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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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Risk management plans – Working in partnership with healthcare professionals to mitigate risks of health products — Pg 3 - 4

- A risk management plan (RMP) involves a set of pharmacovigilance and risk minimisation activities aimed at minimising key safety risks associated with a health product.
- Physician and patient educational materials, Dear Healthcare Professional Letters and the Pregnancy Prevention Programme are examples of risk minimisation activities to enhance safe use of a health product in RMPs.

Reminder on risk of extrapyramidal side effects with metoclopramide in paediatric patients aged 18 years and below — Pg 5 - 6

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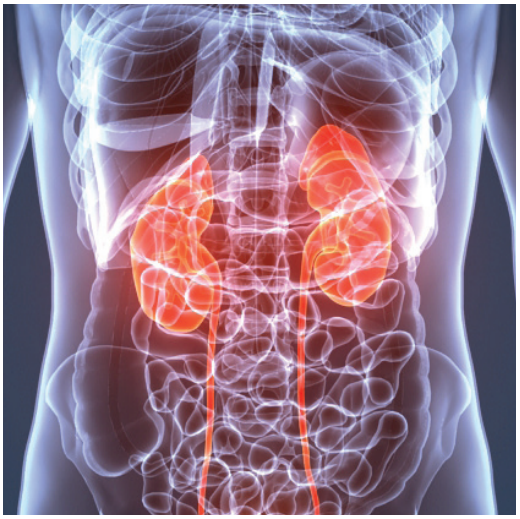
- HSA has observed more cases of metoclopramide-induced extrapyramidal side effects (EPSE) in paediatric patients aged 18 years and below in recent years. Most cases were prescribed oral metoclopramide in the primary care setting for off-label uses such as gastroenteritis, and standard adult dosing (10 mg three times daily) was commonly prescribed.
- Healthcare professionals are reminded that the approved indication of metoclopramide in paediatric patients aged one to 18 years is as a second-line treatment of established post-operative nausea and vomiting (administered via the intravenous route), and that the dose should be administered based on body weight.
- Healthcare professionals are encouraged to consider alternative anti-emetics for paediatric patients, especially for those who are already on medications that increase the risk of EPSE.

AE Case in Focus 1: Test Yourself — Pg 4, 6-7

A 75-year-old male presented to the emergency department with a two-day history of fever, generalised malaise and non-oliguric acute kidney injury (AKI). He had been receiving nivolumab for the last 26 months for the management of metastatic adenocarcinoma of unknown primary site. A FDG PET-CT scan two months prior to presentation demonstrated overall disease stability, except for oligo-progression in the form of a new enlarged FDG-avid left para-aortic node suspicious for metastases. He underwent stereotactic body radiotherapy and was given oral metoclopramide and omeprazole as needed for anticipated side effects of nausea and dyspepsia.



Notably, he had a prior history of immune-related adverse events - Grade 3 nephritis and Grade 2 hypophysitis, which developed during initial treatment with combination CTLA-4 and anti-PD-1 therapy and were managed with prednisolone and mycophenolate mofetil. He was started on nivolumab following renal recovery on disease progression.

Published by the Health Products Regulation Group, HSA and the HSA Product Vigilance Advisory Committee

Systems review and clinical examination were unremarkable. Laboratory investigations were indicative of AKI, where urinalysis showed pyuria and low-grade haematuria and proteinuria. C-reactive protein was elevated, but serum procalcitonin and white blood cells were normal. Renal imaging excluded urinary obstruction and microbiological investigations returned negative.

What could have caused the acute kidney injury in this patient?

AE Case in Focus 2: Test Yourself

Pg 4, 7-8

This is a case of an 88-year-old female who presented with a 20-year history of recurrent hypnopompic visual hallucinations (brief episodes of dream-like imagery occurring just after waking). Her initial hallucinations of plants and insects later progressed to vivid, detailed human figures. The hallucinations occurred almost daily upon awakening from sleep and became increasingly frightening over the last five years. Her past medical history included hypertension, diabetes mellitus and breast carcinoma in remission following mastectomy three years prior. Her regular medications included amlodipine, isosorbide-5-mononitrate, propranolol, gliclazide, metformin and tamoxifen. She did not have any history of neurological or psychiatric disease, or family history of psychiatric illness. Physical and mental state examinations were normal.

What could have caused this patient's long-standing visual hallucinations?

