MADRAC Bulletin

For healthcare professionals only
Volume 46 | Issue 01/2024

In this issue

The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among healthcare professionals.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

DISCLAIMER

The MADRAC Bulletin is published by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. This publication is meant to provide updates on medication safety issues to healthcare professionals, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss whatsoever arising from the use or reliance on this publication. The opinions expressed in all articles are the authors own and do not necessarily reflect the view of the NPRA.

We would like to thank the Director General of Health, Malaysia for his permission to publish the signal and case report articles.

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2]. The signals presented below are intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.*

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition[3], refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Atorvastatin and Photosensitivity Reaction

Written by Lee Sing Chet; Reviewed by Nora Ashikin Mohd Ali

Background

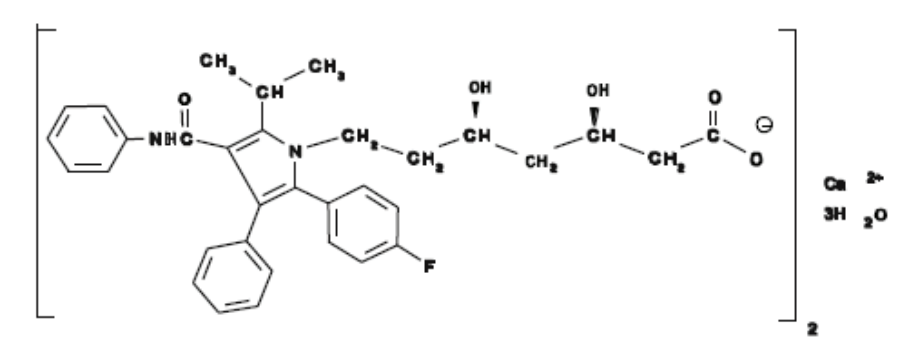


Figure 1: Structural formula of atorvastatin calcium

Atorvastatin is a lipid-lowering agent indicated for hypercholesterolaemia and prevention of cardiovascular disease.[4] It is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, with the structural formula shown in ***Figure 1***. Atorvastatin has been reported to induce photosensitivity reactions.[5]

Drug-induced photosensitivity is an adverse skin reaction that occurs due to exposure to ultraviolet (UV) or visible radiation in some individuals taking systemic or topical drugs with photosensitizing effects.[5-6] Photosensitivity reactions are categorised as either phototoxic or photoallergic reactions, with phototoxic reactions being more common. Statins have been linked with both types of reactions.[5,7]

Phototoxic reactions [5-6,8]	Photoallergic reactions [5-6]
Direct cellular damage caused when the drug absorbs energy from UVA light and releases it into the skin	Type IV (cell-mediated) immune response that can only occur in patients with prior exposure to the antigen
Dose-dependent	Independent of dose
Appear within minutes to hours after exposure	Appear 24 to 72 hours after exposure
Clinical presentation: Exaggerated sunburns with delayed-onset erythema and oedema; hyperpigmentation.	Clinical presentation: Eczematous, with erythema, scaling, pruritus, and sometimes vesicles, which may extend to non–sun-exposed skin

Trigger of Signal

During the routine signal detection activity, NPRA detected a disproportionality in the reporting of photosensitivity reactions associated with atorvastatin (IC025=0.9).[2] As of April 2023, NPRA has received 12 reports from healthcare professionals in public hospitals.[1]

Globally, there were 221 cases reported, mainly from the United States of America, Europe, Canada, and Australia. Almost 75% of the global reports involved patients aged 45 years and above.[2]

Local Reports [1]

The 12 local cases of photosensitivity reactions associated with atorvastatin involved patients aged between 46 and 72 years (median age = 63.5 years). No gender preponderance was observed, with seven males and five females. The time-to-onset varied widely, from five days to three years. Most cases (75%) were confounded by other concomitant drugs that are also associated with photosensitivity reactions, such as frusemide, bisoprolol, esomeprazole, and enalapril. Recovery was reported in nine cases, while one case reported non-recovery, and two cases had unknown outcomes. All reports were assigned causality *C3* (*possibly*-related to atorvastatin).

