

Statin Use in Jordan: Patients Experience and Attitude toward Adverse Drug Reactions

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ABSTRACT

Purpose: the aim of this study is to evaluate patients' experience of adverse drug reactions (ADRs) associated with statins "HMG-CoA-reductase inhibitors" use and the patients' attitude toward these ADRs in Jordan, in terms of reporting ADRs, patient adherence and patients' beliefs, from the patients' point of view.

Methods: A cross sectional study was used via a paper-based questionnaire that was distributed among community pharmacies in the capital Amman to be filled by eligible adult patients. A total of 153 patients had completely answered the questionnaire.

Results: A percentage of (72.5%) of the patients reported experiencing ADRs associated with statin drugs. Percentages of patients experienced symptoms related to myopathy, peripheral neuropathy, and some incidents of memory loss problems were (64.7%) (41.2%) (35.9%), respectively. The prevalence of ADRs was influenced by drug generics; simvastatin showed the highest rate of ADRs. Patient adherence to statin therapy was affected by the presence of ADRs, only 58.2% of participants were adherent to their statin drug.

Conclusion: There were differences between different statin agents in the pattern of reporting ADRs. The variability between associated ADRs needs to be considered by physicians when prescribing this drug. Determining the best tolerated statin drug may enhance the patient's adherence.

Keywords: Adverse drug reactions, HMG-CoA-reductase inhibitors, Statins, Cardiovascular, Pharmacovigilance.

INTRODUCTION

An adverse drug reaction (ADR) is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product¹. ADRs are the third leading cause of death after heart disease and cancer in the United States¹, making it a heavy burden on governments, health care organizations and patients. Medically and economically,

ADRs information acquired during clinical trials cannot cover all drug related adverse effects due to many factors including: inadequate sample size, tight restrictions and regulations, limited trial duration and the exclusion of the patients most likely to experience adverse effects such as the children, elderly and those with polypharmacy and comorbidities². Therefore, the post marketing reporting systems represented by patients and medical health providers is considered the first line reference for the detection of any new and unexpected drug related adverse effects.

The use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase inhibitors known as "statins" for

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cardiovascular diseases is growing rapidly among Jordanian patients. The use of these agents showed a significantly reduced risk of cardiovascular morbidity and mortality³. The most common identified ADRs related to statins use are musculoskeletal symptoms including myopathy and myositis, rhabdomyolysis and liver failure. Peripheral neuropathy might also occur, especially after long-term use³. However, they are readily prescribed and are generally considered to be well tolerated drugs. Limited studies have assessed patients' experience of ADRs related to the use of "statins" in Jordan. This will be the first study –up to our knowledge- to evaluate the prevalence and pattern of "statin" adverse reactions and their effects on patient's attitude in Jordan.

2. Experimental

2.1. Study design and study site

A cross-sectional study was conducted in the capital Amman and some of its suburbs. The study was carried out during the period between January 2017 and March 2017.

A convenient sample of patients was recruited;

The inclusion criteria were:

1. The participant should be an adult (aged over 18 years)
2. The participant should be taking one of statin agents for at least one month
3. Participant's consent to take part of the study

The exclusion criteria: incomplete questionnaires

The questionnaire was distributed to a convenient sample of community pharmacies. The pharmacist in charge was responsible to recruit eligible patients who visit the pharmacy. Thirteen community pharmacies were included in the study, each pharmacy was provided by a number of paper-based structured questionnaires to be filled by adult patients taking "statin" drug. The recruitment of the participant was during the prescription refill in the pharmacies and the main cause for the people who declined to participate was the time limit.

2.2. Questionnaire

Having drafted the questionnaire, copies were presented to pharmacy teaching fellows in Al-Isra University, Amman-Jordan and adjustments were made as advised. The first 5 completed questionnaires were used to test any potential issues regarding its contents. Paper-based type of questionnaire was chosen since patients were recruited from community pharmacies and it was convenient for them to use this tool.

A self-reporting questionnaire, modified from previously published studies⁵⁻⁶⁻⁷, was used as a screening tool to identify potential adverse symptoms experienced by the patients that are suspected to be related to their statins. Arabic language was used to develop the questions in the questionnaire. On the first page of the questionnaire, potential participants were welcomed in an introductory information page which included information about the study. Data was collected for each participant by anonymous questionnaire and the return of the complete questionnaire implies the consent of participant. The questionnaire consisted of 19 questions, the first question had to be filled by the pharmacist, i.e. "what is the generic name of statin drug the patient takes", followed by some demographic questions regarding patient's age, gender and educational level. The patients were also asked about the number of daily medicines and the duration of statin drug use.

