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ORIGINAL RESEARCH ARTICLE

Amyotrophic Lateral Sclerosis Associated with Statin Use: A Disproportionality Analysis of the FDA's Adverse Event Reporting System

Beatrice A. Golomb[1] · Abril Verden[2] · Alexis K. Messner[1] · Hayley J. Koslik[1] · Keith B. Hoffman[2]

Abstract

Introduction Apparent elevations in reporting of amyotrophic lateral sclerosis (ALS)-like conditions associated with statin use have been previously described from data obtained via US and European databases.

Objective The aim of this study was to examine US FDA Adverse Event Reporting System (FAERS) data to compare reporting odds ratios (RORs) of ALS and ALS-like conditions between statins and other drugs, for each statin agent.

Methods We assessed for disproportional rates of reported ALS and ALS-related conditions for each statin agent separately by using the ROR formula. FAERS data were analyzed through September 2015.

Results RORs for ALS were elevated for all statins, with elevations possibly stronger for lipophilic statins. RORs ranged from 9.09 (6.57–12.6) and 16.2 (9.56–27.5) for rosuvastatin and pravastatin (hydrophilic) to 17.0 (14.1–20.4), 23.0 (18.3–29.1), and 107 (68.5–167) for atorvastatin, simvastatin, and lovastatin (lipophilic), respectively. For simvastatin, an ROR of 57.1 (39.5–82.7) was separately present for motor neuron disease.

Conclusion These findings extend previous evidence showing that significantly elevated ALS reporting extends to individual statin agents, and add to concerns about potential elevated occurrence of ALS-like conditions in association with statin usage.

Key Points

Past evidence has suggested a possible link between statin use and risk of amyotrophic lateral sclerosis (ALS)/motor neuron disease.

Both statin muscle effects and ALS have documented mediation through oxidative stress and mitochondrial injury.

FDA Adverse Event Reporting System (FAERS) data were examined to calculate reporting odds ratios (RORs) for reporting of ALS and ALS-like conditions with each statin, relative to other medications.

Standalone statin drugs were *each* associated with significantly elevated RORs for ALS, with RORs from 9.1 to 107, extending prior evidence for statins as a group.

1 Introduction

Statin cholesterol-lowering drugs (HMG-CoA reductase inhibitors) are among the most widely prescribed drugs in the world. Recent guideline revisions, both in the US and the European Union, further increase the fraction of the adult population deemed candidates for statin treatment [1–4]. Like all drugs, statins have the potential to produce adverse events (AEs). Particular focus has gone to muscle

✉ Beatrice A. Golomb
bgolomb@ucsd.edu

[1] Department of Medicine, University of California, San Diego, 9500 Gilman Drive # 0995, La Jolla, CA 92093-0995, USA

[2] Advera Health Analytics, Inc., Santa Rosa, CA, USA

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AEs, which are the best recognized class of AEs and the most commonly reported AE class by patients [5].

Statin muscle AEs are commonly reported, and include pain, weakness, and increased fatigability [5–8]. Recognized serious muscle effects of statins include rhabdomyolysis [9–19], necrotizing autoimmune myopathy [20–24], and triggering (or 'unmasking') of mitochondrial myopathy [8, 25–32].

Concerns have been raised about possible occurrence of amyotrophic lateral sclerosis (ALS)-like muscle wasting conditions associated with statin use [33]. ALS is a fatal neurodegenerative disease affecting upper and lower motor neurons that characteristically involves rapidly progressive paralysis culminating in death from respiratory failure [34, 35]. Implicated mechanisms include a vicious cycle of oxidative stress and mitochondrial dysfunction [36–43]—also features of other neurodegenerative conditions. Apparent excess reporting of ALS-like conditions has been identified from analysis of both European databases [44] and a US patient-targeted pharmacovigilance effort [45], as well as an early FDA data mining study [46]. The database studies were each based on <100 reported cases of ALS on statins ($N = 43$ and $N = 91$), and did not address whether reporting of ALS was elevated for individual statin agents. Studies have reported acceleration of ALS functional decline (overall [47] or in women [48]), and selective depletion of spinal motor neurons with some statins in vitro [49]. Additionally, one study showed reduced survival with statins in SOD1 'ALS' mice, an effect that was not rescued by coenzyme Q10 [50].