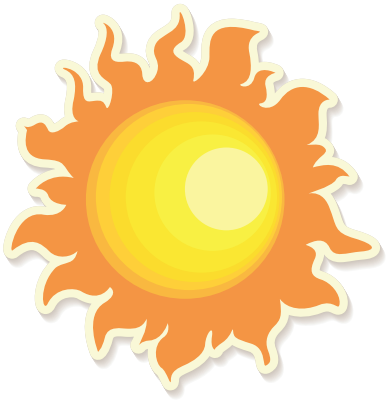
One case was reported as *serious*. This involved a 65-year old female who experienced photodermatitis on her face, back, and upper limbs two months after starting treatment with atorvastatin and perindopril/indapamide. These two suspected drugs were subsequently withdrawn and replaced with simvastatin and perindopril, which the patient had previously taken. Following the withdrawal of the suspected drugs and treatment with steroids, improvement was observed and no new rash was reported.

Potential Class Effect

NPRA has also received reports of photosensitivity reactions associated with other statins, namely simvastatin (24 reports), lovastatin (3), and rosuvastatin (2).[1-2] Simvastatin also showed a disproportionality in the reporting, with a slightly lower IC_{025} value of 0.25. Its association with photosensitivity has already been mentioned in the simvastatin package insert as a feature of hypersensitivity syndrome, which has been reported rarely.[9] For lovastatin and rosuvastatin, there were no recent cases since 2019.[1] Therefore signal detection activities were not conducted by NPRA on these two medicines.

Conclusion & Advice

The association between atorvastatin and photosensitivity reactions is *plausible*. Healthcare professionals must be aware of this potential risk and report all suspected adverse reactions related to statin use to the NPRA. It is important to advise patients at risk of photosensitivity to follow proper sun protection measures.



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Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that healthcare providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.

Clozapine-Induced Myocarditis

By Foo Wei Fuen

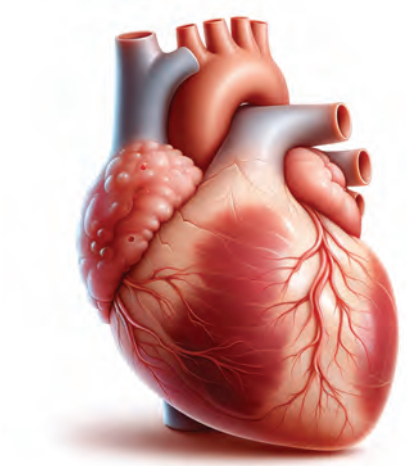
Case Report 1 [1]

This case involves a 24-year-old male with underlying schizophrenia, on clozapine 50 mg twice daily and haloperidol (unspecified dose). He presented with complaints of chest pain for one week. The pain radiated throughout his body and was associated with shortness of breath and fever. Clozapine was discontinued, and haloperidol was also stopped two days later.

During hospital admission, his cardiac enzymes were found to be elevated [creatine kinase (CK): 1156 U/L (normal range 24 – 196 U/L), lactate dehydrogenase (LDH): 305 U/L (normal range 0 – 248 U/L) and troponin: 8.0 µg/L (normal range < 0.1µg/L)]. The patient was suspected to have **drug-induced myocarditis**. Following discontinuation of clozapine, both the CK and LDH levels gradually decreased to 305 U/L and 216 U/L respectively over a span of two days. On the same day, haloperidol was also stopped. The patient's electrocardiogram (ECG) revealed sinus bradycardia, while the echocardiography findings were normal. Due to the presence of concomitant drugs, the adverse event was given a causality *possibly*-related to the clozapine.

Case Report 2 [1]

A 41-year-old male with underlying hypertension was initiated on clozapine therapy for the treatment of schizophrenia. While his dose was being titrated up, he experienced shortness of breath or pedal oedema on three occasions, as illustrated in ***Figure 2.*** An echocardiogram was performed and the cardiologist confirmed the diagnosis of **clozapine-induced myocarditis**. Due to the presence of underlying medical conditions and concomitant drugs, the adverse event was given a causality *possibly*-related to the clozapine.



