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ORIGINAL RESEARCH

Understanding the Patient Perception of Statin Experience: A Qualitative Study

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ABSTRACT

Introduction: Statin intolerance (SI) occurs in patients with dyslipidemia treated with statins. Statin-associated symptoms have been reported, but the overall patient experience is poorly understood. No instruments are available to collect this patient experience. Our aim is to develop a patient survey to define SI from the patient's perspective, inform clinical practice, and identify potential patient characteristics and barriers associated with discontinuing treatment when statin-related difficulties are encountered.

Methods: We conducted qualitative concept elicitation interviews with 65 patients across 12 European study sites. A semi-structured qualitative interview guide was developed based on literature review and clinician interviews. Concept elicitation interviews with patients were used to describe the patient experience and develop the conceptual framework for the survey.

Results: Symptoms experienced by patients included muscle and non-muscle-related pain and discomfort; other muscle-related symptoms; gastrointestinal, cardiovascular, cold-like, fatigue-related, and sensory and systems symptoms; mood changes; and cognitive and memory problems. Impacts included limitations on general physical functioning; physical activities; social functioning; emotional impacts; sleep disturbances; decreased productivity; and increased healthcare use. Conceptual framework elements to support survey goals include demographic and clinical characteristics, health information and beliefs, statin side-effect history, symptom severity, and impact severity.

Conclusions: Symptoms and impacts described by patients showed a wider range of symptoms

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and impacts than usually discussed clinically. The patient survey is designed to capture information from patients who experience difficulties with statin therapy and may be useful in identifying patients who are at higher risk for giving up or discontinuing their treatment.
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INTRODUCTION

Statins are a highly effective treatment for dyslipidemias [1]. They have been shown to reduce the risk of ischemic heart disease and stroke, and are one of the most commonly prescribed medications. In 2011, 13.0% of Britain's population and Slovakia's population were prescribed a statin or statin-like drug, followed by Belgium (12.2%), Norway (11.6%), and Denmark (11.5%), and with similar patterns throughout Europe [2]. In light of their prevalence, it is important to understand potential adverse drug reactions (ADRs) reported by patients that are associated with the use of statins.

While a number of studies have explored statin-associated adverse effects, there remains a lack of standard definitions of statin intolerance [3] or a clear clinical presentation of statin-related symptoms (e.g., myalgia) [4]. No biomarkers are currently available to detect the most common symptoms, statin-associated muscle symptoms [5] or additional symptoms that patients report. Differences in study design and nonuniformity of assessment tools have contributed to conflicting conclusions about the prevalence and severity of statin-associated ADRs [6]. This is further complicated by differing rates of reported adverse effects in clinical practice versus clinical trials, with clinical trials showing very low rates of ADRs [7]. Symptoms that have been reported to be associated with statin use are primarily muscle symptoms, but also include gastrointestinal, renal, and hepatic issues, mood and psychological disorders, and problems with cognition and memory [8, 9]. The symptoms and severity of statin intolerance vary from patient to patient and from medication to medication [10]. Notably, most patients who experience statin intolerance to one medication can tolerate subsequent trials of other statins [9].

We aimed to identify and understand the characteristics of statin intolerance from the perspective of the patient who is taking statins and experiencing difficulties. The overall objective of this work is to produce a patient survey to describe the burden of patient-perceived statin intolerance and potentially identify prospective patients who may have the same types of difficulties with statin treatment. This manuscript describes the qualitative study conducted to support the development of the content included in the patient survey.

METHODS

Literature Review

The first step in the development of the survey was to conduct a review of the literature to identify key elements of the patient experience that could be relevant in assessing symptom severity and life impacts in patients experiencing statin intolerance. We conducted a systematic search of articles published during 2001–2016 in PubMed. Additional articles were provided by the European Atherosclerosis Society. A total of 35 full articles that reported concepts of statin-related symptoms or impact were reviewed. Symptoms reported in the literature reviewed included muscle-related, gastrointestinal, renal/hepatic, mood/psychological, and cognition symptoms and pain (Supplemental Table S1). Impacts identified from the literature review included limitations on physical functioning and daily activities, fatigue, sleep, and the patient–clinician relationship.

Clinician Interviews

A steering committee was formed to identify a sample of cardiovascular clinicians working in

dyslipidemia across seven European countries: the Czech Republic, Italy, Norway, Slovakia, Spain, Sweden, and the UK. Sites were selected to represent different cultures and different types of practice settings. All clinicians had a current practice treating hyperlipidemia, experience using statins, and a concern about patients who experience difficulties with their statin treatment. Clinicians participated in two 60-min telephone interviews using a semi-structured interview guide. Interviews were transcribed and used to summarize responses against key questions and topics.

Results from the literature review and clinician interviews were used to inform the content of the interview guide for patient concept elicitation interviews with patients.