One common method to evaluate whether there is a relationship between a drug and an undesirable outcome is to compare whether reporting of the problem occurs disproportionately, relative to reports of the same outcome on other drugs [51]. Previous studies have identified elevated reporting of ALS or ALS-like conditions for statins as a class, relative to other drugs. It is desirable to assess whether elevated ALS reporting on statins has been upheld since prior reports. Since the previous analysis of FDA data, statin guidelines, use of lipid targets/thresholds, statin dosing, statin agents used, the demographic characteristics of statin users, and the maximum length of time people have received treatment with statins have each shifted. Additionally, the larger number of (accrued) AE reports allows examination of whether findings previously observed for the statin class apply to individual statin agents. We sought to conduct such disproportionality assessments, separately for each statin drug, for ALS or ALS-like conditions using FDA (MedWatch) Adverse Event Reporting System (FAERS) data.

2 Methods

Statin-containing agents examined using FAERS data included simvastatin, pravastatin, atorvastatin, rosuvastatin, simvastatin + ezetimibe, lovastatin, simvastatin + niacin, fluvastatin, amlodipine besylate + atorvastatin, and pitavastatin.

FAERS data processing, drug name mapping, AE coding, and disproportionality analysis were all conducted as previously described [52]. In brief, post-marketing AE data were processed by obtaining publicly available FAERS ASCII data files from the FDA's website [53]. Raw FAERS data (current to September 2015) were extracted with open-source technologies (Oracle MySQL, Python, and PHP). Key identification fields were validated and case reports that were missing or contained malformed key identification fields were discarded.

Drug name text-mapping was accomplished by normalizing multiple drug names into a single brand name by automated matching processes that used a combination of fuzzy string matching, string distance, and phonetic matching algorithms [54] to correct for drug name misspellings and incorrect data within major fields. Duplicate case reports were removed by using the earliest Individual Case Safety Report for the same patient identification number in the same calendar year.

AE information was coded according to MedDRA® version 18.0 [55]. Only 'primary suspect' drug designations in FAERS were quantified in order to restrict analysis to drugs directly suspected of causing the AE.

In order to identify drug/AE pairs that are reported more frequently than expected, we used the reporting odds ratios (RORs), a standard formula for disproportionality analysis, that is viewed as a quantitative method for signal detection [51]. The ROR was used to compare expected AE reporting frequencies (based upon all drugs and all AEs in the FAERS database) with reporting for each statin drug. ROR results >1.0 indicate a higher-than-expected reporting rate for a given drug/AE combination. Two-sided values <0.05 designated statistical significance.

3 Results

Table 1 shows the top statin drugs by number of prescriptions over the time period studied. Patient usage data were provided by Evaluate Pharma (http://www.evaluategroup.com/).

Table 2 shows summary data across statins and statin-containing agents. Where estimates are derived based on <10 reported cases, the row is grayed out. RORs show disproportional reporting for each standalone statin, though

Table 1 Top ten statin-including drugs by annual prescription estimate (2010–2015)

Drug	Prescriptions
Simvastatin	86,372,608
Pravastatin sodium	24,775,636
Atorvastatin calcium	19,953,049
Rosuvastatin calcium	18,190,192
Simvastatin + ezetimibe	4,312,604
Lovastatin (mevacor)	3,230,427
Simvastatin + niacin	806,582
Fluvastatin sodium	563,878
Atorvastatin calcium + amlodipine besylate	447,167
Pitavastatin calcium	433,796

Data for agents with low prescribing (estimated annual prescriptions < 1,000,000) are grayed out

Patient usage data (number of prescriptions written per drug) were based upon information derived from the Medical Expenditure Panel Survey (MEPS) [88] and Evaluate Pharma® (http://www.evaluategroup.com). MEPS data "includes a representative survey of 'the consumption of prescription medicines in the USA, analysing approx. 350,000 prescriptions dispensed each year. The survey results have been scaled-up to provide an estimate of total pharmaceutical drug consumption, retail sales, prescription volume and number of persons taking the drug, in the USA. The focus of the survey is primary care dispensing of prescriptions and does not cover hospital prescribed drugs. The survey is conducted and published each year by AHRQ (Agency for Healthcare Research and Quality), US Department of Health and Human Services, in October" [89]