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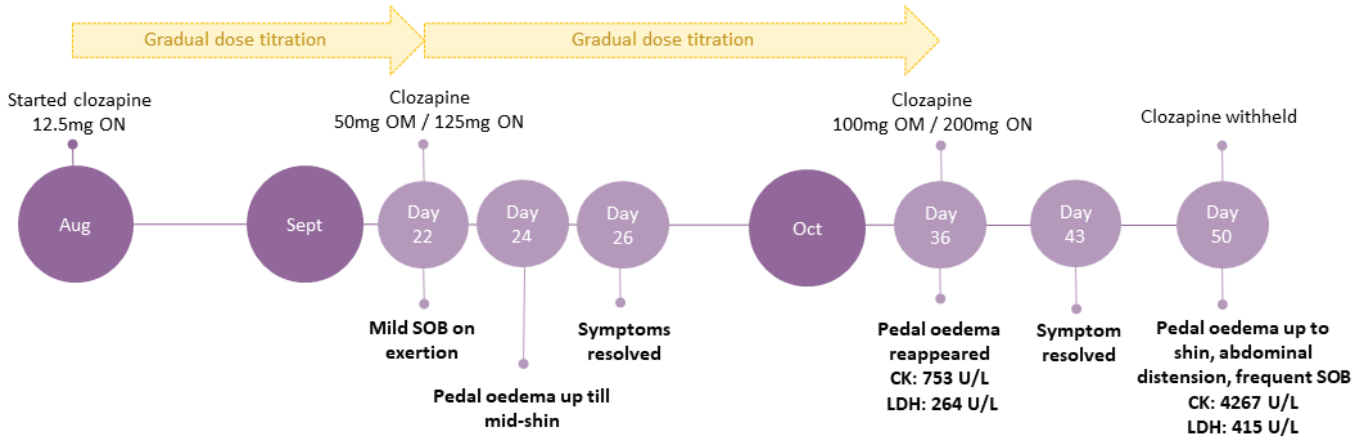

Figure 2. The timeline of the clinical manifestations in relation to clozapine use.
ON indicates omni nocte (every night); OM, omni mane (every morning); SOB, shortness of breath; CK, creatine kinase; LDH, lactate dehydrogenase

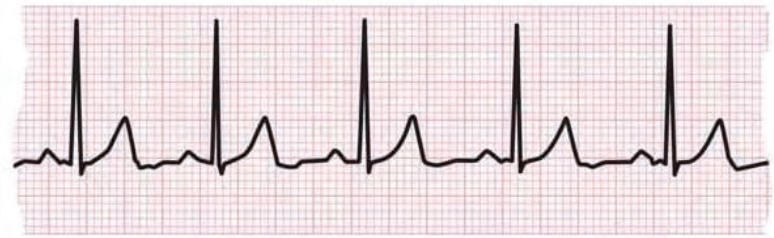

Image source: https://www.heart.org/

Discussion

Clozapine is an effective atypical antipsychotic indicated for treatment-resistant schizophrenia.[2] There are currently nine registered products containing clozapine in Malaysia, available in the form of tablets and oral suspension.[3] Clozapine has proven superior over other atypical antipsychotics in terms of reduced risk of suicide, lower extrapyramidal symptoms, and decreased relapse.[4] Clozapine exhibits high potency for the D4 receptor but has weak dopamine D2 receptor-blocking activity, which may explain the lower risk of extrapyramidal symptoms. However, these advantages are often overshadowed by the risk of serious adverse reactions such as agranulocytosis, hepatitis, seizures, metabolic syndrome and cardiovascular effects. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminic, and serotonergic receptors.[2,4]

Myocarditis is an inflammatory disease of the myocardium, induced predominantly by viral infections. Myocarditis can also be caused by a variety of other infectious and non-infectious etiologies. The clinical manifestations of myocarditis are highly variable, ranging from asymptomatic states or vague symptoms such as fever or fatigue that may resolve without specific therapy, to severe myocardial necrosis whereby patients can develop acute cardiomyopathy with severe arrhythmias, cardiogenic shock and sudden cardiac death.[5-7] Myocarditis is documented as a rare event associated with clozapine.[2] Clozapine-induced myocarditis (CIM) is potentially life-threatening if not recognised and managed early.[2,8]