Dear Healthcare Professional Letters on safety concerns

Scan/click on QR code

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 September 2025.

Risk management plans – Working in partnership with healthcare professionals to mitigate risks of health products

Key Points

- A risk management plan (RMP) involves a set of pharmacovigilance and risk minimisation activities aimed at minimising key safety risks associated with a health product.
- Physician and patient educational materials, Dear Healthcare Professional Letters and the Pregnancy Prevention Programme are examples of risk minimisation activities to enhance safe use of a health product in RMPs.

A risk management plan (RMP) is an essential part of pharmacovigilance (PV) and involves a set of activities aimed at identifying, characterising and minimising safety risks related to health products. This article provides healthcare professionals with an overview of typical RMP activities, such as educational materials to facilitate the safe use of health products, and highlights the important role played by healthcare professionals in the effective implementation of RMPs to ensure patient safety and optimal therapeutic outcomes.

Risk management plans for health products

Under the requirements for marketing authorisation, pharmaceutical companies are responsible for ensuring the quality, safety and efficacy of their products by putting in place systems and processes to monitor and manage product-related issues throughout the lifecycle of the product. This includes developing RMPs, which comprise a product's known or potential safety concerns, as well as the PV and risk minimisation activities (RMAs) that will be put in place to manage them (Figure 1). PV activities aim to identify and characterise safety signals and clinically relevant risks, while RMAs are designed to reduce the probability or severity of adverse events. These activities can be further categorised into routine activities (i.e., standard requirements) or additional activities intended to provide an extra level of monitoring or risk minimisation to maintain a favourable benefit-risk balance.[1]

Additional risk minimisation activities

Physician and patient educational materials, Dear Healthcare Professional Letters and the Pregnancy Prevention Programme are examples of RMAs to enhance safe use of a health product in RMPs.

i) Physician and/or patient educational materials

Educational materials communicate important treatment-associated adverse events and risk minimisation advice to healthcare professionals and patients by focusing on specific safety concerns and pertinent actions to be taken. They are intended to supplement the information in package inserts or patient information leaflets (PILs) and comprise three main types:

- Physician Educational Material (PEM)
- Patient Medication Guide (PMG)
- Patient Alert Card (PAC)

HSA-approved educational materials are mandated and reviewed by HSA prior to distribution. They bear the statement, "This document has been approved by HSA on [Date]" and are published online on the HSA website.[2] When counselling a patient, healthcare professionals may consider using the PMG and/or PAC developed for specific products to reinforce the patient's understanding of important safety information about their medications, as these materials provide more targeted information on specific significant concerns and their management. They differ from PILs which provide general information for Pharmacy-Only or General Sales List (GSL) products to support appropriate medicine use by patients in lieu of the close medical supervision required for Prescription-Only products.

Healthcare professionals may also receive materials initiated and distributed by pharmaceutical companies as part of the company's RMP for their products. Although these company-initiated materials are not subjected to HSA's approval and are therefore not published on the HSA website, the company is required to ensure that they are aligned with the latest approved local package insert.

ii) Dear Healthcare Professional Letter (DHCPL)

A DHCPL alerts healthcare professionals to important new or updated safety information regarding a health product and any actions they may need to take due to the safety information. HSA-initiated DHCPLs will usually be issued for safety matters regarding pharmacotherapeutic classes of products or following a review of a significant safety issue with updates on regulatory actions taken (if any), whereas DHCPLs regarding company-specific or product/brand-specific safety information are disseminated by the pharmaceutical companies.

The distribution of DHCPLs occurs through:

- Email to locally registered healthcare professionals via the MOH Alert portal for HSA-initiated DHCPLs.
- Direct dissemination from pharmaceutical companies to healthcare professionals for company-initiated DHCPLs.