Patient Interviews

Qualitative interviews were conducted with patients having difficulty with their prescribed statin treatment. These interviews were used to identify concepts relevant to the patient experience, and of interest to have included in the patient survey. Participants were identified and recruited by clinicians from 12 different study sites in the EU. These were two sites each in the Czech Republic, Italy, Spain, Slovakia, and Sweden and one site each in the UK and Norway. Ethics committee approval was obtained for each study site (Supplemental List S1), and all participants provided written informed consent prior to initiation of any study activity.

Eligible participants were $\geq$ 18 years of age at screening, had been treated with $\geq$ 1 statin within the 3 years prior to screening, and their prescribing physician had taken at least one of the following actions to address a side effect or symptom attributable (by either the patient or physician) to the prescribed statin therapy:

1. Statin therapy had been discontinued completely;
2. A switch to another statin occurred or prescribed dosage was lowered; and/or
3. Additional therapy (including nonprescribed medications, herbal medications, vitamins) was initiated.

Patients were excluded from the study if the action to change statin therapy was not based on a statin-related symptom (e.g., symptom related to a different medication or other pre-existing condition), had a pre-existing neuromuscular condition (e.g., fibromyalgia, multiple sclerosis, muscular dystrophy), or untreated hypothyroidism.

Patients completed a demographic questionnaire during their enrollment visit and were scheduled for an individual face-to-face interview session. All interviews were conducted in person, in the native language of each country, and were audio-recorded and transcribed. During each interview, the semi-structured interview guide was used to elicit descriptions of the patient experience with statin-related difficulties. Interviews were all conducted in commercial research facilities and monitored by senior project staff. Simultaneous translation was used to provide the monitor with details of the interview in real time and to generate an English voice file for transcription. The transcripts were coded using Atlas-ti software by multiple coders to identify predominant statin-related symptoms and impact concepts.

To evaluate the consistency between coders and reliability of the coding process, a formal assessment of inter-rater agreement was conducted. Approximately 10% of concept elicitation transcripts were independently dual-coded; the resulting transcript pairs were compared to evaluate any differences in the code assignment between the two coders. Upon completion of the coding process, saturation of concept (the point at which no new information is forthcoming from the concept elicitation interviews) was evaluated. Transcripts were ordered chronologically by the date conducted and divided into six groups. Each group of interviews was evaluated to identify the appearance of new information (new codes) and compared to the previous group to identify the point at which the interviews were no longer providing new information. This would indicate that no further information would be expected by continuing interviews with this population.

During the interview process, patients were asked to rate the severity of their symptoms on a scale of 0 (none) to 10 (extremely severe), and

the bothersomeness of their symptoms on a scale of 0 (not bothersome at all) to 10 (extremely bothersome). Patients were also asked to rate the difficulty of the impacts of statin intolerance on their lives using a scale of 0 (not at all difficult to cope with) to 10 (extremely difficult to cope with).

Survey Development

The concept elicitation interview results were presented to the Steering Committee for discussion and decisions regarding the content that should be covered by the patient survey. Following these discussions, a conceptual framework was developed to reflect the proposed structure and subdomains, and a preliminary draft of the patient questionnaire was developed in English. Once the measure was approved by the team, the contents were translated into the appropriate language for each participating country. Country-specific information (such as the statin list that might be prescribed in each country) was reviewed by the site investigators, and the patient survey was prepared for the next step of assessment, in which the clarity and understandability of the items are checked with patients using cognitive interviews prior to the use of the survey for data collection.

RESULTS

Clinician Interviews

Fourteen clinicians participated in interviews, representing two hospital practices, five outpatient clinics, six specialty lipid clinics, and one private practice. Eight clinicians had > 20 years of clinical experience. The frequency reported for patient visits for dyslipidemia ranged between 2 and 3 months up to 6 months or annually. The clinicians' perceptions of specific symptoms and impacts of statin intolerance are shown in Supplemental Table S2, and clinician quotations defining statin intolerance are reported in Supplemental Table S3. Most complaints received by clinicians were described by them as being about general activity limitation and reduced quality of life, tied largely to the types of activities that the patients felt were restricted (including choice of sports, everyday work, and walking for health and exercise). Two clinicians reported patient complaints that affected their sleep, and therefore had other quality of life repercussions on their subsequent days, such as chronic tiredness and fatigue.

When asked about determining whether or not a symptom was statin-related, 11 clinicians (79%) indicated that they would base their decision on the typical practice of statin challenge, whereby the statin is discontinued and the patient is watched to see if the symptoms disappear, and 10 clinicians (71%) indicated they would base their decisions on the results of medical tests (e.g., liver function, thyroid function, creatine kinase levels).

Patients

A total of 65 patients participated in concept elicitation interviews from the Czech Republic (n = 10), Italy (n = 10), Norway (n = 8), Slovakia (n = 10), Spain (n = 10), Sweden (n = 9), and the UK (n = 8). The mean age was 61.5 years [standard deviation (SD) 11.5] and slightly over half of the participants were male (54%) (Table 1). More than half of the patients (60%) were no longer using a statin and several of these patients remarked during the interview process that they discontinued their statin treatment without consulting or informing their clinician.

