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Identify and Assess Drug Interactions with Atorvastatin in Inpatient Care

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Atorvastatin is a recent HMG-COA reductase inhibitor used to treat primary hypercholesterolemia, homozygous familial hypercholesterolemia, and mixed dyslipidemias. It is also taken to prevent heart disease, including strokes and heart attacks. In addition, Atorvastatin is

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used to lower bad cholesterol low-density lipoproteins (LDL) levels, increase good cholesterol high-density lipoprotein (HDL) levels, and lower triglycerides. It works by reducing the amount of cholesterol produced in the body, hence reducing the amount of cholesterol that may build up on the walls of arteries. Atorvastatin is long-acting, has few adverse effects, and is low in price. Nevertheless, it interacts with a wide variety of medications. These interactions may be lead to adverse drug reactions.

Objective: The study aims to identify and asset atorvastatin interactions with other medicines at King Abdulaziz Hospital. Also, to prevent atorvastatin interactions in the future.

Methods: The retrospective study investigated 280 electronic prescriptions inside the inpatient clinic at King Abdulaziz Hospital in Saudi Arabia between January and April 2021 to identify and asset interactions among atorvastatin and different medications.

Results: Most atorvastatin interactions are category C (44.64%) and category B (41.43%). Atorvastatin had the most common interactions with esomeprazole (16.07%), clopidogrel (14.64%), and sitagliptin (12.14%). Atorvastatin had clinical interactions with medications metabolized by the cytochrome P450 3A4 (CYP3A4). Use of atorvastatin with cyclosporine or clarithromycin increased the risk for atorvastatin toxicities such as myopathy and rhabdomyolysis. In addition, Atorvastatin decreases clopidogrel's antiplatelet effect and increases the risk of skeletal muscle toxicity of daptomycin.

Conclusion: The majority of atorvastatin interactions may be avoided by adhering to best practices in clinical care and clinical pharmacology, such as avoiding complicated treatment regimens, utilizing a single pharmacy for all prescriptions, and recognizing patient risk factors. Health care professionals should use drug-drug interaction checkers such as Medscape and Micromedex, as well as a book such as the Handbook of Drug Interactions.

Keywords: Atorvastatin; statins; statin-drug interaction; hypercholesterolemia.

1. INTRODUCTION

Statins compounds are structural analogs of HMG-CoA (3-hydroxy-3- methylglutaryl-coenzyme A). a torvastatin ,fluvastatin, pravastatin, pitavastatin, simvastatin, rosuvastatin, and lovastatin belong to this class. They are particularly effective in lowering low-density lipoproteins LDL cholesterol. Additionally, oxidative stress and vascular inflammation are diminished, resulting in a rise in the stability of atherosclerotic lesions [1,2].

Atorvastatin is the most potent LDL-reducing agent currently available in the class. It has a dose-dependent effect with maximum reduction at 80 mg of 60% in LDL with an initial reduction of 39% at 10 mg. In addition, it has been shown to lower triglycerides in patients with primary hypertriglyceridemia by up to 40% and was the first statin to demonstrate this action [3].

Atorvastatin action Inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis; this causes a compensatory increase in the expression of LDL receptors on hepatocyte membranes and stimulation of LDL catabolism.

Two indirect mechanisms are proposed to compensate for atorvastatin's triglyceride-lowering effect. First, significant suppression of cholesterol synthesis would hamper the assembly and release of very-low-density lipoprotein VLDL particles, of which cholesterol is a critical component, resulting in triglyceride levels being reduced. Second, decreased hepatocyte cholesterol levels induced by significant suppression of cholesterol production would result in enhanced LDL-receptor expression and hence more significant binding of VLDL particles and LDL, resulting in decreased cholesterol and triglyceride levels [4–6].

Atorvastatin may be taken with or without food at any time of day. Side effects are muscle weakness, nasopharyngitis, increased serum transaminases, rhabdomyolysis, allergic reactions, Insomnia, and urinary tract infection [7,8]. Atorvastatin is contraindicated in pregnant women or may become pregnant or breastfeeding or unexplained persistent elevations of serum transaminases [9]. It is not recommended used with abametapir or boceprevir or telaprevir, or simeprevir [10].

