

## NEUROLOGICAL ADVERSE DRUG REACTIONS AND STATIN THERAPY

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## ABSTRACT

Statin is the drug of choice to reduce cholesterol and incidence of cardiovascular events. Majority of Malaysian cardiac patients uses statin. Most of adverse drug reactions (ADRs) induced by statin are mild to moderate during therapy. Objectives of study were to find out incidences of neurological ADRs and their severity during therapy. Also risk factors contributed in shifting the incidences of these ADRs. Cross-sectional design used to conduct this study. This study carried out in cardiac clinic of Penang General Hospital of Malaysia. Patients voluntarily participated in this study. Validated questionnaire used in collecting patients' complains about the neurological ADRs during statin therapy. Severity of ADRs assessed based on mild, moderate and severe. The other information like demographic data, dyslipidemia type, statin information, and concurrent diseases and medications collected from patients' progress files. The incidences of headache, dizziness and paresthesia were; 32.8%, 36.4%, and 36.6%, respectively. Patients with paresthesia had highest incidence of severe cases (4.6%) when compared to the other two adverse reactions. Males showed significantly higher incidence of headache (29.34%, OR=1.79, CI=1.075 - 2.978) and dizziness (33.33%, OR=1.66, CI=1.014 - 2.714). Alcohol found significantly increased the incidence of paresthesia (53.2%, OR=2.74, CI=1.25 - 6.03). Patients used statin more than 5 years significantly increased the incidence of headache (47.73%, OR=1.9, CI=1.16 - 3.11). Patients on lovastatin 60 mg had significantly highest incidence of headache than other doses (63.64%, OR=5.01, CI=1.39 - 18.11). High incidence of ADRs induced in cardiac patients who are on chronic use of statin. Males, alcohol consumption, duration of therapy more than 5 years, and lovastatin high dose (60mg) considered as risk factors to neurological ADRs induced by statin.

**Keywords:** Neurological adverse reactions, Statin, alcohol, Duration and dose

## INTRODUCTION

Statin considered the drug of choice to decrease abnormal cholesterol level and incidence of cardiac diseases like hypertension, diabetes, angina and other cardiovascular mortalities<sup>1,2</sup>. In world, about 2.5% to 91.7% of dyslipidemic patients use statin<sup>3</sup>. In US at least one third of all patients use statins, while 90% in Canada and 85% in Australia<sup>1,4</sup> used these medications. In Malaysia, about 90% of cardiac patients use statin<sup>5</sup>. Although the benefits significantly associated to statin therapy, undesired symptoms named adverse drug reactions (ADRs) found commonly during therapy. The ADRs of statin are either symptomatic or serious ADRs. Serious ADRs included; muscle damage<sup>6</sup>, liver dysfunction<sup>7</sup>, renal failure<sup>8</sup> and polyneuropathy<sup>9</sup>. For symptomatic ADRs, many symptoms found during statin therapy, most of them considered mild<sup>10,11</sup>. However, some published studies found ADRs increased in their intensity to be moderate or even severe<sup>12,13</sup>. It believed that symptomatic ADRs considered the early symptoms of serious ADRs like polyneuropathy, myopathy and extrapyramidal disorders<sup>14</sup>.

Polyneuropathy also known as peripheral neuropathy which is irreversible damage, characterized by weakness, tingling sensations in the limbs, hand and foot pain and walking difficulty. Gaist supposed these symptoms only occur in patients use statins after 2 years or more duration of therapy<sup>9</sup>. Few international and local studies found the relation between statin therapy and neurological ADRs. The objectives of this study were to find out the incidence of common symptomatic ADRs during statin therapy and prediction the common risk factors which contributed to worsen these ADRs. Also, to measure the severity of neurological ADRs severity in cardiac patient were on statin therapy for long duration of use.

## METHOD

Cross-sectional study conducted for 500 cardiac outpatients at a general hospital in Northern part of Malaysia Peninsula. The approval was granted from the Ethical Committee of hospital and patients were voluntarily participated in this study by self-reporting of the common ADRs during their therapy.

Validated self-administered questionnaire used in reporting the neurological symptoms during statin therapy. Filling of questionnaires depending on patients' experience to common ADRs, and if symptoms were continuous or not. The incidence of ADRs depended on patients' response by yes or no, while

severity assessed depending on mild, moderate, or severe. The answerable neurological symptoms found depending on previous report were<sup>15</sup>; dizziness, headache, and limbs tingling and pricking during sleep. Patients' information like demographic, statin therapy, concurrent medications and diseases got from patients progress file. Patients included in this study were; age more than 18 years old, use statin, can understand English or Bahasa language. All patients came from other clinics, change in type or dose of statin, or had serious neurological disorders excluded from this study.