Copies of these DHCPLs are saved in the archives of the MOH Alert database for ease of access by healthcare professionals via their respective healthcare professional board or council websites, with abstracts published on HSA's website.[3]

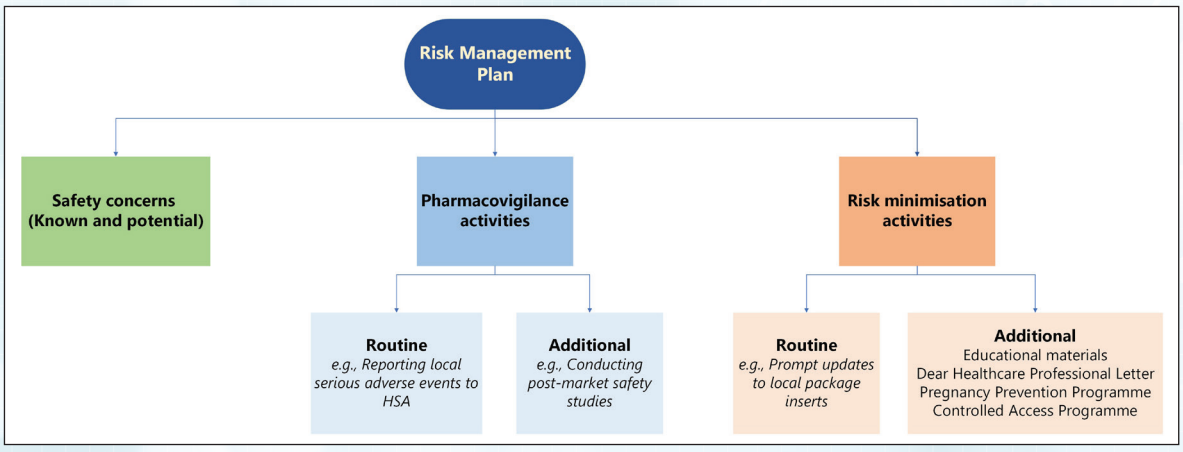


Figure 1. Key components of a risk management plan

iii) Pregnancy Prevention Programme (PPP)

A PPP may be required for health products with known or potential teratogenic effects to minimise the likelihood of pregnancy during treatment and drug exposure during pregnancy. Currently, the implementation of pregnancy prevention measures is required for products containing thalidomide or its analogues (i.e., lenalidomide and pomalidomide), as well as oral retinoids, comprising activities such as:

- Exclusion of pregnancy prior to and during treatment.
- Patient counselling about the risk of teratogenicity and the need for effective contraception throughout treatment.
- Acknowledgement by healthcare professionals and patients regarding their understanding of the programme.
- Provision of educational materials for healthcare professionals and/or patients.

HSA is currently reviewing the local PPP framework to develop a set of fit-for-purpose regulatory requirements that are not overly burdensome on stakeholders, including healthcare professionals. Once finalised, the updated PPP requirements and relevant materials will be shared with all stakeholders.

Healthcare professionals as the cornerstone of effective risk management plan implementation

RMPs can be a combination of risk mitigation measures mandated by HSA under its regulatory framework[1] or additional RMAs initiated by companies. The active participation of healthcare professionals and their collaboration with HSA and pharmaceutical companies in implementing RMP measures is key to an effective RMP that safeguards the health of patients.

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AE Case in Focus 1: Test Yourself

A 75-year-old male presented to the emergency department with a two-day history of fever, generalised malaise and non-oliguric acute kidney injury (AKI). This occurred against a background of metastatic adenocarcinoma of unknown primary site, with sites of disease involving the right submandibular gland, liver, and multiple lymph node regions. He has been heavily pre-treated and has been on nivolumab (an anti-programmed cell death protein (PD)-1 immune checkpoint inhibitor (ICI)) for the last 26 months. A FDG PET-CT* scan two months prior to presentation demonstrated overall disease stability, except for oligo-progression in the form of a new enlarged FDG-avid left para-aortic node suspicious for metastases. He was referred to Radiation Oncology and underwent stereotactic body radiotherapy (SBRT), receiving a total dose of 50 Gy in 5 fractions. In view of nodal proximity to the stomach, he was given oral metoclopramide 10 mg three times daily as needed and omeprazole 20 mg every morning as needed for anticipated side effects of nausea and dyspepsia.

Notably, he had a prior history of immune-related adverse events (irAE) - Grade 3 nephritis (acute interstitial nephritis (AIN) subtype), and Grade 2 hypophysitis, which developed during initial treatment with combination anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-PD-1 therapy in a clinical trial five years ago. He was managed with prednisolone and mycophenolate mofetil, which were subsequently tapered. He remained on maintenance hydrocortisone replacement for hypophysitis-related adrenal insufficiency. He was started on nivolumab following renal recovery on disease progression and last received nivolumab one week prior to current presentation. Regular medications include amlodipine for hypertension.