Atorvastatin is a recent HMG-COA reductase inhibitor used to treat primary hypercholesterolemia, homozygous familial hypercholesterolemia, and mixed dyslipidemias. In addition, It enhances endothelial function,

inhibiting smooth muscle proliferation and decreasing platelet aggregation. Nevertheless, atorvastatin interacts with various medications. Resulting in rhabdomyolysis, myopathy, and reduced kidney function [11].

Drug interactions can reduce a drug's effectiveness, induce unanticipated adverse effects, or enhance a drug's action. It occurs when a patient's response to a drug is altered by food, medication, or illness. When two or more medications react with one another, this is referred to as a drug-drug interaction. Drug interactions are a frequent cause of adverse medication responses and increased patient hospitalization rates [12,13].

According to a recent study in Ireland, over 30% of statin users take concurrent medications that can impair statin metabolism and potentially result in rhabdomyolysis [14]. Combining atorvastatin with nicotinic acid, erythromycin, fibric acid derivatives, or azole antifungals is likely to increase the risk of adverse effects such as myopathy or rhabdomyolysis. Therefore, it should be avoided wherever feasible [15,16].

It is possible to prevent most atorvastatin medication interactions by adhering to best practices in clinical care and clinical pharmacology. However, until writing, no study has been done to identify and assess atorvastatin interactions with other medicines at King Abdulaziz Hospital.

Atorvastatin is the most used drug daily in inpatient clinics and one of the drugs that have interactions with other drugs. Therefore, our study objectives are to identify and assess these interactions and get evidence information to prevent it in the future.

2. METHODOLOGY

A retrospective study investigated 280 electronic prescriptions. Inside the inpatient clinic at King Abdulaziz Hospital in Saudi Arabia between January and April 2021 to identify and assess interactions among atorvastatin and different medications.

2.1 Inclusion Criteria

Prescriptions with an atorvastatin drug-drug interaction. Prescriptions of patients above 21 years old. All oral atorvastatin dosage 10MG,20MG,40MG, and 80MG.

2.2 Exclusion Criteria

Prescriptions without atorvastatin drug-drug interaction. Prescriptions without oral dosage form drug-drug interaction. Prescriptions of patients less than 21 years old. Prescriptions were written before January 2021 and after April 2021.

The data collection was saved, and analyses were done using the Excel program. Percentages and frequencies were used to convey the descriptive data.

Lexicomp® Drug Interactions are used to check for drug-drug interactions in prescriptions. According to Lexicomp® Drug Interactions, the interactions' severity was classified as A, B, C, D, or X [17].

A (No Known Interaction) means data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.

B (No Action Needed) means data demonstrate that the specified agents may interact with each other. However, there is little to no evidence of clinical concern resulting from their concomitant use.

C (Monitor Therapy) means data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.

D (Consider Therapy Modification) means data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken to realize the benefits and/or minimize the toxicity resulting from the concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, or choosing alternative agents.

X (Avoid Combination) means data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with the concomitant use of these

agents usually outweigh the benefits. Therefore, these agents are generally considered contraindicated [18].

3. RESULTS

Between January and April 2021, this study examined 280 electronic prescriptions to identify and assess drug interactions between atorvastatin and other drugs. Around 146 (52%) of prescriptions were written for females, whereas 134 (48%) were written for males with atorvastatin medication interactions (Fig.1).

The majority of atorvastatin interactions in patients aged 60 and above is about 44.28 %, and in patients aged between 50 to 59, about 31.8 %.Table 1. Show the age of patients who had atorvastatin drug interactions

Atorvastatin interactions mostly category C (44.64%), need to monitor therapy and category B (41.43%) no action needed. Only category X (0.71%) Avoid combination.

The common interactions were atorvastatin with esomeprazole (16.07%), clopidogrel (14.64%), and sitagliptin (12.14%). Table 2 displays the medications that were attracting atorvastatin and the number of prescriptions with a percentage.

Approximately 44.64% of interactions were category C need to monitor. Atorvastatin has a category C interaction with amiodarone, spironolactone, ticagrelor, azithromycin, digoxin, fenofibrate, sitagliptin, and colchicine.

Approximately 41.43% of the interactions were category B no action was needed. Atorvastatin interacts category B with amlodipine, clopidogrel, esomeprazole, everolimus, sildenafil, and tacrolimus.