Table 2 Reporting odds ratios for amyotrophic lateral sclerosis, by individual statin[a]

Drug	Listed in Label?	Cases	ROR	95% CI
Lovastatin	**NO**	**20**	**107**	**68.5-167**
Simvastatin	**NO**	**78**	**23.1**	**18.3-29.1**
Pitavastatin calcium	**NO**	**2**	**19.3**	**4.8-77.6**
Atorvastatin calcium	**NO**	**128**	**17.0**	**14.1-20.4**
Pravastatin sodium	**NO**	**14**	**16.2**	**9.6-27.5**
Fluvastatin sodium	**NO**	**4**	**13.7**	**5.1-36.7**
Rosuvastatin calcium	**NO**	**38**	**9.1**	**6.6-12.6**
Lovastatin + niacin	NO	*1*	*14.8*	*2.08-105*
Simvastatin + ezetimibe	NO	3	6.9	2.2-21.5
Atorvastatin calcium + amlodipine besylate	–	0	0.00	–
Simvastatin + niacin	–	0	0.00	–

Statins as standalone agents are in bold. Data for agents with low prescribing are grayed out

Italic values indicate concerns associated with generating an ROR based on a single report

[a]Based on the Designated Medical Event (DME) list, which consists of roughly 80 serious side effects that are considered "inherently serious and often drug-related" by the FDA. The DME list was obtained from the FDA's Center for Drug Evaluation and Research (CDER) via a Freedom of Information Act (FOIA) request

ROR reporting odds ratio

for the two least frequently prescribed of these, this is based on few reports. For the remaining statins—rosuvastatin, atorvastatin, simvastatin, lovastatin, and pravastatin—the ROR elevations are statistically significant. RORs were approximately 9, 14, and 16 for hydrophilic statins (rosuvastatin, fluvastatin, and pravastatin); and 17, 19, 23, and 107 for lipophilic statins (atorvastatin, pitavastatin, simvastatin, and lovastatin, respectively). The 95% confidence interval (CI) for the ROR, for the longest available (and lipophilic) agent, lovastatin (95% CI 69–167), did not overlap with that of any other statin. At the other extreme, the ROR for the most recent (and hydrophilic) among the well used agents, rosuvastatin (95% CI 6.6–13), did not overlap with those of any well used lipophilic statin (atorvastatin, simvastatin, or lovastatin). (It did overlap with that of pitavastatin, for which the very small number led to very broad confidence intervals.) CIs for other statins overlapped with one another.

Table 3 shows the RORs for ALS, and provides a comparison of these with RORs for other muscle

Table 3 Comparison of reporting odds ratios (RORs) for amyotrophic lateral sclerosis with RORs for other muscle conditions for each statin-including agent