The exact mechanisms underlying CIM are not fully understood. Links with immunoglobulin E (IgE)-mediated hypersensitivity reaction, cholinergic dysfunction and genetic predisposition have been proposed. Globally, the incidence of myocarditis associated with clozapine exposure varies from less than 0.1% to as high as 8.5%, with the higher rate seen in Australia.[8-11] CIM may be underreported due to inconsistencies in the diagnosis criteria and presence of non-specific symptoms.[5,8-10]

CIM usually occurs in the first two to eight weeks of therapy, although delayed reactions after two years of clozapine therapy have been reported.[10-13] Several factors predisposing to CIM have been proposed, including rapid dose titration, increased age and concomitant medications such as sodium valproate, but CIM does not appear to be dose-dependent.[9,10,13]

Management of CIM involves withdrawal of clozapine, followed by supportive therapy if required. Clozapine withdrawal usually leads to a spontaneous resolution of symptoms within days.[8,10-12] Early detection and prompt intervention prevents further myocardial damage, thereby improving the patient's outcome.[8,10,11] The implementation of clozapine monitoring protocols which include cardiac monitoring is highly recommended to allow early detection and management of CIM. Close monitoring is particular important during the first four weeks of treatment.[8,9,11]

To date, NPRA has received **367 local adverse drug reaction (ADR) reports with 617 adverse events** suspected to be related to clozapine. The most commonly reported adverse events are salivary hypersecretion (43 reports), tachycardia (34), constipation (32), weight increased (16), and white blood cell count increased (14). There are **six local reports** associated with myocarditis, including the two cases discussed above.[1] As of January 2024, a search of the World Health Organisation (WHO) global ADR database revealed **4,375 global reports** of myocarditis suspected to be associated with clozapine.[14*]

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Healthcare Professionals

1. Remain vigilant on the potential risk of myocarditis in patients prescribed with clozapine, particularly in the first few weeks of treatment.

2. Clozapine is contraindicated in patients with severe cardiac disorders including myocarditis.

3. Monitoring: Cardiac biomarkers and an ECG should be obtained at baseline and then monitored regularly for the first 4 weeks of clozapine treatment.

4. Counselling: Patients and caregivers should report any signs or symptoms of illness, such as fever, cough, shortness of breath, nausea, vomiting or chest pain. Patients should be educated to monitor their pulse rate at home and inform their doctor if there is an increase by 20-30 beats above their normal rate.

5. If myocarditis is suspected, promptly consult a cardiologist for further evaluation and management. Early detection of CIM can help to mitigate the risks associated with this rare but potentially life-threatening side effect.