About 10.36% of the interactions were category D Consider therapy modification. Atorvastatin interacts category D with clarithromycin, daptomycin, verapamil, itraconazole, rifampin, and ritonavir.

Around 2.86% of the interactions were category A no known interaction. Atorvastatin interacts category A with warfarin and phenindione.

Only 0.71% of the interactions were category X avoid combination. Atorvastatin interacts category X with cyclosporine and gemfibrozil. Table.3 shows the severity of atorvastatin drug interactions.

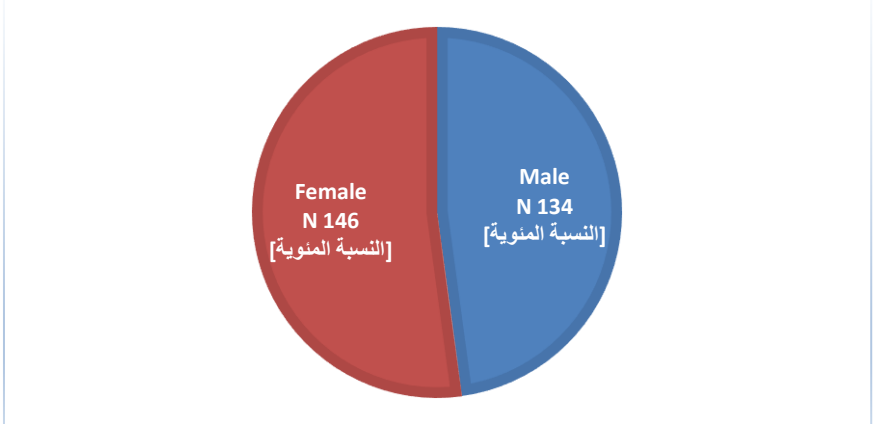

Fig 1. Show the number of prescriptions for males and females

Table 1. Show the age of patients who had atorvastatin drug interactions

Age	Number Of Prescriptions	Percentage
21-29	8	2.86 %
30-39	13	4.64 %
40-49	46	16.43 %
50-59	89	31.8 %
≥ 60	124	44.28 %
Total	280	100%

Table 2. Displays the medications that were attracting atorvastatin and the number of prescriptions with a percentage

Drug Name	Number of Prescriptions	Percentage
Esomeprazole	45	16.07%
Clopidogrel	41	14.64%
Sitagliptin	34	12.14%
Amlodipine	30	10.71%
Spironolactone	27	9.64%
Verapamil	24	8.57%
Ticagrelor	23	8.21%
Digoxin	20	7.14%
Fenofibrate	15	5.35%
Warfarin	8	2.9%
Azithromycin	2	0.71%
Cyclosporine	2	0.71%
Others	9	3.21%

Table 3. Show the severity of atorvastatin drug interactions

Severity	Number Of Prescriptions	Percentage
A (No known interaction)	8	2.86 %
B (No action needed)	116	41.43%
C (Monitor therapy)	125	44.64%
D (Consider therapy modification)	29	10.36%
X (Avoid combination)	2	0.71%

4. DISCUSSION

In this study, female prescriptions more than half 52% compared with 48% male prescriptions. That indicates dyslipidemia is more common in females than males. Opoku et al. estimated the overall prevalence of dyslipidemia in rural and urban people in China to be 43.2 % and 43.3 %, respectively, in 2019. In both rural and urban locations, dyslipidemia was more prevalent in women [19].

Around 44.28 % of atorvastatin interactions occur in patients 60 years and older, compared to 31.8 % in patients 50 to 59 years. Because the patients 60 years and older have several chronic diseases such as diabetes, hypertension, and heart disease, they also take multiple medications.

Most atorvastatin interactions are classified as category C (44.64 %) and category B (41.43%), meaning that the patient's medication should be monitored. Additionally, the patient has a substantial chance of an adverse drug reaction, which increases the likelihood of hospitalization.

Concurrent use of atorvastatin and other medications may increase or decrease the effectiveness of some medications. Also, increased atorvastatin toxicity such as myopathy, rhabdomyolysis, and renal failure (Table 4).

The use of atorvastatin in conjunction with esomeprazole, clarithromycin, amiodarone, and colchicine may cause a myopathic and rhabdomyolysis. Therefore, Carefully monitor for signs of muscle pain or weakness with concomitant therapy.

