

Physician Response to Patient Reports of Adverse Drug Effects

Implications For Patient-Targeted Adverse Effect Surveillance

Beatrice A. Golomb,^{1,2} John J. McGraw,^{1,3} Marcella A. Evans¹ and Joel E. Dimsdale⁴

1 Department of Medicine, University of California, San Diego, California, USA

2 Department of Family & Preventive Medicine, University of California, San Diego, California, USA

3 Department of Anthropology, University of California, San Diego, California, USA

4 Department of Psychiatry, University of California, San Diego, California, USA

Abstract

Objective: Using a patient targeted survey, we sought to assess patient representations of how physicians responded when patients presented with possible adverse drug reactions (ADRs). As a demonstration case, we took one widely prescribed drug class, the HMG-CoA reductase inhibitors ('statins'). This information was used to assess whether a patient-targeted ADR surveillance approach may complement provider reporting, potentially fostering identification of additional patients with possible or probable ADRs.

Methods: A total of 650 adult patients taking statins with self-reported ADRs completed a survey. Depending on the problems reported, some patients completed additional surveys specific to the most commonly cited statin ADRs: muscle, cognitive or neuropathy related. Patients were asked to report drug, dose, ADR character, time course of onset with drug, recovery with discontinuation, recurrence with rechallenge, quality-of-life impact, and interactions with their physician in relation to the perceived ADR. This paper focuses on patients' representation of the doctor-patient interaction and physicians' attribution, when patients report perceived ADRs.

Results: Eighty-seven percent of patients reportedly spoke to their physician about the possible connection between statin use and their symptom. Patients reported that they and not the doctor most commonly initiated the discussion regarding the possible connection of drug to symptom (98% vs 2% cognition survey, 96% vs 4% neuropathy survey, 86% vs 14% muscle survey; $p < 10^{-8}$ for each). Physicians were reportedly more likely to deny than affirm the possibility of a connection. Rejection of a possible connection was reported to occur even for symptoms with strong literature support for a drug connection, and even in patients for whom the symptom met presumptive literature-based criteria for probable or definite drug-adverse effect causality. Assuming that physicians would not likely report ADRs in these instances, these patient-submitted ADR reports suggest that targeting patients may boost the yield of ADR reporting systems.

Conclusions: Since low reporting rates are considered to contribute to delays in identification of ADRs, findings from this study suggest that additional putative cases may be identified by targeting patients as reporters, potentially speeding recognition of ADRs.

Background

Adverse drug reaction (ADR) rates in clinical trials often understate those in practice.^[1] Postmarketing surveillance is employed to help overcome the limitations in ADR identification in clinical trials. These arise from many factors including: inadequate sample size, limited trial duration, restricted range of assessed outcomes, and relative exclusion of precisely those patients most likely to experience adverse effects, such as the elderly and those with polypharmacy and co-morbidities.^[2]

Because of such factors, "...the challenge of early detection [of ADRs] has largely shifted to ... postmarketing systems,"^[3] which seek to capture 'real-world' ADR experiences and are a major mechanism undergirding drug withdrawals.^[4,5] Postmarketing surveillance "provides vital information of clinical importance,"^[6] it may lead to the identification of new ADRs, and may modify knowledge about known ADRs.

But detection is not always 'early'.^[7] Both physician- and patient-initiated postmarketing ADR reporting are inherently subjective, and physicians may not report a putative ADR because they are unfamiliar with it; because for other reasons they do not attribute the patient's symptoms to a prescribed drug; or because of time pressures and other factors. Indeed, physician surveys suggest reporting is infrequent even when an ADR is recognised.^[8] Underreporting compromises the effectiveness of postmarketing surveillance^[9] and may contribute to lags in identification of problems.^[7] Although patients may also report ADRs, the US FDA and industry are both "dependent on practicing clinicians to actively participate in national postmarketing drug surveillance."^[10] However, patients have been proposed as a reliable supplemental source of reports.^[11]

We sought to determine whether a patient-targeted ADR surveillance approach may foster

identification of additional patients with possible or probable ADRs that might not be captured through efforts directed at physicians. (This paper does not present data that characterise specific ADRs. These will continue to be presented in other venues.^[12,13]) We therefore focus on patients' representation of the doctor-patient interaction and physicians' attribution, when patients report perceived ADRs. We used a commonly prescribed drug class as a demonstration case, the HMG-CoA reductase inhibitors ('statins').

