



# **Prevalence and Management of Symptoms Associated With Statin Therapy in Community Practice Insights From the PALM (Patient and Provider Assessment of Lipid Management) Registry**

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## Prevalence and Management of Symptoms Associated with Statin Therapy in Community Practice: Insights from the Patient and Provider Assessment of Lipid Management (PALM) Registry

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When compared against placebo in randomized trials, statins are extremely well tolerated, causing muscle related side effects in 1% or fewer of treated patients.<sup>1</sup> Yet in routine practice, patients often report having symptoms which are misattributed to their statin.<sup>2-4</sup> Using data from the Patient and Provider Assessment of Lipid Management (PALM) Registry, we examined patient-reported rates of statin intolerance, characteristics of patients with perceived side effects, and response to perceived statin intolerance in contemporary practice.

### Methods and Results

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results. The PALM Registry enrolled 7,938 patients from 140 primary care, cardiology, and endocrinology practices in the United States (05/27/2015–11/12/2015), and has been described in detail.<sup>5</sup> Trained study coordinators identified eligible patients (patients on a statin, at risk for cardiovascular disease (CVD), or with prevalent CVD-Supplementary Material) at the time of their visit, who were then sequentially enrolled. Of 9788 eligible patients, n=7937 (81%) consented and enrolled in the

study. Patients were then surveyed regarding statin use, perceived statin-related symptoms and response to symptoms, beliefs about statins and CVD, and sociodemographic characteristics (response rate 95.3%, Supplementary Material).

Clinical characteristics and medications were abstracted from the medical record by study coordinators. All patients had core laboratory lipid levels (LabCorp, Burlington, NC). Categorical variables were compared with Mantel-Haenszel chi-square tests and continuous variables using Wilcoxon rank-sum tests. Multivariable logistic regression modeling was used to evaluate factors associated with symptoms using generalized estimating equations to account for clustering within site, with backward model selection at  $p < 0.05$  for variable retention. Candidate variables were chosen based on either associations with statin use (e.g., demographics, ASCVD history, education, insurance) or prior associations with statin intolerance (e.g., thyroid disease, BMI). Continuous variables were modeled using splines to account for nonlinearity. Statistical analyses were performed using SAS version 9.4 (Cary, NC). All participants provided signed informed consent. Each site obtained institutional review board approval for participation.

### Frequency and Types of Statin-associated Symptoms

Among 7,563 patients, 5,916 (78.2%) reported ever using a statin (5,316 current, 600 former). Among former users, the time since the last statin use was <1 month for 13%, 1 month–<1 year for 29%, 1–5 years for 33%, and >5 years for 17%. Overall, 2,600 reported at least one symptom while on statin therapy, including 41.8% of current users and 63.2% of prior users. The most commonly reported symptoms were muscle aches/cramps (29% current, 51% former), fatigue (14% current, 20% former), and weakness (10% current, 20% former). Memory loss was reported by 10% of current and 9% of prior statin users, followed by constipation (9% current, 8% former), nausea (5% current, 8% former), hives/itching (3% current, 5% former), and other (1% current, 2% former).

### Factors Associated with Symptoms

Table 1 shows the characteristics of patients with and without self-reported statin-associated symptoms. In multivariable modeling among current statin users, female sex (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.24–1.55), coronary artery disease (CAD; OR 1.29, 95% CI 1.15–1.43), increasing BMI (BMI; 1.22 per 5 increase up to 30, 95% CI 1.09–1.37), decreasing age (1.04 per 5 year decrease, 95% CI 1.01–1.07), thyroid disease (1.22, 95% CI 1.06–1.40), higher education (at least some college vs. none, OR 1.17, 95% CI 1.03–1.33), and diabetes (OR 1.13, 95% CI 1.00–1.27), were associated with increased odds of reporting symptoms. Among former statin users, non-Hispanic ethnicity (OR 2.23, 95% CI 1.42–3.49), increasing BMI (1.22 per 5 increase, 95% CI 1.05–1.42), CAD (OR 1.54, 95% CI 1.07–2.21), and female sex (OR 1.45, 95% CI 1.05–2.00) were associated with increasing odds of reporting symptoms.

Those with symptoms reported lower beliefs in statin efficacy and safety and were less likely to report “completely trusting” their doctor (Table 1). Symptomatic patients reported increased worry about CVD compared with those without symptoms.