For statistics, SPSS version 18 used to analyze the collected data, descriptive analysis used to determine the incidence of neurological ADRs and their severity. Logistic regression and reporting odd ratio (OR), and chi-square used to predict the risk factors contributed in elevating the incidences of ADRs like demographic data, statin information, dyslipidemia type, concurrent diseases and medications. All results considered statistical significant if their *p* values were less than 0.05.

## RESULTS

The percentage of males was higher than females (70%, 351 patients, versus 30%, 149 patients). Chinese had the highest incidence (37.6%, 188 patients), followed by Malay (34.4%, 172 patients), Indian (26.6%, 133 patients), and other (1.4%, 7 patients). Low incidence of smoking (12%, 59 patients) and consumption of alcohol (9%, 47 patients) found in this study. The mean age of patients was 60±10 years, geriatric patients were 30% (148 patients). For duration of statin therapy, the mean duration of statin therapy was 3.5 years. Patients used statin more than 5 years were 17.6% (89 patients), while 1-5 years were 52.5% (262 patients), 3-month - 1-year were 26.7% (26.7%), and less than 3 months were 3.2% (16 patients). Primary dyslipidemia type had higher incidence than secondary (51.5%, 247 patients versus 48.5%, 233 patients). Lovastatin was the common type used by patients (81%, 405 patients), followed simvastatin (9.4%, 47 patients), atorvastatin (8%, 40 patients), and others (1.6%, 8 patients). About 7% (35 patients) only used combination therapy for dyslipidemia. Most of patients had concurrent diseases, hypertension about 68.8% (68.8%, 344 patients), ischemic heart diseases (60.8% 304 patients), and diabetes (44.2%, 221 patients). Beta-blockers were the common use (80.4%, 402 patients), aspirin (70.6%, 353 patients), and angiotensin converting enzymes inhibitors (64.8%, 324 patients).

The incidences of headache, dizziness and paresthesia (limbs tingling and pricking during sleep) were; 32.8%, 36.4%, and 36.6%, respectively. Patients with paresthesia had highest incidence of severe cases (4.6%), as shown in Table 1. These ADRs found

concurrently with each other significantly. The incidence of patients had the three neurological ADRs was 11.8%. Patients with headache and dizziness had significantly the highest combined ADRs (22%) than others, as shown in Table 2.

**Table 1: Incidence of neurological ADRs and their severity in cardiac outpatients**

Neurological ADRs	Overall % (no)	Mild % (no)	Moderate % (no)	Severe % (no)
Headache	32.8% (164)	22.4% (112)	7.60% (38)	2.8% (14)
Dizziness	36.4%(182)	26.2% (131)	7.8% (39)	2.4% (12)
Paresthesia (limbs tingling)	36.6% (183)	22.2%(111)	9.8% (49)	4.6% (23)

**Table 2: Incidence of multiple neurological diseases in cardiac outpatients on statin therapy**

Neurological ADRs	Number (%)	p value
Headache + dizziness + paresthesia	59 (11.8%)	0.002
Headache + dizziness	110 (22%)	< 0.001
Headache + paresthesia	78 (15.6%)	0.001
Dizziness + paresthesia	90 (18%)	< 0.001

After prediction of the neurological ADRs, males had significant higher incidence of headache (29.34%,  $p=0.025$ , OR=1.79, CI=1.075 - 2.978) and dizziness (33.33%,  $p=0.044$ , OR=1.66, CI=1.014 - 2.714). Alcohol found significantly increased the incidence of paresthesia (53.2%,  $p=0.012$ , OR=2.74, CI=1.25 - 6.03). Patients

used statin more than 5 years significantly increased the incidence of headache (47.73%,  $p=0.01$ , OR=1.9, CI=1.16 - 3.11). Patients on lovastatin 60 mg had significantly highest incidence of headache than other doses (63.64%,  $p=0.014$ , OR=5.01, CI=1.39 - 18.11), as shown in Table 3.

