

MADRAC *Bulletin*

For healthcare professionals only

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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 health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

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.



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Highlights



- **Understanding Immunisation Stress-Related Responses (ISRRs)** ... 2

Articles Based on Case Reports



- **Sleepwalking with Zolpidem** ... 5

Features



- **Welcome MADRAC 2025-2027** ... 7

What's New



- **List of Safety Alerts/Directives Related to Drug Safety Issues** ... 8

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 health care 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 of 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 NPRA.

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report article(s).

Highlights

Understanding Immunisation Stress-Related Responses (ISRRs)

By Nur Ayuni binti Ahmad

Case Scenario 1¹

A 13-year-old girl received the human papillomavirus (HPV) vaccine through a school-based vaccination program. She had a prior history of fainting when a blood sample was taken. On the day of vaccination, she was the last girl in her class to be vaccinated and had been standing, watching her classmates receive the vaccine. As the nurse prepared to administer the vaccine, she began sweating profusely. She also experienced nausea and palpitations, but she did not inform the vaccinator of her condition. Less than 2 minutes after immunisation, she experienced hyperventilation, difficulty in breathing, and a sense like she was about to faint.

Case Scenario 2¹

A 50-year-old man received a COVID-19 vaccine shot at a mass vaccination site. Just before receiving the vaccine, he had read on social media about its potential side effects. During the vaccination, he suddenly felt dizzy while seated. Less than 5 minutes after the vaccination, while walking to the observation room, his vision began to blur, and he lost consciousness. He was immediately attended to by a physician and placed in supine position, at which point his vital signs showed low blood pressure and a low heart rate. Subsequently, he rapidly regained consciousness without any treatment.

Discussion

Receiving a vaccine can cause feelings of worry and anxiety for some individuals, which may present as an adverse event.^{1,3} The rollout of mass vaccinations such as COVID-19 vaccination has led to an increase in reports involving **immunisation stress-related responses (ISRRs)**.^{1,2} Prompt recognition and management of ISRRs are crucial for maintaining public trust in vaccines and ensuring the success of immunisation programmes by minimising adverse events and preventing future vaccination hesitancy.^{1,3,4}

ISRRs, considered as *adverse events following immunisation* (AEFI) (**Figure 1**), encompass the entire spectrum of symptoms and signs that arise in response to stress surrounding the immunisation process.¹ These reactions are **not directly caused** by the vaccine itself, a defect in vaccine quality, or an immunisation error.

Adverse Events Following Immunisation (AEFI)

Any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Vaccine Product-Related Reaction	Vaccine Quality Defect - Related Reaction	Immunisation Error Related Reaction	Immunisation Stress-Related Response	Coincidental Event
An AEFI that is caused or precipitated by one or more of the inherent properties of a vaccine.	An AEFI that is caused or precipitated by one or more defects in the quality of a vaccine, including its administration with a device provided by the manufacturer.	An AEFI that is caused by inappropriate handling, prescribing or administration of a vaccine.	An AEFI arising from anxiety about the immunisation.	An AEFI that is caused by something other than a vaccine, immunisation error or immunisation anxiety.

Figure 1: Adverse Events Following Immunisation (AEFI) and five cause-specific categories, as defined by Council for International Organizations of Medical Sciences (CIOMS) and the WHO Working Group on Vaccine Pharmacovigilance¹⁻³

ISRRs can be explained according to a conceptual biopsychosocial model.^{1,4} A variety of interacting factors might influence an individual's response, including **physiological/biological** characteristics (e.g., age, gender, weight), and **psychological** aspects (e.g., personal expectation of pain, fear of needle or blood, and prior knowledge or preparedness). Such responses can be further influenced by certain **social** settings (e.g., trust in healthcare, other people's responses, and social media). Understanding these factors can aid in the prevention, diagnosis, and management of an ISRR.