Methods

Patients with perceived ADRs associated with statin use gave informed consent and completed a University of California, San Diego (UCSD) Institutional Review Board (IRB)-approved survey. Recruitment was passive, as is physician-targeted postmarketing surveillance. Of those offering source information (n = 433), patients learned of the study through Internet (72%), newspaper (25%) and television news (3%) reports that discussed the UCSD Statin Effects Study and its intent to learn about patient experiences with statin adverse effects. A total of 94% of subjects were from the US. The remaining 6% were from 11 nations spanning five continents. Patients were well educated on average, with a mean and median 16 years of education (range 7–25 years). The most commonly reported ADRs (all buttressed by a supportive literature) related to muscle,^[14,15] cognition^[16–18] and neuropathy.^[19–21] For consenting patients who completed the main ADR survey and reported one or more of these symptoms, we probed their symptom experience with additional IRB-approved surveys targeting these areas.

These surveys elicited information on patient characteristics, drug, dose, ADR character, time course of onset with drug, severity, quality-of-life

Table I. Reported physician response by adverse drug reaction (ADR) category

ADR questionnaire	Patients (n)	Mean age (y)	Patients who [n (%)]		Physicians who reportedly [n (%)] ^a		
			talked to their physician	received an answer	endorsed possibility of symptom link to statins	dismissed possibility of symptom link to statins	neither endorsed nor dismissed possibility of symptom link to statins
General	650	63	563 (87)	473 (84)	185 (39)	151 (32)	137 (29)
Muscle	207	62	175 (85)	167 (95)	53 (29)	85 (47)	44 (24)
Cognition	113	62	73 (65)	72 (99)	16 (19)	40 (47)	29 (34)
Peripheral neuropathy	85	62	66 (78)	63 (95)	17 (27)	32 (51)	14 (22)

a Numbers are higher than the number of patients who talked to their physician in order to reflect the fact that some patients spoke to more than one physician.

Statins = HMG-CoA reductase inhibitors.

impact, recovery with discontinuation, and recurrence with reinitiation¹ (these data are reported elsewhere^[12,13]).

This paper focuses on patient reports of patient-physician interactions in relation to possible adverse effects; and the implications of these interactions for patient-targeted reporting. Thus, patients were asked if a drug contribution was discussed with their physician. They were asked whether the physician acknowledged/dismissed the possibility of a connection; whether patient or physician initiated discussion of a possible drug relation; and for specific surveys, whether the patient perceived their physician to appreciate the quality-of-life impact of the ADR (muscle and cognition survey). Optional narrative comments were elicited regarding the physician interaction. Surveys were abstracted for presumptive ADR causality criteria, based on factors such as whether symptoms arose on drug, abated with discontinuation and recurred with challenge.^[22]

Results

A total of 650 patients, with a mean age of 63 years, completed a general ADR questionnaire. Of these patients, 54% of respondents were male. In total, 207, 113 and 85 patients completed supplemental targeted muscle, cognitive and neuropathy ADR surveys, respectively (48–58% male). Of the

patients completing the muscle survey, 79% met presumptive literature criteria for probable or definite ADRs, whereas 77% of patients completing the cognition survey met presumptive literature criteria for probable or definite ADRs.

According to patients, physicians reportedly more commonly dismissed than acknowledged the possibility of a statin link to evaluated symptoms (table I). The likelihood of dismissal varied by ADR ($p < 0.05$) and was most common for neuropathy (51%). Physician response did not differ significantly by patient sex or age (<70 vs ≥ 70 years). Reportedly, the patient rather than the physician most often initiated discussion of a possible connection between drug and symptom (98% vs 2% cognition survey, 96% vs 4% neuropathy survey, 86% vs 14% muscle survey; $p < 10^{-8}$ for each). The physician initiated discussion more often for the best recognised ADR, muscle adverse effects, than for cognitive or neuropathy symptoms ($p < 0.01$). Thus, patients may consider a drug connection when a doctor does not and the disparity may be greater for lesser known adverse effects – where reporting may be most important. Many patients perceived that their physician did not appreciate the impact of their symptoms (61% muscle survey; 48% cognition survey).

A number of patients stated their physician attributed their problems to age or imagination, dismissed

1 General, muscle, cognitive and neuropathy ADR instruments comprised semi-structured surveys with 20, 55, 39 and 29 items, respectively (survey instruments available from author). More items pertained for patients citing more than one drug.

the importance of their symptoms or stated that a connection of symptoms to statins was not possible. Optional narrative comments on physicians' response are illustrated in table II.