Adverse event	Listed in label?	Cases	ROR	95% CI
Atorvastatin				
ALS	No	128	17.0	14.1–20.4
Motor neuron disease	No	11	6.87	3.74–12.6
Motor dysfunction	No	49	1.35	1.02–1.79
Muscle atrophy	No	555	13.2	12.1–14.4
Muscle disorder	No	590	15.3	14.0–16.6
Muscle fatigue	Yes	94	9.41	7.63–11.6
Muscle rigidity	No	41	0.79	0.58–1.07
Muscle spasms	Yes	2656	4.72	4.54–4.91
Muscle tightness	No	112	2.11	1.75–2.55
Muscle twitching	Yes	105	1.10	0.90–1.33
Musculoskeletal disorder	No	85	1.65	1.33–2.04
Musculoskeletal stiffness	No	457	2.06	1.88–2.26
Rosuvastatin				
ALS	No	38	9.09	6.57–12.6
Motor neuron disease	No	3	3.58	1.14–11.19
Motor dysfunction	No	7	0.38	0.18–0.80
Muscle atrophy	No	142	6.16	5.22–7.29
Muscle disorder	No	168	7.88	6.76–9.20
Muscle fatigue	Yes	33	6.25	4.42–8.84
Muscle rigidity	No	21	0.80	0.52–1.23
Muscle spasms	No	1403	4.89	4.63–5.16
Muscle tightness	No	74	2.76	2.20–3.48
Muscle twitching	No	49	1.01	0.77–1.34
Musculoskeletal disorder	No	28	1.07	0.74–1.55
Musculoskeletal stiffness	No	234	2.08	1.83–2.37
Lovastatin				
ALS	No	20	107	68.5–167
Motor neuron disease	–	0	–	–
Motor dysfunction	No	1	1.22	0.17–8.65
Muscle atrophy	No	17	16.3	10.1–26.4
Muscle disorder	No	20	20.7	13.3–32.2
Muscle fatigue	Yes	1	4.14	0.58–29.5
Muscle rigidity	–	0	–	–
Muscle spasms	Yes	78	6.06	4.82–7.62
Muscle tightness	No	3	2.49	0.80–7.72
Muscle twitching	Yes	1	0.46	0.07–3.28
Musculoskeletal disorder	No	1	0.85	0.12–6.06
Musculoskeletal stiffness	No	3	0.59	0.19–1.83
Simvastatin				
ALS	No	78	23.1	18.3–29.1
Motor neuron disease	No	34	57.1	39.5–82.7
Motor dysfunction	No	10	0.64	0.34–1.19
Muscle atrophy	No	330	17.7	15.8–19.8
Muscle disorder	No	213	12.0	10.4–13.7
Muscle fatigue	Yes	32	7.16	5.04–10.2
Muscle rigidity	No	38	1.72	1.25–2.36
Muscle spasms	Yes	1277	5.27	4.98–5.58
Muscle tightness	No	47	2.06	1.55–2.75
Muscle twitching	Yes	61	1.49	1.16–1.92
Musculoskeletal disorder	No	45	2.04	1.52–2.73
Musculoskeletal stiffness	No	244	2.57	2.27–2.92

Table 3 continued

Adverse event	Listed in label?	Cases	ROR	95% CI
Pravastatin				
ALS	No	14	16.2	9.56–27.5
Motor neuron disease	–	0	–	–
Motor dysfunction	No	6	1.61	0.72–3.59
Muscle atrophy	No	51	10.8	8.21–14.3
Muscle disorder	No	48	10.9	8.21–14.5
Muscle fatigue	Yes	11	10.2	5.60–18.4
Muscle rigidity	No	5	0.94	0.39–2.26
Muscle spasms	Yes	268	4.54	4.01–5.13
Muscle tightness	No	15	2.75	1.65–4.56
Muscle twitching	Yes	13	1.33	0.77–2.29
Musculoskeletal disorder	No	5	0.94	0.39–2.26
Musculoskeletal stiffness	No	44	1.92	1.43–2.59
Fluvastatin				
ALS	No	4	13.7	5.14–36.7
Motor neuron disease	–	0	–	–
Motor dysfunction	No	6	4.84	2.17–10.8
Muscle atrophy	No	21	13.3	8.66–20.5
Muscle disorder	No	9	6.07	3.15–11.7
Muscle fatigue	Yes	1	2.74	0.39–19.5
Muscle rigidity	No	8	4.53	2.26–9.08
Muscle spasms	Yes	77	3.87	3.08–4.86
Muscle tightness	No	2	1.09	0.27–4.38
Muscle twitching	Yes	4	1.22	0.46–3.27
Musculoskeletal disorder	No	2	1.13	0.28–4.52
Musculoskeletal stiffness	No	13	1.70	0.99–2.93
Simvastatin-ezetimibe				
ALS	No	3	6.90	2.22–21.5
Motor neuron disease	No	1	11.8	1.65–84.0
Motor dysfunction	No	5	2.71	1.12–6.51
Muscle atrophy	No	29	12.4	8.56–17.8
Muscle disorder	No	34	15.6	11.1–21.9
Muscle fatigue	Yes	2	3.68	0.92–14.8
Muscle rigidity	No	1	0.38	0.05–2.69
Muscle spasms	Yes	132	4.49	3.77–5.34
Muscle tightness	No	5	1.84	0.76–4.42
Muscle twitching	Yes	1	0.21	0.03–1.46
Musculoskeletal disorder	No	8	3.04	1.52–6.09
Musculoskeletal stiffness	No	22	1.93	1.27–2.94
Atorvastatin-amlodipine				
ALS	–	0	–	–
Motor neuron disease	–	0	–	–
Motor dysfunction	–	0	–	–
Muscle atrophy	No	4	4.03	1.51–10.75
Muscle disorder	No	7	7.58	3.60–15.94
Muscle fatigue	Yes	1	4.40	0.62–31.27
Muscle rigidity	–	0	–	–
Muscle spasms	Yes	34	2.71	1.93–3.81
Muscle tightness	No	1	0.88	0.12–6.24
Muscle twitching	Yes	3	1.47	0.47–4.58
Musculoskeletal disorder	No	1	0.91	0.13–6.43
Musculoskeletal stiffness	No	6	1.26	0.56–2.80