Systems review and clinical examination were unremarkable. Apart from fever, clinical vitals were stable. The patient was non-toxic and euvolemic. Laboratory investigations were indicative of AKI, with a peak serum creatinine (sCr) of 335 µmol/L (baseline sCr 137 µmol/L). Urinalysis showed pyuria (WBC 58/µL) and low-grade haematuria and proteinuria. C-reactive protein was elevated, but serum procalcitonin and white blood cells were normal. Serum complements were normal and the autoimmune screen performed to evaluate for glomerular disease was largely unremarkable. Renal imaging excluded urinary obstruction. Microbiological investigations performed as part of septic evaluation subsequently returned negative.

**Fluorodeoxyglucose positron emission tomography and computed tomography*

Q: What could have caused the acute kidney injury in this patient?

HSA would like to thank Dr Seow Hean Howe Leon, Medical Officer, Medical Oncology, National Cancer Centre Singapore; Clin Asst Prof Lee Jie Xin Joycelyn, Senior Consultant, Medical Oncology, National Cancer Centre Singapore; and Clin Asst Prof Tan Hui Zhuan, Consultant, Renal Medicine, Singapore General Hospital for contributing this article.

Answers can be found on page 6 to 7.

AE Case in Focus 2: Test Yourself

This is a case of an 88-year-old female who presented with a 20-year history of recurrent hypnopompic visual hallucinations (brief episodes of dream-like imagery occurring just after waking).[1] Initially, she experienced hallucinations of plants and insects, which later progressed to vivid, detailed human figures. The hallucinations occurred almost daily upon awakening from sleep, lasting 10–20 seconds each time. While initially pleasant and inoffensive, they became increasingly frightening over the last five years. She did not report any auditory, gustatory, or tactile hallucinations. Her past medical history included hypertension of 40 years, diabetes mellitus of 11 years, and breast carcinoma in remission following mastectomy three years prior. Her regular medications included amlodipine 5 mg daily, isosorbide-5-mononitrate 30 mg daily, propranolol 40 mg twice daily, gliclazide 160 mg twice daily, metformin 850 mg daily, and tamoxifen 20 mg daily. She did not have any history of neurological or psychiatric disease, or family history of psychiatric illness. Physical and mental state examinations were normal, with best-corrected visual acuity of 20/50 due to dry age-related macular degeneration in both eyes.

What could have caused this patient's long-standing visual hallucinations?

HSA would like to thank Dr Denise Au Eong Tian Min, Department of Accident & Emergency, Khoo Teck Puat Hospital for contributing to this article.

Answers can be found on page 7 to 8.

Reminder on risk of extrapyramidal side effects with metoclopramide in paediatric patients aged 18 years and below

Key Points

- HSA has observed more cases of metoclopramide-induced extrapyramidal side effects (EPSE) in paediatric patients aged 18 years and below in recent years. Most cases were prescribed oral metoclopramide in the primary care setting for off-label uses such as gastroenteritis, and standard adult dosing (10 mg three times daily) was commonly prescribed.
- Healthcare professionals are reminded that the approved indication of metoclopramide in paediatric patients aged one to 18 years is as a second-line treatment of established post-operative nausea and vomiting (administered via the intravenous route), and that the dose should be administered based on body weight.
- Healthcare professionals are encouraged to consider alternative anti-emetics for paediatric patients, especially for those who are already on medications that increase the risk of EPSE.

Metoclopramide has been registered in Singapore since 1989 for the prevention and treatment of nausea and vomiting due to various conditions. It inhibits dopamine receptors both centrally in the chemoreceptor trigger zone (CTZ) and peripherally in the upper gastrointestinal tract, blocks the action of serotonin at the 5-hydroxytryptamine (5-HT_3) receptors in the CTZ and has prokinetic activity.[1] Six registered products are available locally in various dosage forms (i.e., tablets, syrups and injections).

Since 2023, HSA has observed more cases of metoclopramide-induced extrapyramidal side effects (EPSE) in paediatric patients aged 18 years and below. Most cases (82.6%) were prescribed oral metoclopramide in the primary care setting (i.e., General Practitioners (GPs), polyclinics) for off-label uses such as vomiting secondary to gastritis, gastroenteritis or other viral illnesses. Standard adult dosing (10 mg three times daily) was commonly prescribed regardless of patient weight.