Discussion

Among a sample of patients with possible to definite statin ADRs who completed surveys related to their experience, physicians were commonly reported to deny the possibility of a relationship of symptoms to drug, and to do so even when the patient noticed and reported an apparent association, when there was literature support for the ADR and when cases met literature criteria for probable or definite ADR causality. According to patients, physicians seldom initiated the conversations regarding a possible relation of the drug to the symptom (in fact, literature suggests that idiopathic polyneuropathy – i.e. after excluding other recognised causes –

occurs with 16-fold elevated odds in statin users^[19]). Since these patients considered a possible connection between a drug and new symptoms even when their physicians did not, ADR reporting by physicians may be complemented by patient reporting.

This study focused on known ADRs. Numbers for potential 'new' ADRs would be smaller, limiting inferences; thus dismissals of a possible drug connection to such symptoms might be thought justified. The finding that physicians (reportedly) dismiss the possibility of a relationship to the drug even for *known* ADRs meeting presumptive causality criteria provides concern they may do so, *a fortiori*, for 'new' hitherto unrecognised adverse effects.

Since this study is aimed at identifying whether patient targeting may add yield to postmarketing surveillance, by its nature it has limitations inherent to surveillance approaches: there is no defined base population or control group precluding generation

Table II. Comments attributed to physicians^a

Physician response	Sample comments attributed to physicians
Attributed to age (n = 11)	Just normal aging process. Can expect some problems at your age. Well, you're no youngster. No way, you're just getting old
Dismissed importance of symptoms (n = 69)	Doctor said would have to live with side effects and did not seem to care. Ignored complaints about side effects. Doctor shrugged and said some people just live with it, then laughed. Did not seem to be concerned with side effects. Didn't take seriously. Made me feel I was alone in my inability to take statins because of 'minor discomfort'. Said I must continue [statins], protecting the heart was most important
Dismissed existence of symptom (n = 16)	Acted as if it was in imagination. Doctor suggested it was imagination. Don't think doctor believed me. Told me I just didn't like taking pills. Nothing wrong with me, it's all in my head. She 'pooh-poohed' me and said keep taking Lipitor®
Dismissed relation to statins (n = 55)	Almost impossible. Cannot be statins. Not possible. Denied possibility. Can't be. Statins are not cause of problems. Said problems couldn't be due to Lipitor®. Said: "This has nothing to do with the Pravachol®." Said: "That's not a side effect of this drug." They [doctors] were very skeptical even though I presented Pfizer's own report on side effects. Statins could not be cause of symptoms. Neither doctor [internist, neurologist] believed me – my pharmacist suggested Lipitor® as a cause. My chiropractor suggested it may be the Lipitor®, my MD didn't think so
Dismissed relation to statins, muscle-specific (n = 43)	CPK didn't indicate statin-related adverse effect. Didn't think Lipitor® caused muscle weakness because there was no pain. Wouldn't consider Lipitor® the cause of body aches. Specific muscle pain would not indicate medication, only general muscle pain. Doctor didn't think cramps were caused by statins. Doctor felt that there was no connection between pain and the statin drugs
Dismissed relation to statins, cognition-specific (n = 18)	Statins do not cause memory loss and may, in fact, help it. No research linking statins to memory problems. Doctor said statins would improve (not worsen) memory. Memory and peripheral neuropathy are not acknowledged side effects of statins. Avoided discussion of Lipitor®, focused elsewhere. I was the first to tell him [doctor] about this significant side effect [memory problems, coordinating thoughts/complex tasks] and since then he has had other patients with similar symptoms
Disbelief that statins cause ADRs in general (n = 12)	Doctor said there were no side effects. Doctor had heard of no difficulties. Said Lipitor® has minimum to no ADRs. Literature did not support ADRs. Can't be the statins, thinks it is a miracle drug. Said that only 1% of patients have side effects

a From total n = 478 providing comments.