To collect data on statins ADRs, the patient was asked about specific symptoms related to statin use such as myopathy⁴⁻⁵, peripheral neuropathy⁵⁻⁶, and memory loss⁵⁻⁷. As an example, symptoms of muscle pain, muscle weakness, unexplained fatigue or weakness and muscle cramps were related to myopathy.

Patient education about statin use by either the physician or pharmacist and their response to patient reports of ADRs were also evaluated.

The last section of the questionnaire contained close-ended question asking whether patients had stopped taking statin or changed its regimen because of suspected adverse events. Based on this direct question, the patients were classified either adherent or non-adherent to statin

therapy. Non-adherence was defined as stopping or not taking statin regimen as instructed. Another close-ended question was asked about whether the patients had concerns from statin use or they felt it was important for health.

2.3. Statistical analysis

Data was analyzed using statistical package for social science version 21 (IBM SPSS Statistics, Inc., Chicago, IL, USA). The descriptive analysis was done using frequency test to calculate percentage of variables and Pearson Chi- Square test was used to calculate p-values for categorical variables.

3. Results

3.1. Participant's Characteristics

Total number of (460) questionnaires were distributed, yet 153 patients (33.3%) took part in this cross-sectional study. The required sample size was calculated based on the Jordanian Ministry of Health statistics in 2016. By knowing that 54% of Jordanian population are adults and a 36% of the adult population

has dyslipidemia, the sample size was estimated using Yamane formula with a level of precision of 0.1 to be at least 100 patients. Fortunately, the required sample size was overridden in the present study and 153 patients have been participated. The study population in the present study was clearly identified, the inclusion and the exclusion criteria were set, and the required size of the sample was matched, therefore, selection bias has been avoided.

The demographics of the study sample are described in Table 1. From the total of 153 completed questionnaires atorvastatin was reported as the most commonly prescribed type of statins (n=55; 35.9%) followed by rosuvastatin (n=44; 28.8%), simvastatin (n=34; 22.2%) and fluvastatin (n=15; 9.8%) as illustrated in Figure 1. Most patients were males (n=82; 53.6%) with an average age between 36 and 55 years. About half of the participating patients (54.9%) took statin medicine for less than 3 years and the majority was taking it in combination with other medications.

Table 1. Demographic characteristics of the study sample (n=153)	
Parameter	Results
Patient's age (years)	N (%)
18-35	10 (6.5)
36-55	89 (58.2)
>55	54 (35.3)
Gender	N (%)
Male	82 (53.6)
Female	71 (46.4)
Educational level	N (%)
Less than high school	26 (17.0)
High school	30 (19.6)
Community college	25 (16.3)
Bachelor's degree	63 (41.2)
Postgraduate degree	9 (5.9)