Use of metoclopramide in paediatric patients

HSA would like to remind healthcare professionals about the approved indications of metoclopramide-containing products to reduce the risk of neurological and other dose-related adverse reactions.[2] Metoclopramide is contraindicated in infants less than one year old. In patients aged one to 18 years, metoclopramide is approved as a second-line treatment of established post-operative nausea and vomiting, administered via the intravenous route. The approved dose for paediatric patients is 0.10 to 0.15 mg/kg body weight, up to three times daily. The recommended maximum dose in 24 hours is 0.5 mg/kg body weight, up to 30 mg daily.

As potentially serious neurological adverse events are dose-related, healthcare professionals are recommended to use the minimum effective dose of metoclopramide. Treatment should be kept as short as possible and treatment beyond 12 weeks should be avoided unless the therapeutic benefit outweighs the risk.

Local Situation

As at 1 August 2025, HSA has identified 84 cases of metoclopramide-induced EPSE (e.g., oculogyric crisis, dystonia, akathisia and tardive dyskinesia) in paediatric patients over the past five years, with increasing number of cases observed since 2023 (Figure 1). These included reports to HSA by healthcare professionals and cases detected from electronic medical records of patients who visited the emergency department or were admitted in public hospitals. There were more reports in females (n=52, 61.9%), and the affected patients ranged from 8–18 years old (median: 16 years). Majority of the patients were Chinese (n=57, 67.8%), followed by Indians (n=14, 16.7%), Malays (n=8, 9.5%) and patients of other ethnicities (n=5, 6.0%). None were reported to have irreversible tardive dyskinesia.

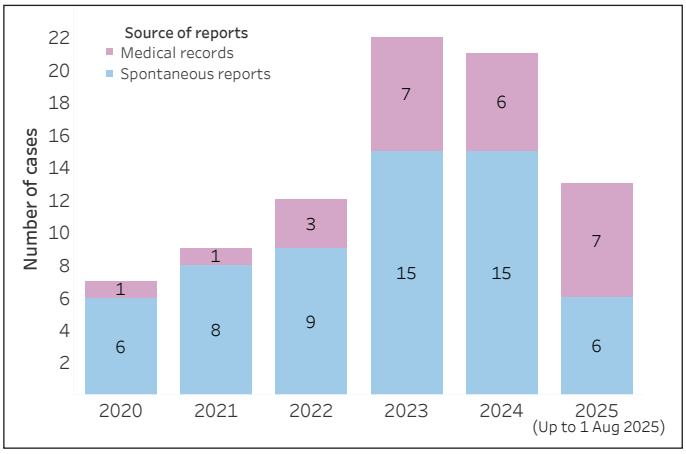

Figure 1. Local cases of metoclopramide-induced extrapyramidal side effects among paediatric patients aged 18 years and below in the past five years (January 2020 – August 2025)

Of the 69 cases with documented sources of metoclopramide, majority (n=57, 82.6%) were prescribed oral metoclopramide in the primary care setting (GPs 79.7%, polyclinics 2.9%). Seven (10.1%) patients received metoclopramide while admitted in public hospitals, with four administered intravenously and three orally. The remaining five patients self-medicated with oral metoclopramide. Majority of the patients (n=58/64, 90.6%) were prescribed metoclopramide for off-label indications such as vomiting secondary to gastritis, gastroenteritis or other viral illnesses. Patients were most frequently prescribed metoclopramide at a dose of 10 mg three times daily regardless of their weight, which ranged from 34 kg to 82 kg where documented. Notably, concurrent use of other drugs (e.g., fluoxetine, olanzapine, domperidone and prochlorperazine) in seven cases could have increased the risk of EPSE.

Choice of anti-emetics in paediatric patients

Where the use of anti-emetics is warranted, healthcare professionals could consider alternative anti-emetics for paediatric patients aged 18 years and below due to the risk of potentially serious neurological and cardiovascular adverse events with metoclopramide. The incidence of EPSE was found to be 9% (95% confidence interval 5–17%) in a meta-analysis of children administered metoclopramide although the dose of metoclopramide used in these studies varied widely.[3] Risk factors for metoclopramide-induced EPSE include[4]:

- Use in paediatric patients
- Females
- Doses exceeding recommended doses
- Extended duration of therapy (>12 weeks)
- Kidney impairment
- Concurrent use of drugs that can cause EPSE (e.g., anti-psychotics)
- Concurrent use of strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, bupropion)

Domperidone, promethazine and ondansetron are among the anti-emetics recommended by PaedsENGAGE, a pilot programme led by KK Women's and Children's Hospital and National University Hospital to partner GPs across Singapore in determining the appropriate care setting for mild and moderate paediatric conditions. Recommended paediatric doses from the PaedsENGAGE drug reference guide are shown in Table 1.