Case report. After six weeks of concurrent therapy with esomeprazole and three doses of clarithromycin, a 51-year-old patient who had been stable on atorvastatin for more than a year developed clear signs of rhabdomyolysis with third-degree heart block. According to reports, associated symptoms appeared shortly after initiating esomeprazole and became more severe following the initiation of clarithromycin [20].

A retrospective review of Austrian claims data found concurrent clarithromycin treatment with a cytochrome P450 3A4 (CYP3A4) metabolized statin (atorvastatin, lovastatin, or simvastatin) was related to a 2.11-fold increased risk of death or hospitalization compared to individuals receiving clarithromycin alone [21].

According to the medical advice for amiodarone, lower starting and maintenance dosages of

CYP3A4 substrates, such as atorvastatin, may be required because amiodarone enhances exposure to these medications. A case report details a 55-year-old patient who began on high-dose atorvastatin (80 mg daily), progressed to amiodarone loading dose (400 mg three times a day) a week later, and then progressed to high-dose ciprofloxacin six days later (750 mg twice daily). He developed rhabdomyolysis, increased urine myoglobin, and renal failure three days after receiving this triple medication and nine days after receiving atorvastatin and amiodarone combined [22].

Colchicine and statins have been associated with myotoxicity independently; in one assessment of 475 patients hospitalized for rhabdomyolysis, statins and colchicine were among the most frequently implicated prescription drugs [23]. Additionally, colchicine and statins are processed extensively by CYP3A4, with some in vitro evidence showing colchicine may inhibit CYP3A4. These findings imply that colchicine, at least for certain statins, may increase statin concentrations, hence raising the risk of myotoxicity [24].

In this study, atorvastatin was prescribed with clopidogrel in 41 (14.64 %) of 280 prescriptions. Atorvastatin may impair clopidogrel's antiplatelet action. The postulated mechanism for this potential interaction was that the CYP3A4 substrate atorvastatin or other statins inhibited clopidogrel metabolism to its active metabolite via CYP3A4.In a study of 44 patients undergoing stent placement who were receiving clopidogrel alone or in combination with atorvastatin or pravastatin, concurrent atorvastatin treatment reduced platelet inhibition in a dose-dependent manner (% platelet aggregation = 34%, 58%, 74%, and 89 % with atorvastatin doses of zero, 10mg, 20mg, and 40mg, respectively) [25].

The combination of atorvastatin and ticagrelor may increase atorvastatin's serum concentration. As a result, patients should be carefully monitored for signs and symptoms of atorvastatin toxicity. A randomized, placebo-controlled crossover trial found that when atorvastatin was coupled with ticagrelor, the maximum serum concentration and area under the curve (AUC) of atorvastatin were increased by 23% and 36%, respectively, compared to atorvastatin alone. This apparent interaction is thought to occur because ticagrelor inhibits atorvastatin metabolism through CYP3A4. CYP3A4 mainly metabolizes atorvastatin, and ticagrelor is a mild inhibitor of this enzyme, resulting in elevated plasma concentrations [26,27].

Concurrent use of cyclosporine with atorvastatin is contraindicated due to an increased risk of atorvastatin-related adverse events such as myopathy and rhabdomyolysis. Instead, consider switching to a statin that is less susceptible to this interaction, such as pravastatin or fluvastatin, or another type of LDL-lowering medicine. According to the American Heart Association, these medicines may be combined if the atorvastatin dose is limited to no more than 10 mg daily and patients are closely monitored for signs or symptoms of muscle-related toxicity [28]. This interaction is presumably the result of both cyclosporine inhibition of atorvastatin's CYP3A4 metabolism and cyclosporine impairment of atorvastatin's hepatic absorption via the OATP1B1/SLCO1B1 pathway. According to published case studies, patients treated with atorvastatin suffered rhabdomyolysis after initiating or increasing the dose of cyclosporine [29,30].

Combining atorvastatin and daptomycin may enhance the risk of daptomycin toxicity in the skeletal muscle. Consider discontinuing atorvastatin medication momentarily before commencing daptomycin to reduce the risk of skeletal muscle harm. In a study using spontaneous reporting data from Japan, it was discovered that taking daptomycin in combination with a statin increased the incidence of muscle toxicity complaints when compared to taking daptomycin alone (ROR 3.4, 95% CI [1.4 to 8.4]) [31].