Results of Concept Elicitation Interviews

A total of 5485 different quotations were coded as concepts from the 65 transcripts, and grouped by similarity of content. Symptoms expressed by patients included muscle-related pain and discomfort, non-muscle-related pain and discomfort, muscle-related symptoms that were different than pain, gastrointestinal symptoms, cardiovascular symptoms, cold-like symptoms, mood changes due to medication, cognitive and memory problems, fatigue-related symptoms, and sensory and systems symptoms (Table 2). Impacts expressed by patients included limitations on physical

Table 1 Demographic and clinical characteristics of participating patients

	Czech Republic (*n* = 10)	Italy (*n* = 10)	Norway (*n* = 8)	Slovakia (*n* = 10)	Spain (*n* = 10)	Sweden (*n* = 9)	United Kingdom (*n* = 8)	All patients (*n* = 65)
Age, mean years (SD)	62.2 (7.4)	60.8 (7.1)	59.5 (8.9)	59.9 (14.9)	63.5 (11.6)	63.1 (17.9)	NA	61.5 (11.5)
Sex, *n* male (%)	5 (50)	7 (70)	4 (50)	4 (40)	7 (70)	6 (67)	2 (25)	35 (54)
Highest education level, *n* (%)								
High school only	0	0	0	0	1 (10)	0	0	1 (2)
Some college	6 (60)	5 (50)	2 (25)	6 (60)	5 (50)	7 (78)	0	31 (48)
Bachelor's degree	1 (10)	3 (30)	1 (13)	4 (40)	3 (30)	2 (22)	3 (38)	17 (26)
Graduate/professional school	3 (30)	2 (20)	5 (63)	0	1 (10)	0	5 (63)	16 (25)
Employment status, *n* (%)								
Employed full-time	4 (40)	5 (50)	3 (38)	3 (30)	4 (40)	2 (22)	0	21 (32)
Employed part-time	1 (10)	0	0	0	0	1 (11)	0	2 (3)
Self-employed	1 (10)	2 (20)	0	1 (10)	1 (10)	0	3 (38)	8 (12)
Retired	4 (40)	3 (30)	4 (50)	6 (60)	4 (40)	6 (67)	5 (63)	32 (49)
Unable to work	0	0	1 (13)	0	1 (10)	0	0	2 (3)
Select comorbid conditions, *n* (%)								
Cardiovascular disease	5 (50)	6 (60)	3 (38)	4 (40)	6 (60)	6 (67)	4 (50)	34 (52)
Hypertension	4 (40)	3 (30)	2 (25)	6 (60)	5 (50)	9 (100)	3 (38)	32 (49)
FH	4 (40)	8 (80)	4 (50)	4 (40)	2 (20)	0	1 (13)	23 (35)
Diabetes	0	0	1 (13)	4 (40)	0	2 (22)	0	7 (11)
Depression	0	0	0	0	0	0	0	0
Sleep apnea	0	0	3 (38)	0	0	0	0	3 (5)
Time since first statin prescription, mean years (SD)	9.9 (9.4)	8.5 (6.7)	14.9 (13.9)	6.9 (6.8)	9.9 (11.8)	12.2 (8.0)	10.1 (8.4)	10.3 (9.4)
Satisfaction with current treatment,[a] mean score (SD) [*n*]	5.2 (4.9) [8]	3.9 (3.9) [7]	5.3 (4.5) [6]	4.9 (3.9) [10]	6.2 (4.4) [7]	10.0 (0.0) [3]	4.0 (NC) [1]	5.4 (4.1) [42]
Current number of statins, *n* (%)								
0	8 (80)	5 (50)	3 (38)	7 (70)	2 (20)	8 (89)	6 (75)	39 (60)
1	2 (20)	3 (30)	2 (25)	3 (30)	6 (60)	1 (11)	2 (25)	19 (29)
2	0	2 (20)	3 (38)	0	2 (20)	0	0	7 (11)

FH familial hypercholesterolemia, *[n]* patients with data available, *NA* not available, *NC* not calculated, *SD* standard deviation

[a] Satisfaction with treatment was scored on a numerical rating scale from 0 (not satisfied at all) to 10 (extremely satisfied)

Table 2 Statin intolerance symptom code frequencies

Symptoms	No. patient language expressions within concept	% of 2069 symptom expressions (%)	No. transcripts contributing to concept expression	% of 65 transcripts contributing (%)
Non-muscle-related pain and discomfort	289	14		
Arthritis and bone symptoms	181	8.7	33	50.8
Bone and joint weakness	5	0.2	3	4.6
Burning and stinging	21	1.0	6	9.2
Headache	23	1.1	7	10.8
Non-muscle neck and back pain	15	0.7	7	10.8
Non-muscle pain or discomfort	44	2.1	11	16.9
Muscle-related pain or discomfort	574	28		
Muscle ache	106	5.1	33	50.8
Muscle burning	7	0.3	1	1.5
Cramps	152	7.3	32	49.2
Muscle pulls and tears	6	0.3	4	6.2
Soreness and tenderness	47	2.3	23	35.4
Muscle pain or discomfort	256	12.4	50	76.9
Non-pain muscle-related symptoms	279	13		
Muscle weakness	116	5.6	32	49.2
Muscle stiffness and tightness	90	4.3	33	50.8
Muscle tingling	27	1.3	8	12.3
Muscle loss	21	1.0	5	7.7
Muscle lump	4	0.2	1	1.5