## Statin Intensity and LDL-C Levels in Current Statin Users

Among current statin users, there was no difference in the rate of high intensity statin use by symptom reporting (30.3% with symptoms vs. 28.2% without,  $p=0.11$ ), but those with symptoms were slightly more likely to be taking non-statin lipid-lowering therapy (27.4% vs. 25.0%  $p=0.049$ ). Low-density lipoprotein cholesterol (LDL-C) levels were higher among those with symptoms compared with those without (median 89.0 vs. 86.0 mg/dL,  $p<0.001$ ).

## Response to Symptoms

Most patients (50.8% overall) tried at least one intervention to stay on statin therapy. Among current statin users, 57.0% of symptomatic patients reported not taking any action to treat the symptom, 24.0% switched statins, 11.3% stopped then re-challenged with the same statin, 12.2% reduced the dose, 8.1% added an additional medication, 5.5% reduced statin frequency, and 2.8% reduced exercise. Among symptomatic former statin users, 25.9% reported no intervention, 33.4% switched statins, 39.1% stopped then re-challenged, 19.1% reduced the dose, 11.1% added an additional medication, 10.9% reduced statin frequency, and 2.6% reduced exercise.

## Impact on Medication Persistence

Adverse effects were the leading reason for discontinuing therapy (51.2% of former users discontinued due to side effects). Willingness to re-try a statin among those who discontinued due to symptoms was high; 26.8% reported they would “not at all” be willing to re-try a statin, 17.8% were “unlikely,” 23.1% “possibly,” 18.2% were “very likely,” and 11.5% reported they would “almost certainly” re-try a statin.

## Comment

Despite data from randomized trials supporting the safety of statin therapy and very low rates of excess muscle related complaints when statins are compared with placebo, very high numbers of adults who take statins continue to report statin-associated symptoms. In our study of adults currently or formerly on statin therapy in routine clinical practice, 41.8% of current and 63.2% of former statin users reporting at least one symptom on statin therapy. This is consistent with prior observational studies, with rates of muscle-related complaints ranging from 10% to 69% in different analyses.<sup>3,6</sup>

Groups most likely to report symptoms included women and those with diabetes or thyroid disease, consistent with other studies.<sup>6</sup> Patients with CAD and those with higher levels of education were also more likely to report symptoms. Symptomatic patients felt less sure that statins were efficacious and were less likely to report “completely” trusting their doctor.

Our study does not establish causation between statin use and symptoms. In clinical trials, statins have not been shown to cause any of the symptoms participants were asked about except for muscle-related symptoms. Further, the rates of muscle related symptoms seen in PALM exceed that shown in trials.<sup>4</sup> This suggests that patients are likely misattributing symptoms with a high background incidence to their statin. Furthermore, patients with negative expectations about statin adverse effects may be more likely to experience them

(the “nocebo effect”).<sup>7</sup> Adults who reported symptoms on statins were more likely to worry about CVD, potentially reflecting a higher level of health-related anxiety. Whether “real” or not, perceived statin-related symptoms often led patients to discontinue therapy. Our data offer hope for improving statin utilization. Many adults with symptoms successfully continued statin therapy and nearly half of former users were willing to re-try a statin. This is consistent with previous studies showing that many who discontinue statin therapy can tolerate re-challenge.<sup>8,9</sup> Although current guidelines recommend that patients presenting with symptoms be re-challenged to establish causation before switching to an alternate statin,<sup>10</sup> patients who continued on therapy were more likely to report switching to another statin or changing the dose. In contrast, re-challenge was more common among those who ultimately stopped therapy. Optimal strategies to identify true vs. perceived statin intolerance while balancing patient preferences remain unclear.

### Limitations

First, patients were queried about symptoms rather than “side effects” while on a statin. The patient survey was intentionally designed this to prevent patients from inferring causation between statins and all the symptoms listed, which included symptoms that are not known to be associated with statins. Second, our analysis of the interventions that were tried after symptom onset was based on patient report, which may be subject to recall bias. Third, only current therapy was confirmed by chart review, not prior therapy. Fourth, participants who volunteered for PALM may have been more likely to have stronger opinions regarding statins than the general population, due to volunteer bias. Finally, though the survey was pilot tested during development, formal reliability and validity testing was not performed.