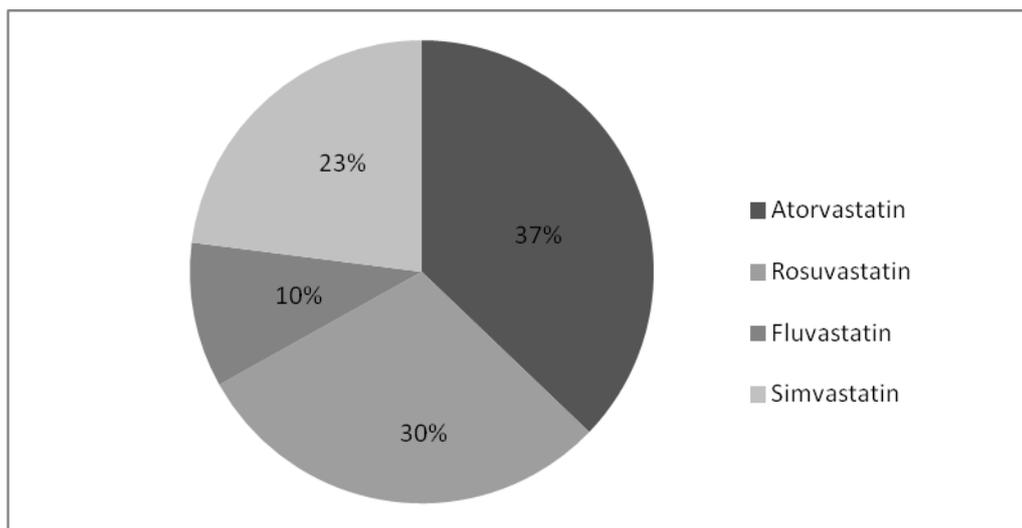


Figure 1: Percentages of prescribing pattern of statin generics

3.2. Adverse drug reactions occurrence

It was found that only 67 (43.8%) of the participants had measured baseline liver enzymes before starting statin and within 3 months of starting treatment as recommended by guidelines⁸.

It was found that 111 (72.5%) of the participants claimed that they experienced at least one ADRs after statin use, 99 (64.7%) of them experienced muscular related side effects, 63 (41.2%) of them reported peripheral neuropathic side effects, and 55 (35.9%) of them claimed that statin use affected their memory and their ability to remember. The incidence of side effects occurrence was not the same among different drug generics, atorvastatin, here, was associated with the least rate of side effects occurrence (63.6%) while simvastatin was associated with the highest rate of side effect

occurrence (86.6%). Figure 2 shows each statin generic and its related ADRs as stated by the patients.

There was no statistically significant link between the occurrence of the side effects and the duration of statin use, however there was a significant link ($P= 0.021$) between memory related problems and the number of patient daily medicines, i.e. patients who were taking higher number of medications reported memory related ADR.

As reported by the patients, about half of the participating patients were educated by their doctor or by pharmacists (46.4% and 51.6% respectively) about the precautions and possible ADRs which may occur after statin use. Remarkably, medically educated patients on possible side effects had higher rate of side effect occurrence than non-educated patients ($P<0.01$).

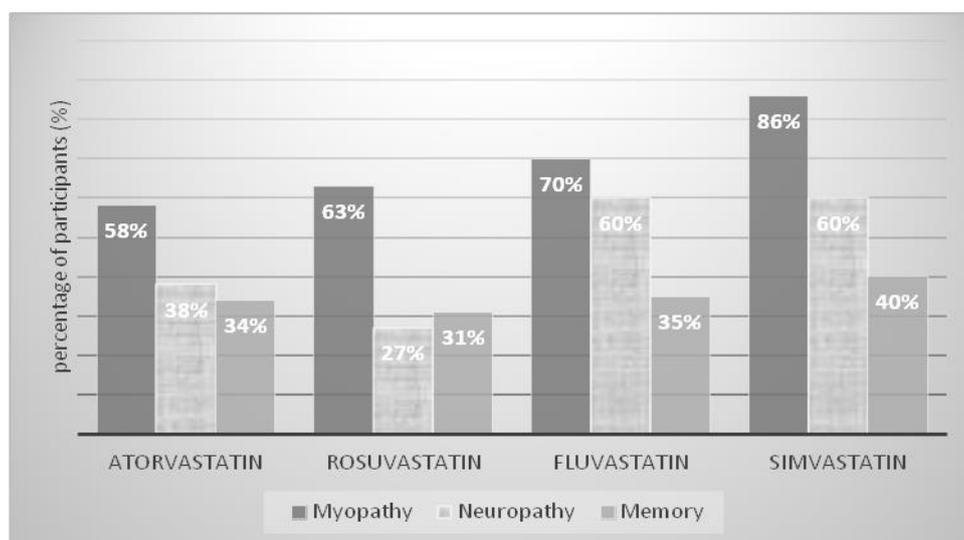


Figure 2: ADRs associated with different drug generic names from participants' point of view

Univariate analysis showed non-significant predictors for reporting symptoms related to myopathy included patient age ($P = 0.715$), gender ($P= 0.299$), having more concomitant drugs ($P=0.580$), and duration of therapy ($P =0.098$). Non-significant results were found also for reporting neuropathy symptoms. In contrast, memory loss was highly reported in patients having more concomitant drugs ($P=0.021$).