Table 2 continued

Symptoms	No. patient language expressions within concept	% of 2069 symptom expressions (%)	No. transcripts contributing to concept expression	% of 65 transcripts contributing (%)
Other muscle issues[a]	21	1.0	8	12.3
Gastrointestinal symptoms	115	6		
Abdominal discomfort	8	0.4	3	4.6
Abdominal pain or cramps	29	1.4	11	16.9
Acid reflux	4	0.2	2	3.1
Bloating	4	0.2	2	3.1
Constipation	8	0.4	4	6.2
Diarrhea	32	1.5	11	16.9
Nausea	23	1.1	8	12.3
Stool changes	4	0.2	1	1.5
Vomiting	3	0.1	1	1.5
Cardiovascular symptoms	28	1		
Arrhythmia	4	0.2	1	1.5
Blood pressure changes	6	0.3	3	4.6
Chest pain	4	0.2	2	3.1
Difficulty breathing	9	0.4	5	7.7
Heart palpitations	3	0.1	1	1.5
Increased heart rate	2	0.1	1	1.5
Cold-like symptoms	127	6		
Chills	7	0.3	6	9.2
Coughing	3	0.1	2	3.1
Dizziness	32	1.5	12	18.5
Feels hot	12	0.6	3	4.6
Feels sick or poorly	44	2.1	18	27.7
Runny or stuffy nose	7	0.3	6	9.2

Table 2 continued

Symptoms	No. patient language expressions within concept	% of 2069 symptom expressions (%)	No. transcripts contributing to concept expression	% of 65 transcripts contributing (%)
Sneezing	2	0.1	2	3.1
Throat symptoms	19	0.9	9	13.8
Other cold-like symptoms[b]	1	< 0.1	1	1.5
Mood changes due to medication	94	5		
Anxiety	28	1.4	10	15.4
Apathy	4	0.2	1	1.5
Depression	45	2.2	16	24.6
Hostility or agitation	11	0.5	5	7.7
Lack of confidence	5	0.2	1	1.5
Other mood changes[c]	1	< 0.1	1	1.5
Cognitive and memory problems	108	5		
Cognitive problems	44	2.1	14	21.5
Memory problems	64	3.1	16	24.6
Fatigue-related symptoms	299	14		
Exhaustion	45	2.2	21	32.3
Fatigue	50	2.4	22	33.8
Lack of energy	76	3.7	31	47.7
Tiredness	118	5.7	36	55.4
Weakness	10	0.5	6	9.2
Sensory and systems problems	67	3		
Eye symptoms	4	0.2	2	3.1
Ear symptoms	5	0.2	3	4.6
Mouth symptoms	3	0.1	1	1.5
Skin and hair symptoms	55	2.7	12	18.5

Table 2 continued

Symptoms	No. patient language expressions within concept	% of 2069 symptom expressions (%)	No. transcripts contributing to concept expression	% of 65 transcripts contributing (%)
Additional symptoms	89	4		
Allergy	1	< 0.1	1	1.5
High blood sugar	1	< 0.1	1	1.5
Infections	1	< 0.1	1	1.5
Kidney problems	10	0.5	7	10.8
Liver problems	20	1.0	7	10.8
Sweating	8	0.4	5	7.7
Swelling or inflammation	26	1.3	11	16.9
Uncoordinated movement	4	0.2	1	1.5
Weight-related symptoms	18	0.9	5	7.7

[a] Other muscle issues included congestion, creatine kinase, heat, and spine blocked
[b] Other cold-like symptoms included heavy head
[c] Other mood changes included suicidal thoughts

functioning in general, physical activities, and social functioning. Patients also noted emotional impacts, sleep disturbances, impacts on productivity, and increased use of healthcare (Table 3).

While a few new codes were still coming forward in the last transcript group for the saturation analysis, it was clear from the content that the concepts being expressed were not new concepts but the use of different language to describe the same concept, and were basically reflecting the variation between language use in the countries. Therefore, the developers felt confident that all relevant concepts from this group of patients were registered for consideration. Inter-rater agreement ranged between 94.0 to 98.5% for the assignment of codes.

Patients were asked to rate the severity and bothersomeness of statin-related symptoms (Table 4). Notably, some symptoms with higher severity ratings were associated with low levels of bothersomeness (e.g., cold-like symptoms of chills), and conversely, some symptoms with lower severity ratings had higher bothersomeness ratings (e.g., constipation). Patients were also asked to rate the difficulty of statin-related impacts (Table 5). Based on these ratings, impacts on relationships had the highest (i.e., greatest difficulty) ratings. The severity and bothersomeness ratings were used in conjunction with the coded transcript data to determine the most relevant content to include in the design of the survey.