Table 3 continued

Adverse event	Listed in label?	Cases	ROR	95% CI
Simvastatin-niacin				
ALS	–	0	–	–
Motor neuron disease	–	0	–	–
Motor dysfunction	No	2	0.30	0.08–1.21
Muscle atrophy	–	0	–	–
Muscle disorder	No	4	0.51	0.19–1.35
Muscle fatigue	Yes	14	7.30	4.31–12.37
Muscle rigidity	–	0	–	–
Muscle spasms	Yes	248	2.32	2.04–2.63
Muscle tightness	No	17	1.76	1.09–2.83
Muscle twitching	Yes	17	0.98	0.61–1.58
Musculoskeletal disorder	No	1	0.11	0.01–0.75
Musculoskeletal stiffness	No	32	0.79	0.56–1.11
Pitavastatin calcium				
ALS	No	2	19.3	4.82–77.6
Motor neuron disease	–	0	–	–
Motor dysfunction	–	0	–	–
Muscle atrophy	No	1	1.76	0.25–12.6
Muscle disorder	No	4	7.60	2.84–20.3
Muscle fatigue	–	0	–	–
Muscle rigidity	–	0	–	–
Muscle spasms	Yes	45	6.55	4.84–8.86
Muscle tightness	No	2	3.09	0.77–12.4
Muscle twitching	–	0	–	–
Musculoskeletal disorder	No	1	1.59	0.22–11.3
Musculoskeletal stiffness	No	5	1.84	0.77–4.45

ALS amyotrophic lateral sclerosis, *ROR* reporting odds ratio

conditions for each statin-including agent. Of note, for atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin, the ROR for either ALS or motor neuron disease exceeds the ROR for any other analyzed muscle condition.

For fluvastatin, muscle atrophy—some cases of which may reflect motor neuron disease—shows an ROR comparable to, or slightly higher than, the ROR for ALS. RORs for muscle atrophy are among the highest muscle-related RORs for each of the standalone statin agents.

There were no reports of ALS for the combination agents simvastatin–niacin and amlodipine–atorvastatin, the least-prescribed combination agents. However, as Table 1 shows, these were associated with 100–200× fewer prescriptions than simvastatin. Although reasons could be proffered to explain lower reporting of ALS with the addition of niacin or calcium channel blockers, it is not known that reporting is in fact lower with the combination agents. Even if ALS reporting were elevated proportionally to the elevated reporting observed with simvastatin, less than one report would be expected for each of these rarely prescribed combination agents. Table 3 depicts ROR comparisons across reported muscle AEs, by statin.

4 Discussion

4.1 Recap of Findings

Evidence for elevated reporting of ALS on statins has continued to accrue, persisting through revisions in statin guidelines and shifts in statin use—which agents are used, at what doses and potencies, whether treatment is guided by lipid threshold and/or lipid targets, who is recommended to receive a statin agent, and the maximum duration of statin use. Our analysis of FAERS data identified materially and statistically significantly elevated reporting of ALS-like conditions with individual statin drugs relative to other drug classes, extending previous findings linking statins as a class to elevated ALS reporting. RORs ranged from 9 to 19 for hydrophilic statins and 23 to 107 for the most lipophilic agents. These findings add to concerns about a possible connection between statin use and the development of ALS and ALS-related conditions.