3.3. Reporting adverse drug reactions and healthcare providers responses

From the participating patients 72 (47.1%) reported the experienced side effects to their physicians and 75 (49%) reported them to the pharmacists, with 58 (37.9%) patients reported to both the physician and the pharmacist. The most common response from healthcare providers (either the physician or the pharmacist) was educating the patient on the proper way to use statin and how to avoid or reduce this side effect (Table 2), None of the participant have chosen "other responses" specified it.

% of patients	Response
40.5	(HCP) told me how to avoid or reduce the side effect
16.3	(HCP) told me that the side effect is age related
11.8	(HCP) told me to cope with the side effect
11.8	(HCP) told me that this is only illusions
13.1	(HCP) told me the side effect is not related to statin
6.5	Other responses

3.4. Patients' attitudes towards statin adverse drug reactions

Patients were asked about their adherence to statin therapy and it was found that 89 (58.2%) of the participating patients were adherent to their statin drug, however, taking simvastatin or fluvastatin was associated with lower rates of adherence, Figure 3 shows the adherence pattern to different statin generics. In addition, lower adherence rate was found among patients who experienced side effect after using statin therapy ($P < 0.01$). Patients who informed the healthcare providers about the experienced side effects of statin had lower adherence rate than others ($P < 0.01$).

Upon asking the patients about their statin drug, 116 (75.8%) had concerns about the ADRs associated with its use, while 122 patients (79.7%) thought that the medicine is important to their health even with its side effects.

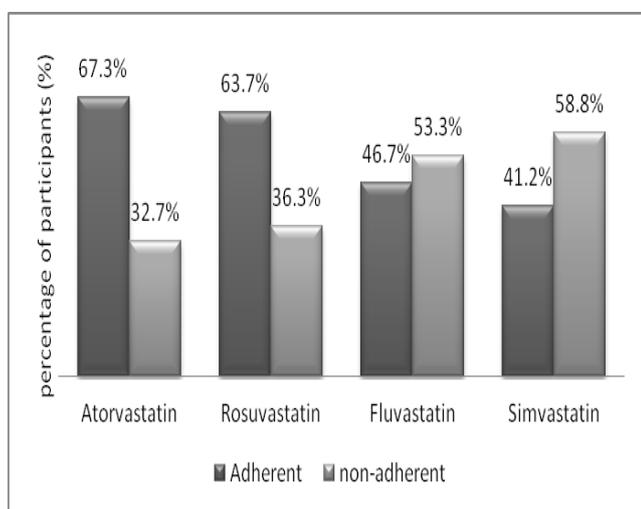


Figure 3. Patient adherence to statin drugs

DISCUSSION

Being one of the top medications prescribed, this is the first study that investigated the ADRs occurrence and patients' attitude toward statin drugs in Jordan. Symptoms related to myopathy were the major ADRs associated with statin use as reported by participating patients. This finding was consistent with other previous

studies in different regions, i.e. Stroeset *al.* (2015) mentioned that patient registries, together with clinical experience, indicate that 7–29% of patients complain of statin-associated muscle symptoms⁹.

The second major ADR was related to peripheral neuropathy which also corresponds with similar previous studies, however, Gaist (2002) found that peripheral neuropathy was associated with long-term use of statin. In our study, we could not find a significant link between long-term use of statin and peripheral neuropathy. Actually, the reason for peripheral neuropathy associated with statin use in some patients is still unclearly defined, but it may be related to its effect on cholesterol levels presented in the cell membrane which appeared on nerves cells more than other cells due to their higher sensitivity⁶.

Few participants thought that they suffered from memory related ADRs, however, no previous studies could relate this ADR to statin drugs [10,11]. Moreover, in the present study we found that memory related ADRs was significantly linked with the number of patient daily medicines. This finding might be linked to other drugs, other diseases or due to drug-drug interactions. Nevertheless, it was beyond the scope of this study to collect other medications the patients take or chronic diseases they suffer from; therefore, further investigation about memory related ADRs is needed.

Simvastatin and fluvastatin had a trend to have higher (although it was not statically significant) adverse effects than rosuvastatin and atorvastatin in the present study. This is might be related to their sensitivities toward other drugs or food. Simvastatin, for example, has very low bioavailability (<5%) due to high first pass effect. Increasing bioavailability with CYP3A4 inhibitors will increase its systemic exposure dramatically, which leads to increase its adverse effects¹².