Conceptual Framework for Statin Intolerance Patient Survey

The goals of the survey are to help describe statin intolerance from the patient perspective, inform clinical practice around statin intolerance, and to identify potential risk characteristics or barriers that may result in patients giving

Table 3 Statin intolerance impact code frequencies

Concept description	No. patient language expressions within concept	% of 1275 impact expressions	No. transcripts contributing to concept expression	% of 65 transcripts contributing
Impacts on physical activities and functioning	461	36		
Falls	6	0.5	2	3.1
Hand function limited	9	0.7	6	9.2
Have to rest more	57	4.5	30	46.2
Physical activities limited	183	14.4	50	76.9
Physical functioning limited	206	16.2	48	73.8
Impacts on social functioning	170	13		
Activity harder	5	0.4	4	6.2
Altered close relationships	20	1.6	11	16.9
Altered relationships with friends	8	0.6	7	10.8
General functioning limited	60	4.7	35	53.8
Lifestyle restrictions	31	2.4	19	29.2
Sexual activity	4	0.3	2	3.1
Social activities affected	42	3.3	26	40.0
Emotional Impacts	283	22		
Anxiety	80	6.3	28	43.1
Apathy	5	0.4	2	3.1
Depression	51	4.0	22	33.8
Frustration	27	2.1	14	21.5
Hopelessness	5	0.4	3	4.6
Hostility or aggression	38	3.0	19	29.2
Lack of confidence	12	0.9	10	15.4
Mental Tiredness	5	0.4	2	3.1
Stress	16	1.3	10	15.4

Table 3 continued

Concept description	No. patient language expressions within concept	% of 1275 impact expressions	No. transcripts contributing to concept expression	% of 65 transcripts contributing
Worry	44	3.5	20	30.8
Sleep disturbances	124	10		
Difficulty falling asleep	30	2.4	22	33.8
Difficulty staying asleep	49	3.8	25	38.5
Poor quality sleep	45	3.5	23	35.4
Impacts on productivity	132	10		
Diminished work	25	2.0	15	23.1
Limitations to chores	34	2.7	17	26.2
Poor performance or productivity	43	3.4	20	30.8
Trouble reading	5	0.4	3	4.6
Work more difficult	25	2.0	17	26.2
Use of healthcare	58	5		
Increased doctor visits	42	3.3	33	50.8
Increased hospitalization	12	0.9	9	13.8
Treatment burden	4	0.3	4	6.2
Additional impacts	47	4		
Altered attire	9	0.7	3	4.6
Dietary changes	3	0.2	2	3.1
Financial burden	2	0.2	2	3.1
Increased dependence	2	0.2	2	3.1
Overall quality of life	31	2.4	22	33.8

up and discontinuing their statin treatment. Six key elements were identified for the conceptual framework for the survey (Table 6): (1) respondent demographics; (2) clinical characteristics; (3) health information and beliefs; (4) statin side effect history; (5) symptom severity; and (6) impact severity.

Table 4 Statin intolerance symptom severity and bothersomeness ratings

Symptoms	All patients (n = 65)			
	Symptom severity		Symptom bothersomeness	
	n	Mean score (SD) [range]	n	Mean score (SD) [range]
Non-muscle-related pain and discomfort				
Arthritis and bone symptoms				
Bone or joint ache	10	7.7 (0.9) [6–9]	4	7.8 (2.1) [6–10]
Bone or joint pain	3	5.7 (2.9) [4–9]	26	7.7 (2.1) [3–10]
Stiff or cracking joints	3	6.7 (3.5) [3–10]	2	10.0 (0) [10]
Soreness	5	7.8 (2.0) [6–10]	7	7.1 (3.0) [3–10]
Tenderness	3	7.0 (1.7) [5–8]	7	7.7 (1.3) [6–10]
Bone or joint weakness				
Joint weakness	0	NA	1	8.0
Burning and stinging				
Burning	2	8.5 (2.1) [7–10]	1	9.0
Stinging	0	NA	1	8.0
Headache	4	7.3 (2.1) [5–10]	5	6.2 (2.2) [5–10]
Non-muscle neck or back pain	0	NA	6	8.2 (3.0) [3–10]
Non-muscle pain or discomfort	21	7.4 (2.0) [2–10]	14	7.6 (1.6) [5–10]
Muscle-related pain or discomfort				
Muscle ache	23	7.4 (2.1) [3–10]	28	6.4 (2.0) [2–10]
Muscle burning	0	NA	1	7.0
Muscle cramps	25	7.4 (2.2) [2–10]	26	7.0 (2.5) [2–10]
Muscle tears	1	10.0	2	9.0 (1.4) [8–10]
Soreness and tenderness				
Soreness	12	8.1 (1.8) [5–10]	14	6.8 (1.9) [4–10]
Tenderness	8	8.3 (1.7) [5–10]	7	7.0 (1.9) [4–10]
Muscle pain or discomfort	39	7.2 (2.3) [3–10]	26	7.1 (2.4) [1–10]
Non-pain muscle-related symptoms				
Muscle weakness				
Muscle fatigue	13	7.7 (2.6) [1–10]	13	7.1 (2.2) [4–10]
Muscle heaviness	18	7.0 (2.5) [1–10]	18	6.9 (2.2) [2–10]
Muscle weakness	19	7.4 (1.9) [5–10]	26	7.0 (2.0) [2–10]
Muscle stiffness	19	7.1 (2.5) [3–10]	28	6.4 (2.2) [1–10]
Muscle tingling	1	5.0	5	6.2 (1.3) [5–8]