### Conclusions

In community practice, more than half of adults formerly or currently on statins reported symptoms while on statin therapy, which was the leading cause of statin discontinuation. Given the preponderance of evidence about statin safety from randomized trials, much of this is likely due to misattribution of background symptoms to statins. Even among those on statins, those with symptoms had higher LDL-C levels, potentially reflecting lower adherence. Those reporting symptoms also had less belief in statin efficacy and safety, and less trust in their doctors. Although many patients did not attempt re-challenge, the majority of adults who discontinued statins due to side effects were willing to be re-challenged. These data underscore the magnitude of perceived statin-associated symptoms in community practice and support the need for more robust intervention strategies to address both real and perceived symptoms of statin therapy.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

**Characteristics of Adults With and Without Symptoms While on a Statin**

	Current statin users			Former Statin Users		
	At Least One Symptom N=2221	No Symptoms N=3095	p-value	At Least One Symptom N=379	No Symptoms N=221	p-value
Age	67.0 (60.0, 74.0)	68.0 (60.0, 75.0)	<b>0.007</b>	69.0 (61.0, 76.0)	68.0 (58.0, 76.0)	0.21
Female	47.4%	41.0%	<b>&lt;0.0001</b>	60.7%	52.5%	<b>0.050</b>
Race						
White	84.9%	86.3%	0.52	87.6%	85.0%	0.50
Black/African American	12.7%	11.6%	.	11.1%	12.7%	.
Asian	2.1%	1.8%	.	1.3%	1.8%	.
Other	0.3%	0.2%	.	0.0%	0.5%	.
Ethnicity						
Hispanic/Latino	9.1%	12.2%	<b>0.0004</b>	8.5%	17.8%	<b>0.0007</b>
Insurance						
Private	58.5%	58.5%	0.94	55.0%	55.5%	0.16
Government	39.8%	39.7%	.	41.8%	38.2%	.
Other (non-U.S.)/none	1.8%	1.8%	.	3.2%	6.4%	.
Highest level of education						
At least some college	66.2%	61.3%	0.0003	65.8%	67.7%	0.63
Obese (BMI ≥30)	52.1%	46.2%	<b>&lt;0.0001</b>	54.8%	42.2%	<b>0.003</b>
Systolic BP (mmHg)	128.0 (118.0, 140.0)	128.0 (118.0, 138.0)	0.04	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)	0.41
Diastolic BP (mmHg)	76.0 (70.0, 80.0)	76.0 (70.0, 80.0)	0.58	75.0 (70.0, 82.0)	76.0 (70.0, 80.0)	0.79
High-intensity statin	30.3%	28.2%	0.11	-	-	
Current non-statin LLT	27.4%	25.0%	<b>0.049</b>	30.5%	22.0%	<b>0.026</b>
CAD	42.1%	38.1%	<b>0.004</b>	35.6%	27.3%	<b>0.036</b>
Peripheral arterial disease	8.0%	7.6%	0.63	7.9%	5.0%	0.17
Prior stroke or TIA	8.2%	6.9%	0.06	7.7%	6.8%	0.71
Diabetes	44.6%	39.2%	<b>&lt;0.0001</b>	38.3%	37.3%	0.81
Hypertension	80.8%	80.9%	0.89	78.1%	73.2%	0.17
Current smoker	10.3%	11.7%	0.11	9.5%	10.0%	0.84
History of elevated liver function tests	3.2%	2.9%	0.58	4.5%	5.0%	0.78

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	Current statin users		Former Statin Users		p-value
	At Least One Symptom N=2221	No Symptoms N=3095	At Least One Symptom N=379	No Symptoms N=221	
History of myopathy	4.2%	3.0%	7.4%	4.6%	0.17
Thyroid disease	18.0%	14.7%	19.6%	17.4%	0.50
Dialysis or CKD	10.2%	10.2%	10.6%	12.7%	0.42
LDL-C	89.0 (72.0–111.0)	86.0 (69.0–107.0)	139.0 (115.0, 165.0)	128.0 (100.0, 152.0)	0.0003
Statins are effective % agree to strongly agree	72.4%	79.7%	53.8%	58.1%	0.10
Statins are safe % agree to strongly agree	49.3%	66.5%	22.3%	43.9%	<0.0001
Statins cause liver damage % agree to strongly agree	38.7%	27.8%	44.0%	30.8%	<0.0001
Statins cause muscle aches % agree to strongly agree	62.2%	28.9%	80.4%	28.9%	<0.0001
Statins cause memory loss % agree to strongly agree	21.2%	8.8%	23.0%	6.7%	<0.0001
How often do you worry about heart attack or stroke? % often or occasionally	44.7%	32.6%	51.5%	41.5%	0.022
How much do you trust your doctor with decisions about your medical care? % completely	61.8%	69.4%	56.8%	62.2%	0.19

BMI indicates body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; LIT, lipid-lowering therapy; TIA, transient ischemic attack; U.S., United States

High-intensity statin defined as atorvastatin 40 mg, rosuvastatin 20 mg. Statin intensity not assessed in former statin users.

Categorical variables presented as median (25th, 75th percentile)