Manifestations of ISRR are classified into three main types (**Figure 2**).^{1,3,4} The response usually begins as an **acute stress response** which activates the sympathetic nervous system. In some individuals, an over-compensatory parasympathetic response may follow, where heart rate or blood pressure significantly decreases, resulting in a **vasovagal reaction**. ISRRs may also manifest as **dissociative neurological symptom reactions (DNSR)**, which are typically observed in clusters of individuals with psychogenic illnesses

	Acute stress responses	Vasovagal reactions	Dissociative neurological symptom reactions (DNSRs)
Symptoms	Increased heart rate, palpitations, difficulty in breathing, or rapid breathing (hyperventilation).	Dizziness, blurred vision, and syncope. May be associated with prodromal symptoms such as nausea, sweating, and pallor.	Weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties, and non-epileptic seizures with no apparent physiological basis.
Onset	May occur before, during or immediately after vaccination (usually within 5 min). Usually transient and resolve spontaneously.		May take hours to days to develop after immunisation

Figure 2: Classification of stress responses and reactions^{1,3,4}



*AI-generated image

ISRR symptoms may occur **immediately before, during or after** immunisation.^{1,3,4} ISRRs vary between individuals and may differ within groups, and may change according to time or context either as solitary events or as clusters (*similar events among several individuals within minutes, hours or days and/or at the same location*).^{1,4}

Most cases of ISRR reported to NPRA occurred within 30 minutes post-immunisation and resolved spontaneously without medical intervention.⁵ At the time of writing, the most commonly reported vaccines associated with ISRRs in Malaysia were COVID-19 vaccines (97.9%), HPV vaccines (1.5%), tetanus vaccines (0.3%), and diphtheria/tetanus combination vaccines (0.1%).

Advice for Healthcare Professionals

It is important to understand, prevent, and manage ISRRs effectively to ensure a more positive vaccination experience for vaccinees. This will strengthen trust in vaccines and immunisation programmes, and improve public health as a whole.

Preventing ISRRs

- Create a calm, private environment to reduce anxiety, especially during group immunisation (e.g., school programmes). Minimise stress by shortening wait times, maintaining a comfortable temperature, and preparing the vaccine out of view.
- Identify high-risk individuals by screening for needle fear, previous vasovagal reactions, and negative experiences with needles.
- Communicate clearly with the individuals, explaining the procedure and offering reassurance to help reduce stress.



*AI-generated image

Managing ISRRs

- It is important to note that **faintish attack (syncope)** can be misdiagnosed as anaphylaxis. Careful observation and clinical judgement are crucial to distinguish between the two.
- Respond to **acute stress responses** with calm, positive, and reassuring communication until symptoms resolve.
- If a patient exhibits a **vasovagal reaction**, place them in a supine position and encourage them to practise muscle tension exercises.
- If an ISRR is identified, explain to the patient that the reaction is not related to the vaccine product, vaccine quality, or procedural error. Reassure the patient that the symptoms are not harmful and will resolve spontaneously without medication.
- For complex cases such as **DNSR**, including non-epileptic seizures, seek input from a multidisciplinary team for both medical and psychological assessment and management.

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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 health care 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 exhaustive but rather represents a selection of clinically relevant items that warrants dissemination.

Sleepwalking with Zolpidem

By Foo Wei Fuen

Case Report¹

A 64-year-old male with underlying hypertension and hyperlipidaemia, both managed with ongoing pharmacological treatment, was prescribed fluvoxamine 200 mg once daily for depression and zolpidem 10 mg at night for insomnia. Following zolpidem initiation, he experienced two episodes of **sleepwalking**, each lasting approximately 5 minutes before he became aware that he was walking and doing other activities while sleeping. He had no prior history of zolpidem use or sleepwalking.

Zolpidem was subsequently discontinued and substituted with lorazepam. Following zolpidem withdrawal, he did not experience any further sleepwalking episodes. Given the presence of underlying medical conditions and concomitant medications, the adverse event was assessed as *possibly* related to zolpidem use.

Discussion

Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class that enhances the inhibitory effect of gamma-aminobutyric acid (GABA).^{2,3} It selectively modulates $\alpha 1$ subunits-containing GABAA receptors, which are predominantly found on brain structures involved in sleep regulation. Zolpidem is indicated only for the treatment of severe sleep disorders in adults with transient or short-term insomnia.² It decreases sleep latency time, lowers night awakenings, increases total sleep time, and improves sleep quality. In Malaysia, there are currently eight registered products containing zolpidem in immediate-release form.⁴

Sleepwalking or somnambulism, is an arousal parasomnia consisting of a series of complex behaviours that usually occurs during slow wave sleep (SWS) and can last from seconds to over 30 minutes.⁵⁻⁸ While frequently harmless, sleepwalking can lead to injury to the sleepwalker or others, and in rare cases, even death.⁷⁻⁸ Most cases likely go unnoticed and unreported, which may reflect inadequate recognition and reporting of sleepwalking, leading to an underestimation of its true prevalence.⁷