Although some muscle problems were reported at elevated rates on atorvastatin–amlodipine (adding a calcium channel blocker to a statin) and on simvastatin–niacin (adding a B vitamin to a statin), there was no evidence for

(and little evidence against) an elevation in reported ALS-like conditions for these combination agents. While other explanations can be tendered, the most obvious explanation is the small number of prescriptions for these agents, which are less than prescriptions, for example, for simvastatin by ~ 100- and 200-fold. Proportional reporting of ALS to that of simvastatin would yield less than one expected case for each of these combination agents, consistent with case counts observed in our analysis. Thus, the absence of cases reported need not preclude elevated risks with these agents.

4.2 Fit with Existing Literature

Previously, elevated reporting of ALS-like conditions in association with statins was observed in a US patient-targeted AE database [45], an examination of data from a European-based World Health Organization (WHO) drug monitoring center [44], and an evaluation of FDA data from a decade ago [46]. The present findings strengthen concerns regarding a possible association between statin use and the development of neurodegenerative and ALS-like conditions. Findings show this association has been sustained with now several times the number of reported ALS cases, in the face of many changes in statin usage and demographics of users. They also extend evidence for an association with each statin agent considered individually.

Case–control studies showed a nonsignificant trend toward *lower* statin use in those with ALS [56]. However, in such a design, reverse causality—presence of ALS (or precursor symptoms) leading to lower statin use—is an expectation. The time horizon of survival in patients with ALS materially reduces concerns about need for long-term protection against cardiovascular disease. Moreover, because statins can produce muscle weakness, which may compound the clinical manifestations of ALS, statins may be withdrawn, or not prescribed, in those with ALS in order not to risk aggravating their condition. Additionally, prior muscle weakness is a reported risk factor for (occurrence and/or recognition of) muscle problems on statins [6], so that those with preclinical or clinical ALS who are placed on statins might disproportionately develop or aggravate symptoms, and shift to nonuser status. Both reduced odds of ALS among current statin users and increased odds in former statin users, in a population-based study in Denmark, could arise from these considerations (though neither reached statistical significance) [57]. This population-based case–control study from Northern Denmark found no increased risk of ALS associated with statin use [57]. The sample size, however, was small and included only 32 current/recent statin users with putative ALS.

Several studies have looked at the relation of statin use to outcomes in those who already have ALS. In one study, statin use was linked to a 63% increase in the rate of functional decline on the ALS Functional Rating Scale-Revised (ALSFRS-R), $p < 0.0001$ [47], and in another study to functional decline selectively in women [48]. The finding cannot plausibly be ascribed to indication bias (i.e., it is unlikely that the true culprit in functional decline is elevated low-density lipoprotein cholesterol [LDL]), since dyslipidemia or high LDL in those with ALS has been linked to relative *protection* from progression, indexed by less respiratory impairment [58] and longer survival [59]. Another study found no relation between statin use and survival in ALS [60]. One study reported a near significant favorable hazard ratio with statin use at baseline ($p = 0.067$) [61], and a 'meta-analysis' comprising two case–control studies and one cohort study found no association. Any nonsignificant trend was toward lower statin use in those with ALS (pooled rate ratio for statin use 0.89; 95% CI 0.55–1.42 [56]). However, again, ALS presence and greater ALS severity or rapidity of progression may be linked to non-prescribing of statins (given known ability of statins to cause muscle weakness), as well as to selective discontinuation of statins. Moreover, statin use may be a marker for higher cholesterol which can predict longer survival in those who have ALS [59], and what would have been a more favorable course (while also reversing the elevated cholesterol, to a variable extent). Such factors would be expected to confer bias in a direction to mask (or appear to reverse) potential adverse implications of statins to ALS.