It was worth to measure the effect of patient counselling on ADRs by healthcare providers and their responses on ADRs occurrence. In our study 57.5% of the participants reported their ADRs to a health care provider

while in Golomb *et al.* (2007) study ², higher percentage of patients reported what they experienced (73.5%). Many studies assessed how physicians responded when patients presented with ADRs of statin use. Our results were similar to those reported by Golomb *et al.* (2007) where they found that 53.1% of the patients were reeducated by their physician or pharmacist about the proper way of using statin and how to avoid or reduce statin-related side effects ². In our study, 40.5% of patients were reeducated.

It was found that the occurrence of ADRs affected patient adherence to statin drugs. In the present study, patient adherence rate was generally low (58.2%). This finding is consistent with other adherence studies on statin drugs and other medications. The results from Degliet *al.* (2012), study found that, only 60.8% of patients were adherent to their statin medication ¹³.

Simvastatin and fluvastatin were associated with lower adherence rate. This was expected since it is known that the higher the side effects associated with a drug the lower the adherence rate ¹⁴. Unfortunately, lower adherence rate of statin drugs is associated with higher risk of cardiovascular diseases, this raises the role of physician and pharmacist in improving patient adherence ¹⁵.

Surprisingly, in our study patients who informed the healthcare providers about the experienced side effects of statin had lower adherence rate than others. Jimmy *et al.* (2011) found similar results and concluded that it was related to patient-physician discordance because physicians may speak in superiority with their patients

leading to decreased patient satisfaction. However, we may relate this lower adherence rate also to the decrease in patient confidence after the responses by physicians and pharmacists toward the experienced ADRs, that the healthcare providers explained the reported ADRs by age, illusions, or not related to statin ¹⁶.

Finally, it was showed that many patients had concerns about statin associated ADRs, although these concerns were not statistically different neither between patients reporting ADRs nor patient adherence.

Only pharmacies located in Amman were involved in the present study. Inclusion of more community pharmacies around the country will improve both the sample size and the generalizability of the results. Since many patients are taking a combination of medicines, further investigations on the effect of combined medicine on statins are warranted.

CONCLUSION

There were differences between different statin agents in the pattern of reporting ADR. The variability between associated ADRs needs to be considered by physicians when prescribing this drug. Determining the best tolerated statin drug may enhance the patient's adherence. Since the symptoms related to myopathy associated with statin use were frequently reported by participating patients, laboratory test monitoring is essential.

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استخدام أدوية الستاتين في الأردن: تجربة المرضى وموقفهم تجاه التفاعلات الدوائية الضارة

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ملخص

تعد أدوية الستاتين واحدة من الأدوية المستخدمة للتخفيف من نسبة الكوليسترول في الدم، مما يساعد على خفض خطر الإصابة بأمراض القلب والشرابين. يهدف هذا البحث لدراسة التفاعلات الدوائية الضارة التي قد تظهر لدى المرضى الذين يتناولون هذه الأدوية في الأردن، وتأثير هذه التفاعلات في التزام هؤلاء المرضى بالعلاج، ومعتقداتهم حول أدوية الستاتين. الدراسة هي دراسة إحصائية مستعرضة، وأداة الدراسة كانت استبانة ورقية تم توزيعها على عدة صيدليات مجمتع في مدينة عمان ليتم تعبته والإجابة عليه من قبل المرضى الذين يستخدمون أدوية الستاتين. قام 153 من المرضى بتعبئة الاستبيان بشكل كامل، وقد أظهرت النتائج ظهور التفاعلات الدوائية الضارة لدى 72.5% من المرضى، والتي كانت متعلقة بالاعتلال العضلي، والاعتلال العصبي المحيطي، ومشاكل الذاكرة. كما أظهرت النتائج اختلاف نسبة التفاعلات الدوائية الضارة باختلاف المادة الدوائية المستخدمة، وتأثير التفاعلات الدوائية الضارة بالالتزام المرضى بالعلاج. استنتجنا من الدراسة أن اختيار المادة الدوائية المناسبة من قبل الطبيب للمريض قد يساعد على خفض نسبة التفاعلات الدوائية الضارة، وزيادة التزام المريض بالعلاج.

الكلمات الدالة: أدوية الستاتين، مثبطات أنزيم HMG-CoA-reductase، التفاعلات الدوائية الضارة، أمراض القلب والأوعية الدموية، اليقظة الدوائية.