In 2007, the NPRA issued a directive [Ref. No.: Bil. (75) dlm. BPFK/02/5/1.3] requiring all local package inserts for sedative-hypnotic products (including zolpidem-containing products) to include a boxed warning on the risk of **complex sleep-related behaviours**, such as sleep driving, making phone calls, as well as preparing and eating food while asleep. Numerous post-marketing observational studies, case series, and case reports have continued to show an association between zolpidem and complex sleep-related behaviours, which can occur after the first or any subsequent use of zolpidem.⁸⁻¹⁰

A 2018 systemic review highlighted zolpidem as the only drug among 29 shown to cause sleepwalking in clinical trials and linked to a substantial number of case reports.⁸ This review of 62 studies identified four primary classes of medications associated with inducing sleepwalking:

- (a) benzodiazepine receptor agonists and other GABA modulators;
- (b) serotonergic antidepressants;
- (c) older-generation antipsychotics;
- (d) beta-blockers.



The review included 24 studies on zolpidem-related sleepwalking, covering clinical trials, surveys, and case reports involving both adults (16 studies) and adolescents (2).⁸ The reported incidence was 0.5% and 1.1% in two adult post-marketing reviews, 2.2% in children, and 5.1% in a psychiatric sample. Most case reports involved patients with complex medical histories or concomitant medications, though some occurred in otherwise healthy individuals. Only one case involved alcohol use, and another reported an interacting anticonvulsant. Sleepwalking was more commonly reported at recommended doses rather than higher doses. A single case noted a childhood history of sleepwalking; most cases were first-time occurrences after zolpidem use, with no reports of prior adult-onset sleepwalking.

The exact mechanisms of zolpidem-induced complex sleep-related behaviours, including sleepwalking, are not fully understood, but several theories have been proposed.^{6,9} One theory suggests that zolpidem suppresses rapid eye movement (REM) sleep and increases slow wave sleep (SWS) duration, predisposing individuals to parasomnias like sleepwalking. Partial arousal from sleep under zolpidem's influence may result in nocturnal events without subsequent recall due to memory loss. The cerebral pattern generators (CPG) theory suggests that zolpidem activates innate motor behaviours, while the serotonergic model links zolpidem's GABA_A receptors binding to a postinhibitory rebound in serotonergic activity, leading to complex sleep behaviours.

At the time of writing, the NPRA had received 52 local adverse drug reaction (ADR) reports with 120 adverse events suspected to be related to zolpidem.¹ The most commonly reported adverse events were dizziness (8%) and somnolence (6%). The NPRA had received 2 reports associated with sleepwalking, including the case described above. As of July 2024, a search of the World Health Organisation (WHO) global ADR database revealed 2,426 global reports of somnambulism suspected to be associated with zolpidem.^{11*}

*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 Health Care Professionals

- 1 Remain vigilant for the potential risk of sleepwalking and other complex sleep-related behaviours in patients taking zolpidem.
- 2 Follow dosing recommendations when initiating zolpidem and start with the lowest possible dose, especially in elderly patients.
- 3 Counsel patients and caregivers on the risk of sleepwalking or other unusual behaviours while not being fully awake following zolpidem administration. Advise patients to avoid alcohol before or after taking zolpidem.
- 4 If a patient exhibits complex sleep-related behaviours, given the potential risk to the patient and others, consider discontinuing zolpidem treatment immediately and assess the need for alternative therapy.
- 5 Report any adverse drug reactions suspected to be related to the use of zolpidem to the NPRA.

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Features

Welcome MADRAC 2025-2027

The 193rd Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) meeting, which was held on 6 March 2025, marked the first MADRAC meeting for the 2025-2027 session.

NPRA extends our utmost welcome to all respectable MADRAC members

NPRA believes that the shared expertise of MADRAC 2025-2027 from a variety of fields and practices will benefit and advance the national pharmacovigilance system for safety monitoring of medicines and vaccines in Malaysia.



Malaysian Adverse Drug Reactions Advisory Committee

MADRAC

2025 - 2027

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What's New

List of Safety Alerts/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	Hydroxychloroquine	Small Increased Risk of Major Congenital Malformations in Children Following in utero Exposure	04-Mar-2025	-
2	Azithromycin	Rare Risk of Cardiovascular Death	24-Apr-2025	-

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:



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