Regarding the report citing accelerated functional decline with statins in ALS, differentially in women, occurrence of muscle adverse effects of statins, including muscle weakness, is greater in women than in men [6, 62]. Functional decline could be accelerated by statins due strictly to muscle effects of statins [5], rather than motor neuron effects, in patients with motor neuron disease. (Such a mechanism could also hasten clinical recognition of ALS in some cases.) However, ability to separate these effects is complicated by the fact that muscle involvement (and mitochondrial injury in muscle), not just motor neuron involvement, is a feature of ALS [63–66], and also a feature of statin muscle adverse effects [8, 62].

4.3 Limitations

We have previously reviewed the limitations of post-marketing surveillance, and of the present analysis approach specifically [67]. Limitations include lack of randomization. However, randomized controlled trials (RCTs) are disadvantaged in AE detection for a number of reasons [33], several of which—including the critical issue of selection bias and bidirectional effects—were reviewed above. Sample sizes may be small relative to those needed for detection of rare conditions. Choice to report an

outcome may be tied to study results. Selection bias can have critical implications, particularly for outcomes that may be subject to bidirectional effects. (Meta-analysis does not mitigate such sources of bias.) Effect modification is a critical and under-recognized issue [68, 69]. Illustrating this, statins can cause proteinuria, which is indeed the subject of an FDA advisory [70], and yet in RCT meta-analyses, proteinuria is unaffected [71] or, in a key group selected for in a statin trial, even protected against [72]. Where the goal is to ascertain whether a drug *may* cause or promote that outcome in some (even if reducing it in others), post-marketing surveillance has advantages over RCTs and population-based studies. To those who experience a problem due to a drug—who otherwise would not have, the potential of the drug to cause the problem is important, irrespective of whether others benefited. Case reports and post-marketing surveillance are commonly responsible for the first identification of important AEs, including those that ultimately lead to regulatory actions such as FDA warnings, 'black box' warnings, and product withdrawals [73, 74]. These were responsible for first identification of statin-induced elevations in blood glucose [75].

Inherently, those experiencing an adverse effect are different, and differences may encompass different past or current other exposures that may drive effect modification (and potentially clinical trial participation). For other exposures to be confounders (spurious causes of an apparent statin relationship), rather than effect modifiers, they must relate to ALS in the non-statin exposed; and must relate to statin use. No agent is obvious that could produce the large RORs seen on statins, through an indirect route. There may be drugs and chemicals that promote oxidative stress, leading to adaptive upregulation of LDL to support antioxidant transport, creating a problem when statins depress coenzyme Q10 and withdraw antioxidant transport; but in that case the statin would remain a causal factor. Indeed, if the statin relation to ALS is causal, this is an important potential mechanism, especially in persons with mitochondrial compromise (at baseline, due to the other agent, and/or due to the statin).

Once an ALS-like condition has been triggered, it typically continues to progress following withdrawal of the inciting exposure. This makes presumptive adverse effect causality criteria like reversal with drug withdrawal [76] problematic to fulfill. Other factors, however, have been noted to support prospects for a causal drug association in at least some statin-associated instances of ALS-like conditions. Prior development of recognized statin AEs bearing shared mechanisms to those involved in ALS has been commonly reported [45]. Moreover, for some patients, symptoms have been reported to initially modestly improve following statin withdrawal (suggesting that statins were at least potentiating the underlying mechanisms), followed by resumption of (sometimes slower) progression [45]. In some instances, arrest and actual reversal of an ALS-like condition, following withdrawal of the statin agent, has been reported [33, 44]. These factors add to concerns that occurrence of ALS or ALS-like conditions might, in some instances, be causally induced or potentiated by statins.

Additional limitations of this analysis include the following: (1) the FAERS database is only as accurate as the information inputted into it from various sources. (2) FAERS does not filter, correct, or make any analysis of the quality or potential bias of inputted data. (3) Exogenous factors such as publicity and marketing can influence reporting. (4) Analyses for some of the statins are based on a comparatively small number of reports; however, inferences are strengthened by the consistency with which RORs are elevated across statin agents. (5) Dose data are not available. (6) Reports submitted to the FDA often contain mistakes, including spelling errors, leading to misclassifications, important data either missing or inadequately reported, and duplicate reports; however, our analysis systems included multiple processing steps, safeguards, and manual oversight to lessen the impact of such factors. (7) Only a minority of post-marketing AEs are believed to be successfully logged into FAERS [77]. Therefore, FAERS data likely substantially underestimate the actual incidence of these side effects in broad consumer populations. We address this limitation by assessing disproportional reporting rates.