Table 4 continued

Symptoms	All patients (n = 65)			
	Symptom severity		Symptom bothersomeness	
	n	Mean score (SD) [range]	n	Mean score (SD) [range]
Muscle loss				
Lack of tone	1	5.0	1	7.0
Muscle loss	1	3.5	4	6.0 (1.8) [4–8]
Muscle wasting	0	NA	1	10.0
Muscle lump	0	NA	1	6.0
Warm/heat in upper leg; blocking spine chest part	2	8.8 (1.8) [7.5–10]	2	8.5 (2.1) [7–10]
Gastrointestinal symptoms				
Abdominal discomfort				
Poor digestion	1	8.0	1	8.0
Abdominal pain or cramps	6	8.0 (1.4) [6–10]	8	6.4 (2.3) [3–9]
Acid reflux	1	10.0	1	10.0
Bloating	2	7.5 (0.7) [7–8]	1	7.0
Constipation	2	5.0 (2.8) [3–7]	3	8.0 (2.0) [6–10]
Diarrhea	9	7.3 (1.9) [4–9]	11	6.1 (2.8) [1–10]
Nausea	5	7.2 (2.6) [4–10]	6	6.7 (3.4) [2–10]
Stool changes	0	NA	1	7.0
Vomiting	4	6.8 (2.8) [4–10]	2	7.5 (3.5) [5–10]
Cardiovascular symptoms				
Difficulty breathing	0	NA	4	9.3 (1.0) [8–10]
Heart palpitations	1	8.5	2	7.0 (2.8) [5–9]
Increased heart rate	1	5.0	0	NA
Cold-like symptoms				
Chills	2	7.0 (1.4) [6–8]	3	5.3 (2.1) [3–7]
Dizziness				
Dizziness	2	8.5 (0.7) [8–9]	2	9.0 (1.4) [8–10]
Feels faint	2	9.5 (0.7) [9–10]	1	10.0
Feels sick or poorly	6	6.8 (1.8) [5–10]	8	6.9 (2.5) [2–10]
Feels hot	2	7.0 (1.4) [6–8]	2	7.5 (2.1) [6–9]
Runny or stuffy nose	3	8.7 (1.2) [8–10]	4	5.3 (3.0) [2–9]
Sneezing	1	8.0	4	4.0 (0.8) [3–5]

Table 4 continued

Symptoms	All patients (n = 65)			
	Symptom severity		Symptom bothersomeness	
	n	Mean score (SD) [range]	n	Mean score (SD) [range]
Throat symptoms				
Sore throat	5	6.5 (2.8) [3–9.5]	8	5.5 (2.7) [1–9]
Mood changes due to medication				
Anxiety				
Anxiety	12	7.8 (2.8) [1–10]	12	8.4 (1.2) [6–10]
Nervous	0	NA	1	8.0
Depression				
Depression	6	9.2 (1.3) [7–10]	7	7.9 (1.7) [5–10]
Low mood	1	5.0	1	6.0
Sadness	2	9.5 (0.7) [9–10]	3	7.7 (1.5) [6–9]
Mood changes	0	NA	1	7.0
Hostility or agitation	5	8.4 (2.2) [6–10]	6	6.8 (2.8) [3–10]
Cognitive and memory problems				
Cognitive symptoms				
Fuzzy thoughts	0	NA	1	9.0
Difficulty concentrating	2	8.5 (2.1) [7–10]	6	8.8 (1.2) [7–10]
Memory problems				
Amnesia	2	10.0 (0.0) [10]	0	NA
Memory problems	10	7.2 (2.3) [4–10]	10	8.2 (2.1) [4–10]
Fatigue-related symptoms				
Fatigue	0	NA	15	7.1 (1.9) [3–10]
Exhaustion	17	7.3 (1.8) [5–10]	22	7.5 (2.0) [2–10]
Lack of energy	24	7.1 (2.2) [3–10]	26	7.4 (2.1) [2–10]
Tiredness	24	6.7 (2.3) [3–10]	21	7.3 (2.0) [5–10]
Sensory and systems problems				
Skin and hair symptoms				
Bruising	1	2.0	1	6.0
Eczema	0	NA	1	6.0
Hair loss	2	9.0 (0.0) [9]	2	10.0 (0.0) [10]
Rash	2	8.5 (2.1) [7–10]	2	10.0 (0.0) [10]
Sensitive skin	0	NA	2	9.5 (0.7) [9–10]