ADRs = adverse drug reactions; **CPK** = creatine phosphokinase; **MD** = medical doctor; **statins** = HMG-CoA reductase inhibitors.

of rates or risk ratios – thus, we draw no inferences regarding these. However, only patients who sustained a putative ADR are relevant to the goal of understanding the experience arising during an ADR, including patients' reported interaction with their physician regarding the ADR. Self-selection to participate may impinge on external generalisability of findings, as in all studies with volunteer participants (physicians who elect to report ADRs to the US FDA MedWatch system are also self-selected and may also be non-representative). Moreover, patients with milder problems may lack the motivation to participate (also for physician-based reporting), while those with severe or fatal problems may be unable to participate. Patients whose physicians dismissed a connection may be more or less likely to participate, depending on whether physician dismissal dissuades patients from inferring a connection (stalling additional inquiry and study participation), or spurs dissatisfaction and additional inquiry. It is possible that findings may differ for statins than for other drugs: physician acknowledgement of symptoms as possible ADRs may either be greater than for many drugs due to more overall knowledge about this class of drugs; or may be lesser, if widespread reports of statins' favourable benefit-risk profile^[23-26] influence physicians to dismiss a possible connection to symptoms. Pharmacist reporting of ADRs is not addressed in the present study. It is unlikely to replace patient reporting since not all patients speak with their pharmacist about their ADR; however, it may serve an important role, augmenting physician and patient reporting.

As in all survey designs, data rely on self-report; therefore, recall and reporting bias may operate. Patients may falsely impute causality. However, for surveillance approaches, the goal of sensitivity overrides that of specificity, since the approach should serve as an early signal of possible unusual patterns of reporting. Moreover, data here suggest physician inferences may also be erroneous, and may do so in a fashion that may perpetuate under-reporting. ADR causality evaluation algorithms enable presumptive external reappraisal of causal likelihood.

A systematic comprehensive active postmarketing surveillance effort targeted to patients as well as clinicians would address many concerns about ADR under-reporting, and about representativeness of ADR reporting. These concerns affect current passive surveillance approaches – targeted to healthcare providers, pharmacists and/or patients as here. However, until routine active surveillance is undertaken, the more reporting the better. Currently, regulatory agencies differ across nations in utilisation and acceptance of patient reporting.^[27-30] These data suggest that patient-targeted reporting may complement provider-targeted reporting, adding yield, at little added cost.

Conclusion

It has been said that “pharmacovigilance – the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems ... is one of the weakest links in drug regulation in the United States”^[31] and that “finding potential drug-safety problems requires skillful observation by clinicians who are attuned to the possibility of drug-related adverse events and aware of the need to report them.”^[32] Physicians commonly fail to report, even when aware of ADRs, contributing to a “gaping hole in the drug safety net”^[8] – particularly given the importance of this reporting as “the most effective source of new ADR reports leading to changes in labeling.”^[33,34] The data here, drawn from one drug class, suggest that awareness itself may also be a major issue: in at least some cases, physicians may fail to contemplate a possible drug connection for symptoms arising in their patients even when there is reason to consider one – and this failure may not be rare. These data suggest that patient-targeting may identify additional putative ADR cases, speeding accrual of reports. Less sparse accrual of ADR reports may facilitate more timely regulatory responses when these are merited, such as notification of potential adverse effects to physicians and the public, and may enable conduct of studies to identify vulnerabilities to mechanisms of and protections

against these ADRs, which may improve patient care and outcomes.

Additional reporting of already-known ADRs is desirable if it can amplify awareness of ADRs, which may improve care for patients. Recognition of hitherto acknowledged ADRs may enable substitution of other, better tolerated medications for a patient, which may reduce morbidity and increase compliance, improving the quality of medication management. However, boosting recognition via patient involvement cannot readily lead to improved treatment unless the physician acknowledges the possibility of a connection.

Future efforts should consider collecting patient-targeted information using population-based, or pharmacy management-based approaches to ADR identification; such approaches will enhance generalisability of findings and may in addition permit determination of ADR rates and risk ratios. But until the resources are devoted to this task, patient-supplemented reporting may boost ADR reporting yield and foster more timely recognition of, and response to, ADRs.

Acknowledgements

We thank Janis Ritchie for administrative assistance; Marvin Hanashiro and all members of the University of California, San Diego, Statin Study and Statin Effects Study group who kindly assisted with this effort; and the study subjects, who generously gave of their time.

The authors have no conflicts of interest to report. This research was funded by a Robert Wood Johnson Generalist Physician Faculty Scholar award to Dr Golomb. The study sponsor did not participate in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

