Does Googling lead to statin intolerance?☆

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1. Introduction

For patients with dyslipidemia, statins are widely known to be beneficial for both primary and secondary prevention of major vascular events, including myocardial infarction, ischemic stroke and cardiovascular mortality [1–4]. Most patients tolerate these medications well, and in randomized controlled trials their adverse effect profile is noted to be minimal and not significantly worse than placebo [1]. However, in observational studies, greater numbers of patients experience statin-associated adverse effects [5,6]. A psychological phenomenon, known as the nocebo effect, is thought to explain the conflicting data on the prevalence of adverse effects between blinded randomized trials and non-blinded observational studies [5]. The nocebo effect, which is the opposite of the placebo effect, occurs when individuals with a preconceived negative expectation for an intervention report harm at a higher rate than anticipated [7]. For example, individuals who have read about muscle adverse effects related to statins may be more likely to notice and therefore attribute any muscle pain to their prescribed statin, compared to patients who have not. The investigators of a large statin outcomes trial recently reported that although muscle-related adverse effects did not differ between randomized groups during the initial blinded trial, patients taking statins in the open label extension phase of the study had a much higher rate of adverse effects [8]. Information in the media about harms or adverse effects can precipitate the nocebo effect [9]. Inaccurate information on the internet may contribute to the nocebo effect for statins in particular [10]. It has been suggested that local media and internet information may contribute to variation in the nocebo effect for statins in different countries and cultures [5]. Our study examines whether the number of websites about the adverse effects of statins found when searching the internet is associated with the prevalence of statin intolerance.

2. Methods

The prevalence of statin intolerance in 13 countries across 5 continents (Australia, Brazil, Canada, France, Germany, Italy, Japan, the Netherlands, Poland, Spain, Sweden, the United Kingdom and the United States) was established by Hovingh et al. [11] Prevalence was ascertained via a web-based survey of 810 primary care physicians and specialists, who were asked what proportion of their patients

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were intolerant to statins. The survey was administered in the physicians’ native languages, and had a response rate of 53% of eligible participants. The planned sample size was achieved in all countries except Australia.

To determine how much online information about the adverse effects of statins a patient in each country would be exposed to, we determined the number of websites found when using the Google search engine of each of the 13 countries (Table 1) to search for “statin” or “statins”, and “side effects”. To account for the overall number of websites about statins available in each country, we divided this number by the number of websites found when searching only for “statin” or “statins”. This ratio is the “standardized number of websites about statin side effects.” For non-English-speaking countries, native-language translations were used for all search terms and searches were restricted to pages in the native language. Translations were provided by professional translators for each language through the translation service at the University Health Network, Toronto (Table 1). Google is offered in more than one native language in Canada, the Netherlands and Spain; we considered English, Dutch and Spanish as the native languages of those countries, respectively. All website searches were performed using the Chrome browser in incognito mode, to ensure that each search was independent of prior searches and not personalized. IronSocket (https://ironsocket.com) was used to connect through a virtual private network to each country to perform the searches. Website searches were conducted on April 24, 2017.

We then determined the sample Pearson correlation coefficient (r) between the prevalence of statin intolerance and the standardized number of websites about statin side effects, using SAS Enterprise Guide version 6.1 (Cary, NC).

3. Results

Fig. 1 and Supplementary Table 1 illustrate the correlation between the prevalence of statin intolerance and the standardized number of websites about statin side effects for each of the 13 countries. English-speaking countries (Canada, UK, USA and Australia) had the largest number of websites about side effects. Once standardized to the overall number of websites about statins in each country, these countries had 5 times the number of websites about side effects of Poland and 4 times that of Brazil. These countries also had the highest prevalence of statin intolerance [11]. The r between these two variables was 0.868, p = 0.0001.

4. Discussion

There is wide international variation in both the consumption of statins [12], and in the prevalence of statin intolerance [11]. This study showed that the prevalence of statin intolerance in a country is directly correlated with the number of websites about statin side effects that a patient would find when searching Google in that country. This was particularly apparent in English-speaking countries, where the prevalence of statin intolerance exceeded that of all non-English speaking countries, and which also had the largest number of websites about side effects, even after standardizing for the overall number of websites about statins found in English. Previous research has shown that internet searches emphasize the negative effects of otherwise safe medical interventions like vaccinations [9]. This phenomenon has also been noted for statins [5]. However, this previous research has only been conducted in English; no previous studies have compared online adverse effect information between English and other languages. Our results suggest that statin-associated adverse effects were not emphasized as much in websites in other languages, and therefore since patients were less likely to read about them, they were less likely to become intolerant to statins. The majority of statin-intolerant patients complain of muscle symptoms [11], which are common and generally subjective, and are therefore particularly susceptible to the nocebo effect.

Our study’s findings corroborate previous research that shows that individuals who are exposed to a negative impression of a drug are more likely to experience adverse effects [13]. In one trial, three groups of men prescribed atenolol were randomized to not knowing the drug name, to knowing the drug name but not its adverse effects, or to knowing the drug name and its adverse effects, including that it could uncommonly cause erectile dysfunction [14]. After 90 days, the percentage of men reporting erectile dysfunction in each group was 3%, 16% and 31%, respectively. A similar nocebo effect may explain why open-label studies find more adverse effects with generic drugs compared to their branded equivalents [15,16]. The media are known to influence the perception of adverse effects [13]. Television coverage of a health scare in New Zealand triggered by a formulation change for Ertomox (levothyroxine) resulted in a marked increase in adverse event reporting for this drug, with larger increases for the specific symptoms that were reported in the news stories [17].

There are several strengths to our study worth noting. Our translations for search terms were confirmed by medical translators who are native speakers of each language. We conducted our searches using the Google search engine, the most widely used search engine in each country studied [18]. We used a VPN service in an effort to attain the same search results that individuals in a particular country would have. However, there are some limitations to note. The internet is dynamic: the number and content of websites and how search engines’ algorithms select pages for display can change regularly, which may limit the reproducibility of our results. Second, there are inherent international differences in genetics, lifestyle behaviors and medical care that could influence the prevalence, perception and ascertainment of statin intolerance. Third, an ecological fallacy is possible in the interpretation of the results: the study only examined national-level correlations, not individual patients’ statin intolerance or internet use. Fourth, as with any cross-sectional study, reverse causality cannot be excluded: countries with higher prevalence of actual statin intolerance could have more individuals posting to local websites about their side effects. However, it is unlikely that the prevalence of true statin intolerance would vary so dramatically between countries, particularly the uniquely high prevalence in English-speaking countries. Finally, the prevalence of statin intolerance was ascertained by physician survey, not by actually measuring statin discontinuation at the patient level.

In summary, countries in which patients using Google are more likely to find websites about statin side effects have a greater prevalence of statin intolerance. Hence, the nocebo effect driven by Google may be contributing to statin intolerance, resulting in patients who might otherwise benefit foregoing a cardiovascular risk reduction of up to 50% [1–4]. Clinicians should try to minimize the nocebo effect; an
optimistic and empathetic communication style can reduce the effect of negative patient expectations [5, 19, 20]. Patients should be reminded that muscle symptoms are common in middle-aged and older adults, whether or not they are taking statins, and that the benefits of statins outweigh potential risks.

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Conflict of interest
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References

Fig. 1. Association between the prevalence of statin intolerance and the number of websites about statin side effects.