**Table 3: Prediction of neurological symptomatic ADRs in cardiac outpatients**

Predictors	ADRs (percentage, p value, OR, CI)		
	Headache	Dizziness	Paresthesia
Gender (male)	29.34% $p=0.025$ , OR=1.79 CI=1.075 - 2.978	33.33% $p=0.044$ , OR=1.66 CI=1.014 - 2.714	NS
Race (Indian)		NS	NS
Smokers		NS	NS
Alcoholic		NS	53.2% $p=0.012$ , OR=2.74 CI=1.25 - 6.03
Age (> 65 yr)		NS	NS
Duration > 5 yr	47.73% $p=0.01$ , OR=1.9 CI=1.16 - 3.11	NS	NS
Statin types (lovastatin)		NS	NS
Atorvastatin doses (20mg)		NS	NS
Simvastatin dose (40mg)		NS	NS
Lovastatin doses (60mg)	63.64% $p=0.014$ , OR=5.01 CI=1.39 - 18.11	NS	NS
Type of dyslipidemia (secondary)		NS	NS
Combination therapy		NS	NS
Hypertension		NS	NS
Diabetes mellitus		NS	NS
Ischemic heart disease		NS	NS
Beta blockers		NS	NS
ACE-I		NS	NS
Aspirin		NS	NS
Gliclazide		NS	NS
Metformine		NS	NS

Reporting Odd ratio (OR) and logistic regression used in prediction the risk factors of neurological ADRs of statin ( $p < 0.001$ )

## DISCUSSION

This study depended on patients complains toward the neurological ADRs during statin therapy. It considered suitable method for reporting the adverse reactions of medications, because most of doctors are unaware or unfamiliar to adverse reactions, also because patients are uncomfortable to express their ADRs to doctors<sup>16,17</sup>. This study concentrated on neurological symptoms during therapy,

and results were more accurate if compared to previous studies. Most of previous studies mentioned these ADRs as secondary results, this is because the severity of neurological ADRs was mild to moderate<sup>10,13,18-21</sup>.

One patient in Morgan et al<sup>22</sup> stopped continuing his medication because having dizziness, headache, tiredness and abdominal pain. The incidence of headache in current study (32.8%) was higher than

incidence (0.2%-2.7%) of Rief et al<sup>23</sup>, Strony et al<sup>24</sup> (11%), Flack et al<sup>25</sup> (2.2%), and Boccuzzi et al<sup>26</sup> (1%). Also, the incidence of dizziness (36.4%) in current study was higher than incidence (4%) of STATT study<sup>27</sup> and Bissonnette et al<sup>10</sup> (0.4%). This because previous studies depended on doctors reporting of these ADRs, which not showed the real incidence patients had during therapy.

The incidence of multiple ADRs significantly found in 11.8% for the three ADRs which showed high incidence of neurological disorder because of statin therapy. No published study before stated the real incidence of neuropathy depending on multiple ADRs. However, it showed high incidence for cardiac outpatients who used statin for long duration of therapy and depending on patients complains.

Logistic regression and reporting odd ratio considered suitable way to determine the factors contributed in increase the incidence of neurological ADRs. Males had highest incidence in headache (OR=1.79) and dizziness (1.66) than females, and this is because males are more susceptible to neurological disorders than females<sup>28</sup>. Alcohol also contributed to increase the incidence of paresthesia by more than 2.74 times than nonalcoholic patients because the neurotoxicity of ethanol<sup>29</sup>. Headache also affected by duration of statin therapy, incidence of headache in patients used statin more than 5 years increased by 1.9 than patients used statin less than 1 year. The result of current study was in line to previous study which showed the severity of headache because of statin significantly appearing after long duration of therapy<sup>30</sup>. Use higher doses of statin caused increase in the incidence and severity of ADRs. Lovastatin 60 mg caused increase by 5 times than 20 mg dose. The significant effect of statin dose was mentioned in previous studies<sup>26,31,33</sup>. Although many patients had several concurrent diseases and use multiple medications, but no significant found for these variables and the incidence of neurological ADRs induced by statin. Reporting of adverse effects of medications preferred to be done depending on patients complains better than physicians reporting because lack in information about the ADRs of medications<sup>34,35</sup>. In conclusion high incidence of neurological ADRs induced by statin with severe complains toward these symptoms. Males, alcohol, duration of therapy, and lovastatin doses contributed to increase the incidence of neurological ADRs. It advised stopping consumption of alcohol, reducing duration of therapy and dose to avoid neurological ADRs induced by statin in cardiac patients which cause serious neurological ADRs in future.

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