6. Report any adverse drug reactions suspected to be related to the use of clozapine to the NPRA.

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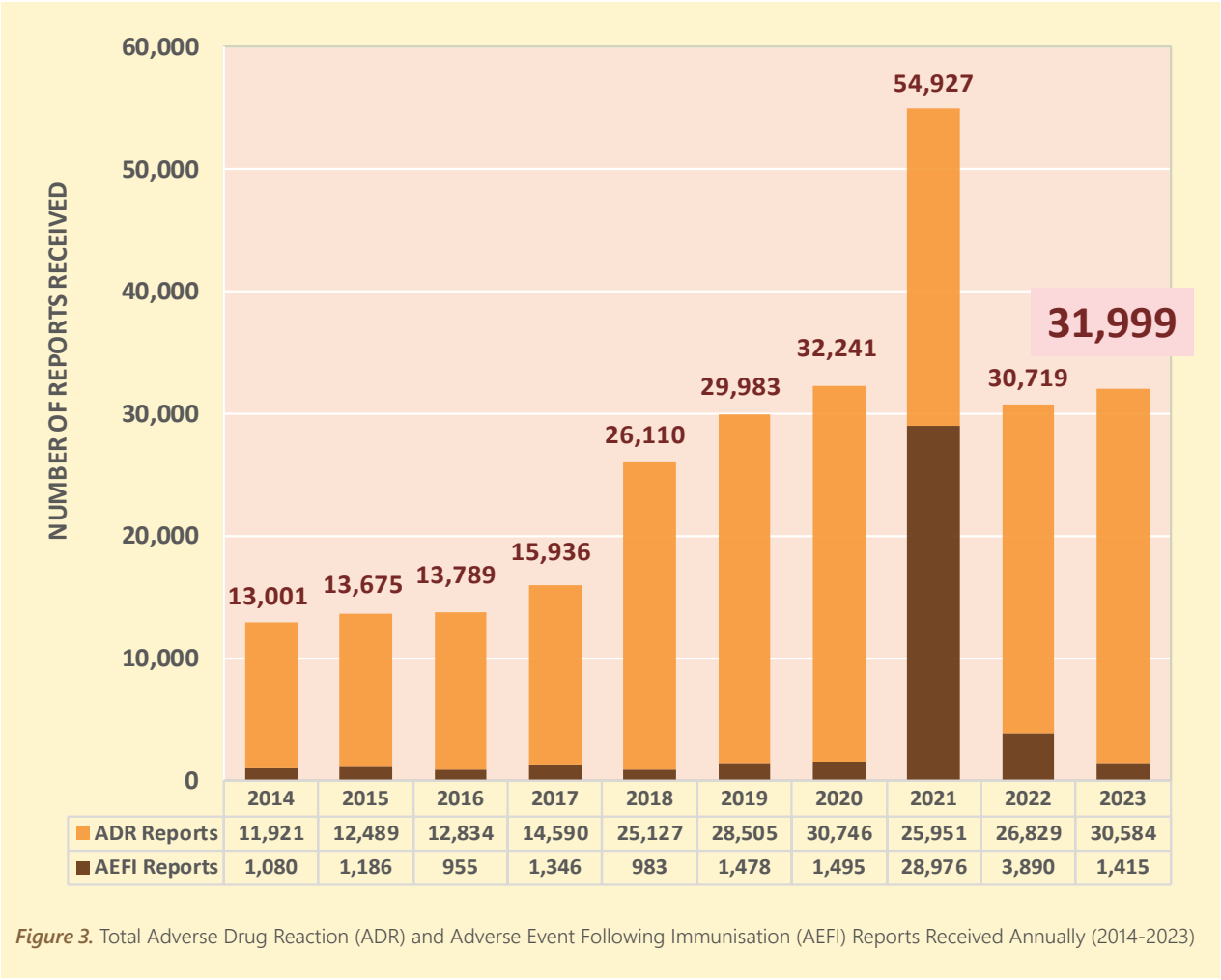
Features

Adverse Event Reports Received 2014-2023

In 2023, the NPRA received **31,999** adverse drug reaction (ADR) and adverse event following immunisation (AEFI) reports from across Malaysia (***Figure 3***).



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
ADR Reports	11,921	12,489	12,834	14,590	25,127	28,505	30,746	25,951	26,829	30,584
AEFI Reports	1,080	1,186	955	1,346	983	1,478	1,495	28,976	3,890	1,415

Figure 3. Total Adverse Drug Reaction (ADR) and Adverse Event Following Immunisation (AEFI) Reports Received Annually (2014-2023)

Every report is screened, evaluated for causality (the likelihood that the reaction is related to the medicine), and submitted to the WHO International ADR database. These reports help to identify new or serious risks, thus ensuring the safety of medicines not just in Malaysia but worldwide.

What's New

List of Safety Alerts and Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Rivastigmine	Risks of QT Prolongation and Torsade de Pointes	19-Jan-2024	NPRA.600-1/9/13 (34) Jld.1 [16 Jan 2024]
2	Imatinib	Risk of Thrombotic Microangiopathy	22-Jan-2024	NPRA.600-1/9/13 (33) Jld.1 [16 Jan 2024]

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit **www.npra.gov.my**
2. Report ADR **as Healthcare Professional**
   a) Choose **Online Reporting** or
   b) Download the **ADR manual form** and submit the completed form via email or post:

fv@npra.gov.my

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