References

- Scott RS, Lintott CJ, Wilson MJ. Simvastatin and side effects. *N Z Med J* 1991; 104 (924): 493-5
- Solomon DH, Avorn J, Coxibs, science, and the public trust. *Arch Intern Med* 2005 Jan 24; 165 (2): 158-60
- Psaty BM, Furberg CD, Ray WA, et al. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *JAMA* 2004 Dec 1; 292 (21): 2622-31
- McNeil JJ, Grabsch EA, McDonald MM. Postmarketing surveillance: strengths and limitations. The flucloxacillin-dicloxacillin story. *Med J Aust* 1999; 170 (6): 270-3
- Arnaiz JA, Carne X, Riba N, et al. The use of evidence in pharmacovigilance. Case reports as the reference source for drug withdrawals. *Eur J Clin Pharmacol* 2001 Apr; 57 (1): 89-91
- Goldman SA. Limitations and strengths of spontaneous reports data. *Clin Ther* 1998; 20 Suppl. C: C40-4
- Lasser KE, Allen PD, Woolhandler SJ, et al. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002 May 1; 287 (17): 2215-20
- Griffin GC, Parkinson RW, Woolley BH. Report every adverse drug reaction! We're all in this together. *Postgrad Med* 1997 Apr; 101 (4): 13-6
- Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance - lack of vigilance, lack of trust. *JAMA* 2004 Dec 1; 292 (21): 2647-50
- Kennedy DL, Goldman SA. Monitoring for adverse drug events. *Am Fam Physician* 1997 Nov 1; 56 (7): 1718, 1721
- van Grootheest K, de Graaf L, de Jong-van den Berg LT. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? *Drug Saf* 2003; 26 (4): 211-7
- Golomb B, Yang E, Denenberg J, et al. Statin-associated muscle adverse effects. *Circulation* 2003 March 5, 107: e7028-9
- Golomb BA, Kane T, Dimsdale JE. Severe irritability associated with statin cholesterol-lowering drugs. *QJM* 2004 Apr; 97 (4): 229-35
- Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002 Oct 1; 137 (7): 581-5
- Sinzinger H, Lupattelli G, Chehne F, et al. Isoprostane 8-epi-PGF2alpha is frequently increased in patients with muscle pain and/or CK-elevation after HMG-co-enzyme-A-reductase inhibitor therapy. *J Clin Pharm Ther* 2001 Aug; 26 (4): 303-10
- Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; 108 (7): 538-46
- Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004 Dec 1; 117 (11): 823-9
- Wagstaff LR, Mitton MW, Arvik BM, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003 Jul; 23 (7): 871-80
- Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002 May 14; 58 (9): 1333-7
- Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother*. 2003 Feb; 37 (2): 274-8
- Phan T, McLeod JG, Pollard JD, et al. Peripheral neuropathy associated with simvastatin. *J Neurol Neurosurg Psychiatry* 1995; 58 (5): 625-8
- Naranjo CC, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45
- Haney DQ. Cholesterol drug is very secret weapon. *San Diego Union Tribune* 1999 Aug 23; Sect. E2
- Brown D. Heart drug far surpasses expectations. *Washington Post* 2001 May 19; Sect. A1
- Dales MJM. Statination. *Intern Med News* 2000; Feb 1: 55
- Roberts M. Statin-fortified drinking water? *BBC News* 2004 Aug 1

27. Van Grootheest K, de Graaf L, de Jong-van den Berg LT. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? *Drug Saf* 2003; 26 (4): 211-7
28. Coulter DM. The New Zealand Intensive Medicines Monitoring Programme. *Pharmacoepidemiol Drug Saf* 1998; 7 (2): 79-90
29. Coulter DM. Privacy issues and the monitoring of sumatriptan in the New Zealand Intensive Medicines Monitoring Programme. *Pharmacoepidemiol Drug Saf* 2001; 10 (7): 663-7
30. US Food and Drug Administration. MedWatch online voluntary reporting form (3500) [online]. Available from URL: <https://www.accessdata.fda.gov/scripts/medwatch/> [Accessed 2007 Jun 4]
31. Lyles A. Postmarketing drug surveillance and death by committee. *Clin Ther* 2006 Jun; 28 (6): 962-3
32. Trontell A. Expecting the unexpected—drug safety, pharmacovigilance, and the prepared mind. *N Engl J Med* 2004 Sep 30; 351 (14): 1385-7
33. Goldman SA, Kennedy DL. MedWatch: FDA's Medical Products Reporting Program. *Postgrad Med* 1998 Mar; 103 (3): 13-6
34. Rossi AC, Knapp DE. Discovery of new adverse drug reactions. A review of the Food and Drug Administration's spontaneous reporting system. *JAMA* 1984 Aug 24-31;252(8):1030-3

Correspondence: Dr *Beatrice A. Golomb*, UCSD Department of Medicine, 9500 Gilman Drive #0995, La Jolla, CA 92093-0995, USA.

E-mail: bgolomb@ucsd.edu