Table 4 continued

Symptoms	All patients (n = 65)			
	Symptom severity		Symptom bothersomeness	
	n	Mean score (SD) [range]	n	Mean score (SD) [range]
Skin ulcers	1	6.0	1	10.0
Additional symptoms				
Kidney problems				
Frequent urination	0	NA	2	7.0 (4.2) [4–10]
Liver problems	1	8.0	2	7.0 (4.2) [4–10]
Sweating	0	NA	2	9.0 (1.4) [8–10]
Swelling or inflammation				
Swelling	2	9.5 (0.7) [9–10]	4	8.3 (1.7) [6–10]
Weight-related symptoms				
Fat loss	0	NA	1	0.0
Weight gain	1	10.0	1	10.0

n number of patients rating symptom, *NA* not applicable, *SD* standard deviation

Table 5 Statin intolerance impact difficulty ratings

Concept description	All patients (n = 65)	
	n	Mean score (SD) [range]
Impacts on physical activities and functioning		
Falls	1	3.0
Have to rest more	17	6.8 (1.6) [4–9]
Physical activities limited	32	6.5 (2.6) [1–10]
Physical functioning limited	26	7.1 (2.5) [1–10]
Impacts on social functioning		
Altered close relationships	5	8.4 (1.7) [6–10]
Altered relationships with friends	2	9.0 (1.4) [8–10]
Sexual activity	1	8.0
Social activities affected	16	5.7 (2.3) [1–8]
Lifestyle restrictions	15	7.2 (1.6) [5–10]
General functioning limited	12	6.0 (2.0) [3–9]
Activity harder	1	6.0
Emotional impacts		
Anxiety	13	6.8 (2.6) [3–10]
Mentally tired	1	10.0
Stress	1	6.0

Table 5 continued

Concept description	All patients (n = 65)	
	n	Mean score (SD) [range]
Worry	16	6.9 (2.1) [2–10]
Depression		
Depression	8	7.3 (1.7) [5–10]
Low mood	3	5.7 (2.5) [3–8]
Sadness	15	6.0 (2.5) [3–10]
Frustration		
Annoyance	1	6.0
Frustration	11	7.9 (1.8) [4–10]
Hostility or agitation		
Anger	4	6.8 (2.1) [4–9]
Irritability	1	8.0
Lack of confidence		
Embarrassment	6	6.2 (3.5) [1–10]
Self-deprecation	1	8.0
Sleep disturbances		
Difficulty falling asleep	10	6.6 (2.9) [3–10]
Difficulty staying asleep	6	8.0 (1.7) [5–10]
Poor quality sleep	23	7.3 (2.0) [3–10]
Impacts on productivity		
Diminished work	10	6.8 (3.1) [0–10]
Limitations to chores	8	7.4 (1.8) [5–10]
Poor performance or productivity	17	6.6 (3.0) [0–10]
Work more difficult	1	5.0
Use of healthcare		
Increased doctor visits	23	5.8 (2.9) [0–10]
Increased hospitalization	4	7.8 (2.6) [4–10]
Additional impacts		
Altered attire	1	10.0
Increased dependence	1	8.0
Overall quality of life	1	8.0

n number of patients rating symptom, *NA* not applicable, *SD* standard deviation

Table 6 Conceptual framework for statin intolerance patient survey

Concept	Items for survey
Respondent demographics	Age
	Sex
	Marital status
	Education level
	Employment status
Clinical characteristics	Statin intolerant group (Y/N)
	Self-reported health status
	Comorbid conditions
	Perception of risk for myocardial infarction
	Diagnosis of familial hypercholesterolemia
	Family history of medical conditions
	History of non-statin side effects
	Knowing others who have discontinued a statin
	Current prescriptions per day
	Current over-the-counter medications per day
	Activity level
	Alcohol
	Smoking
	Patient Health Questionnaire (PHQ-4)
Health information and beliefs	Comfort level with Dr.
	Quality of communication with Dr.
	Type of Dr. providing prescribing statin
	Feels listened to by Dr.
	Willingness to try another statin
	Level of involvement with medical care decisions
	Satisfaction with information from Dr.
	Information sources (frequency of use, level of trust)
	Reason for taking a statin
	Reason for not taking a statin
	Cholesterol under control or not

Table 6 continued

Concept	Items for survey
Statin side effect history	Statins taken
	Current use of a statin or not
	Side effects with previous statin
	Type of side effects
	Side effects with current or most recent statin
	Time to onset of side effects
	Side effect interference with activities
	Type of changes made to address side effects
	Improvements after changes made
	Time to improvement
	Timing of most recent side effect experience
	Current over-the-counter supplement
Symptom severity	Muscle aches
	Muscle cramps
	Muscle pain
	Muscle soreness
	Muscle stiffness
	Muscle weakness
	Bone and joint pain
	Abdominal pain
	Lack of energy
	Tires easily
	Exhaustion
	Fatigue
	Memory problems
	Irritability
	Frustration

