond misinformation, there are radical minorities that are promoting malinformation through cult-like messaging of "statin denial" and fear [50]; in an era of digital and social media, these individuals now have a soap box and a megaphone to amplify their echo chambers. Interrupting the cycle and changing the narrative is critical, and while it is easier to prevent in the first place [51, 52], it can be achieved [53].

## Conclusion

Statins have proven efficacy and, despite being highly affordable, remain profoundly underutilized. The widespread claims of side effects that are amplified and promulgated by the media have been consistently associated with a deleterious impact on statin utilization across the world. While academia must strive to work with the media to harmonize the public health messaging, individual physicians have a critical role to play in mitigating misinformation and proactively interrupting its effects on the vicious cycle of misattributed side effects and the nocebo effect (Fig. 2).

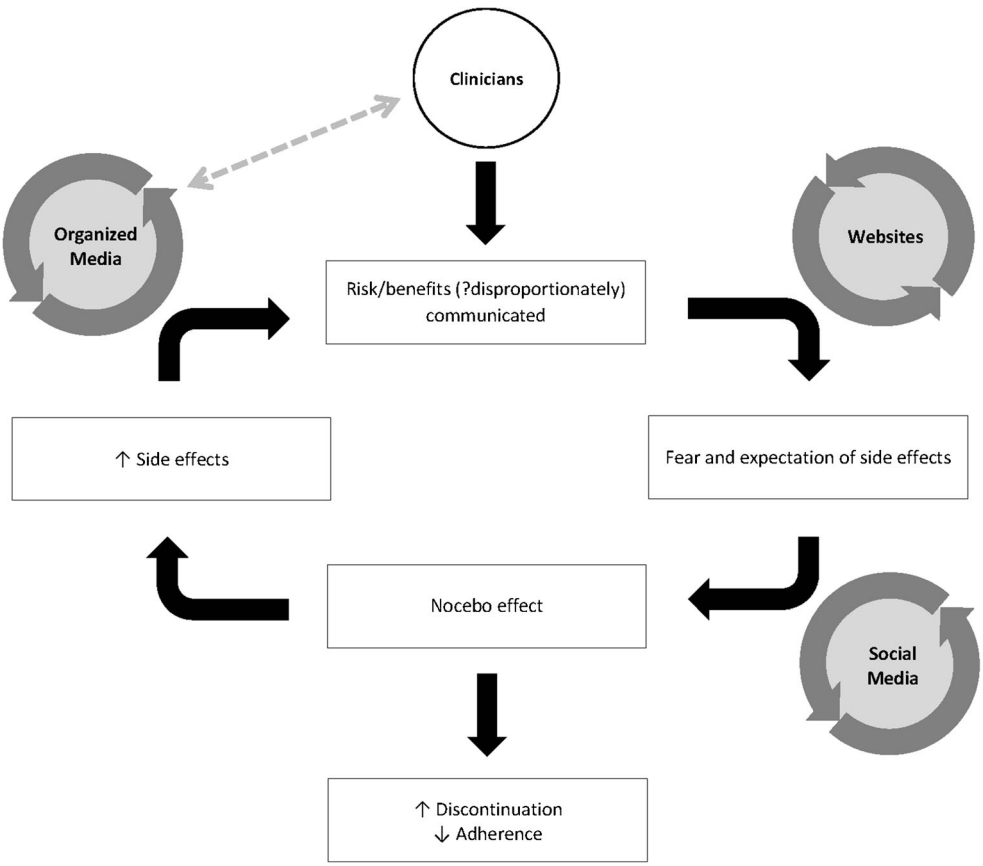


**Fig. 2** Flow diagram representing the vicious cycle of statin misinformation. Risks of statins are overemphasized and amplified by the media such that patients already have a preconceived notion or fear of statins when statins are proposed by an otherwise passive clinician. Patients take the prescription and seek out further information on websites, which are more likely to promulgate a narrative of fear and risk rather than benefit, thereby perpetuating a negative expectation of statin therapy. Patients develop symptoms that are misattributed to the "new" statin, which lead to a false belief of causation and ultimately nonadherence and discontinuation. Patients report the side effects that are falsely misrepresented in non-blinded observational analyses and subsequent media, which positively reinforces a message of harm and restarts the misinformation cycle

## Compliance with Ethical Standards

**Conflict of Interest** A.J.N. has no relationships to disclose.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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