The most frequently reported interactions were atorvastatin with esomeprazole (16.07%), clopidogrel (14.64%), sitagliptin (12.14 %), and amlodipine (10.71%) because these drugs are regularly prescribed to treat chronic diseases.

The majority of atorvastatin medication interactions may be avoided by adhering to best practices in clinical care and clinical pharmacology, such as avoiding complicated treatment regimens, utilizing a single pharmacy for all prescriptions, and recognizing patient risk factors.

Lexicomp® Drug Interactions are used to check for drug-drug interactions in prescription Because the Saudi Ministry of Health approved it in our hospital. Lexicomp simple-to-use medication comparison tool enables search for up to four

Table 4. Explain the possible outcomes of atorvastatin drug interactions

Drug interactions	Severity	Possible outcomes
Esomeprazole with atorvastatin	B	May result in an increase in the adverse effect of atorvastatin such as rhabdomyolysis
Clopidogrel with atorvastatin	B	May result in a decrease in the antiplatelet effect of clopidogrel
Amlodipine with atorvastatin	B	May result in an increase in the serum concentration of atorvastatin
Ticagrelor with atorvastatin	C	May result in an increase in the serum concentration of atorvastatin
Spironolactone with atorvastatin	C	May result in enhancing the toxic effect of spironolactone.
Amiodarone with atorvastatin	C	May result in increased atorvastatin adverse effects such as myopathy.
Verapamil with atorvastatin	D	May result in an increase in the serum concentration of Verapamil
Daptomycin with atorvastatin	D	May result in an increased risk of skeletal muscle toxicity of daptomycin
Clarithromycin with atorvastatin	D	May result in an increase in atorvastatin toxicity, such as renal dysfunction.
Cyclosporine with atorvastatin	X	May result in increased risk for atorvastatin toxicities such as myopathy and rhabdomyolysis.

drugs at a time. It picks pertinent information for the patient, such as adverse effects, pregnancy concerns, contraindications and warnings, and drug-drug interactions. Moreover, it gives information up to date.

Patel and Beckett examined resources for analyzing drug interactions in 2016. They identified 82 drug-drug interactions and 18 drug-dietary supplement interactions. Lexicomp Interactions (97.0 %), Clinical Pharmacology Drug Interaction Report (97.0 %), and Micromedex Drug Interactions (93.0 %) all scored better in terms of scope than the other tools. The complete databases were Lexicomp Interactions and Micromedex Drug Interactions [32].

It is necessary to note some of our study's weaknesses. First, we did not include atorvastatin side effects in our research, nor did we have drug interactions with other statin medications in our study. Second, we use only the lexicomp Interactions program, not Micromedex Drug Interactions, clinical Pharmacology Drug interactions, or Medscape.

We suggest that in the future, we identify and assess statin drug interactions and compare statin and fibrate medication to provide the best possible treatment to patients, minimize drug interactions, and reduce hospitalization rates.

5. CONCLUSION

Atorvastatin is a potent inhibitor of HMG-CoA reductase. It is the highly effective statin currently available in terms of decreasing both LDL and total cholesterol. Atorvastatin was the first statin to demonstrate significant reductions in triglycerides in patients with isolated hypertriglyceridemia. It has a favorable safety profile. Atorvastatin enhances endothelial function, inhibiting smooth muscle proliferation and decreasing platelet aggregation. In addition, it contains anti-inflammatory properties and may help lower blood glucose levels.

Nevertheless, atorvastatin interacts with various medications. Resulting in rhabdomyolysis, myopathy, and reduced kidney function. Additionally, some interactions with other medications reduce its efficacy, while others boost it.

The majority of atorvastatin medication interactions may be avoided by adhering to best practices in clinical care and clinical pharmacology, such as avoiding complicated treatment regimens, utilizing a single pharmacy for all prescriptions, and recognizing patient risk factors. In addition, health care professionals should use drug-drug interaction checkers such as Medscape and Micromedex and a book such as the Handbook of Drug Interactions.

CONSENT

It is not applicable.

ETHICAL APPROVAL

By the nature of this research, this is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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