Table 6 continued

Concept	Items for survey
Impact severity	Needing to rest more
	Reduced ability to be physically active
	Limited social activities
	Increased office visits
	Reduced productivity or performance
	Reduced ability to exercise
	Trouble getting good quality sleep

DISCUSSION

While a number of studies have explored statin-associated adverse effects, the lack of standard definitions of statin intolerance and associated symptoms [3], as well as nonuniformity of the outcomes measured, make it difficult to identify the patients having difficulty with their statin treatment and, more importantly, those at risk for discontinuing their treatment because of the difficulties [11]. Our literature search revealed a notable lack of patient-centered research in the field. There are currently no validated patient-reported outcome measures to assess the symptoms or impacts of statin intolerance. With the introduction of new lipid-lowering therapies for the treatment of dyslipidemias, it is increasingly important to identify patients having difficulties with their statin treatment to ensure timely and clinically beneficial treatment modifications [12]. Our goal is to develop a patient survey to describe the patient experience with statin intolerance to inform clinical practice and assist with identification of patients who may need extra attention to help keep them on a treatment regimen.

This qualitative study identified key symptoms and impacts associated with statin intolerance that were highly relevant to the patient experience. Symptoms of muscle-related pain or discomfort were the most commonly reported statin-related symptoms reported by patients, appearing in 77% of interviews and comprising 28% of symptom expressions. Impacts on physical functioning were the most commonly reported statin-related impacts reported by patients, representing 36% of impact expressions. These observations were consistent with information obtained from the literature review and from clinician interviews. However, the results also showed that the symptom and impact experience from the patient perspective is broader than currently reflected in the literature and assumed by clinicians. While not all of the concepts expressed will be reflected in the survey, those with relevance to larger numbers of the patients interviewed will be included.

Ultimately, results from the patient survey will support clinician awareness for effective decision-making. Evaluation of symptom severity and impact severity will assist with describing the patients who experience a greater symptom and impact burden and have a higher risk of giving up and discontinuing their treatment. While statin side effect histories provide a clinically descriptive picture of the patient's journey through the difficulties with statin treatment, these histories can also provide key information regarding tendencies toward continuing or discontinuing statin use. Other key elements in the conceptual framework are expected to provide insight into which patient characteristics might indicate a possible association with discontinuing statin treatment, and help clinicians identify possible ways to assist those patients in staying on treatment.

Qualitative studies have inherent limitations, including the possibility of selection bias

in the recruitment of sites and patients. The inclusion criteria were selected to intentionally focus on patients who had a recent experience with statins and who returned to their doctor reporting difficulties as a result of the statin. While the patients selected across sites may not be representative of all patients having difficulties with their statins, the group interviewed were from a variety of countries and sites, and the saturation evaluation provides good evidence that sufficient representation of the key concepts from this population came forward in the interview process and was considered.

CONCLUSIONS

Qualitative interviews prompted patients to address a wider range of symptoms and impacts than are usually discussed in clinic visits. A better understanding of the symptoms and impacts that patients experience with statin use may assist clinicians with managing individual patients in a way that provides options that encourage adherence to treatment. The next steps of this research will be to confirm the clarity and understandability of the items in the survey using cognitive interviews, and then to use the survey to obtain a quantitative dataset that can be used to address the outstanding questions of the study.

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REFERENCES

1. Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. Ann Pharmacother. 2012;46:1368–81.
2. Health-at-a-glance-2013. Available from: https://www.oecd.org/els/health-systems/Health-at-a-Glance-2013.pdf. Accessed 23 Aug 2019.
3. Algharably EA, Filler I, Rosenfeld S, Grabowski K, Kreutz R. Statin intolerance—a question of definition. Expert Opin Drug Saf. 2017;16:55–63.
4. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus panel statement on assessment, aetiology and management. Eur Heart J. 2015;36:1012–22.
5. Muntean DM, Thompson PD, Catapano AL, et al. Statin-associated myopathy and the quest for biomarkers: can we effectively predict statin-associated muscle symptoms? Drug Discov Today. 2017;22:85–96.
6. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. Am Heart J. 2014;168:6–15.
7. Vonbank A, Drexel H, Agewall S, et al. Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review. Eur Heart J Cardiovasc Pharmacother. 2018;4:230–6.
8. Tuccori M, Lapi F, Testi A, et al. Statin-associated psychiatric adverse events: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug Saf. 2008;31:1115–23.
9. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013;166:597–603.
10. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015;175:691–700.
11. Alonso R, Cuevas A, Cafferata A. Diagnosis and management of statin intolerance. J Atheroscler Thromb. 2019;26:207–15.
12. Koskinas K, Wilhelm M, Windecker S. Current treatment of dyslipidaemia: PCSK9 inhibitors and statin intolerance. Swiss Med Wkly. 2016;146:w14333.