There could be reporting bias. The fact that statins are recognized to cause muscle problems may disproportionately lead patients on statins, or their doctors, to presumptively link the drug to the condition, and thus to file an FDA report, particularly if the patient previously experienced more 'usual' muscle adverse effects of the statins. However such 'usual' muscle adverse effects of statins have been shown to be tied to statin-induced increases in oxidative stress [78–80] as well as mitochondrial dysfunction [8, 25–27, 62, 81–86], which are also recognized mechanisms of ALS, so the presumption of a link due to this factor may be appropriate. In people who develop muscle (or other) adverse effects on statins, the implicated mechanisms may legitimately place them at elevated risk of developing statin-induced ALS.

4.4 Implications

AE reporting systems seek to capture instances in which a problem is potentially promoted or caused by a drug: cases are not 'masked' by those for whom the problem is protected. This is an advantage where the goal is to ascertain whether a drug *may* cause or promote that outcome in some, as opposed to addressing the balance of protection

versus promotion (in a skewed study sample). To those who may experience a problem due to a drug, who otherwise would not have, the potential of the drug to cause the problem is important, irrespective of whether there are others for whom benefit occurred. Ultimately, the hope is to identify predictors that determine into which group a patient will more likely fall.

High RORs for ALS and ALS-related conditions span many statins, in a setting in which 'negative' randomized and population-based studies cannot exclude causal occurrence (due to expectation of bidirectional effects on relevant mechanisms). Given the seriousness of this condition, the apparent excess reporting of ALS on statins warrants attention.

When patients develop an ALS-like condition on a statin, a possible connection should be considered. This study does not address the impact of statin withdrawal. However, until better evidence is available, prompt statin withdrawal should be considered [44], given (1) the observational relations between higher cholesterol levels and both longer survival and slower progression in patients with ALS [58, 59]; (2) known mechanisms by which this may be causal [45]; (3) reports (though rare) of arrest and even reversal of ALS-like conditions with statin withdrawal [33, 44]; and finally (4) the important context that estimated median expected life extension with statins is minimal [87].

5 Conclusion

This analysis of FAERS data assessed RORs of ALS for statins relative to other drug classes. RORs were based on substantially more cases of ALS attributed to statins (283) than in two early reports (which bore samples of ~ 40 and ~ 90). Elevated statin RORs for ALS were determined to have persisted through shifts in statin guidelines and user demographics. Significantly increased RORs relative to other drug classes were found to apply separately for *each* standalone statin relative to other drug classes. RORs for hydrophilic statins (~ 9, 14, and 16 for rosuvastatin, fluvastatin, and pravastatin, respectively) were lower—albeit not by much—than for lipophilic agents (~ 17, 19, 23, and 107 for atorvastatin, pitavastatin, simvastatin, and lovastatin, respectively). The highest and lowest RORs were for the oldest and newest of the widely used statins. Future studies can assess whether duration of use or time on market influences ROR values, considering that it takes time for the first clinical manifestations of this neurodegenerative condition to emerge. These findings underscore the need to revisit approaches for presumptive adverse effect causality assessment in individual reports for conditions—like ALS—that seldom reverse once clinically evident.

Compliance with Ethical Standards

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Conflict of interest Alexis K. Messner and Hayley J. Koslik declare they have no conflict of interest and their efforts on this were unfunded. Beatrice A. Golomb is the executor of an estate (and will be among the beneficiaries) that includes some stock in drug companies that make statins. The estate lawyer has advised no changes be made to the portfolio until after distribution. Her effort on this project was unfunded. Keith B. Hoffman is a past employee of Advera Health Analytics, Inc. and is a stockholder and stock option holder in the company. Abril Verden is a current employee of Advera Health Analytics, Inc. and is a stock option holder in the company.

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