Table 1. Recommended anti-emetics in the PaedsENGAGE Drug Reference Guide (1st edition)

Drug (Route)	Paediatric dose	Usual adult dose	Remarks
Domperidone (Oral)	0.25 mg/kg three times daily	10 mg three times daily	Maximum one week duration
Promethazine (Oral)	0.25–0.5 mg/kg every 6 – 8 hours	12.5–25 mg every four to six hours	Contraindicated in children < two years old
Ondansetron (Oral / Sublingual)	0.1–0.2 mg/kg every 8 hours	4–8 mg every eight to 12 hours	For use in children > six months old. Only to be given in clinic setting

Some considerations with the use of anti-emetics in paediatric patients

Domperidone has a similar mechanism of action to metoclopramide, but it has a lower risk of EPSE as it penetrates poorly into the central nervous system.[1] Promethazine, an antihistamine and dopamine antagonist, is contraindicated for use in children less than two years old due to the risk of sedation and respiratory depression. Studies have found ondansetron to be effective in cessation of vomiting, reducing the need for intravenous fluids and risk of hospitalisation, even when given as a single dose.[5-7] In a meta-analysis, ondansetron was found to be more effective than domperidone in the cessation of vomiting in children with gastroenteritis.[8] The use of ondansetron is generally well-tolerated, although there is mixed evidence on whether ondansetron increases the frequency of diarrhoea when used in children with gastroenteritis. It is recommended for use in the clinic setting to allow for close monitoring of the child's hydration status and to avoid masking surgical conditions which present with persistent vomiting. In addition, multiple doses of ondansetron have been associated with the risk of QT interval prolongation, which can lead to potentially fatal cardiac arrythmias, although this has been mainly observed in adults.[9] This risk is increased when ondansetron is used in high doses and in patients with risk factors such as pre-existing cardiac disease or disorders associated with electrolyte abnormalities.[6]

HSA's advisory

Although EPSE is generally reversible with drug discontinuation and treatment, its unexpected occurrence can be distressing for both patients and caregivers. Healthcare professionals are encouraged to consider alternatives to metoclopramide when use of anti-emetics is required in paediatric patients, and to adopt weight-based dosing of metoclopramide for patients up to 18 years of age. Treatment duration should be limited, and both patients and caregivers should be counselled on the risk of EPSE.

HSA would like to thank Clin Assoc Prof Sashikumar Ganapathy (Senior Consultant, Head of Children's Emergency) and Dr Junaidah Binte Badron (Senior Staff Physician) of KK Women's and Children's Hospital for their contribution to this article.

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Answer to AE Case in Focus 1: Test Yourself

Pre-renal and post-renal AKI were excluded. In view of recent re-exposure to omeprazole and prior history of renal immune-related adverse events (irAEs), relapsed acute interstitial nephritis (AIN) was clinically suspected and attributed to nivolumab and omeprazole. Empiric high dose prednisolone (1 mg/kg of body weight) was promptly initiated without kidney biopsy on day three of admission. Omeprazole was immediately withheld and substituted with famotidine for gastroprotection, while atovaquone was commenced for pneumocystis pneumonia (PCP) prophylaxis. Improvement in serum creatinine was observed and further dosing of nivolumab was withheld. Oral prednisolone was continued and gradually tapered over eight weeks.

Nivolumab: An Immune Checkpoint Inhibitor

Nivolumab is a monoclonal antibody targeting programmed cell death protein 1 (PD-1) and belongs to a class of anticancer agents known as immune checkpoint inhibitors (ICIs). These agents block inhibitory pathways that normally downregulate the immune response, thereby enhancing the immune system's ability to recognise and attack tumour cells. There are four main classes of ICIs currently in clinical use:

- Anti-CTLA-4 (e.g., ipilimumab)
- Anti-PD-1 (e.g., nivolumab, pembrolizumab)
- Anti-PD-L1 (e.g., atezolizumab, durvalumab, avelumab)
- Anti-LAG-3 (e.g., relatlimab)

Over the past decade, ICIs have become one of the mainstays of cancer therapy and now serve as a key treatment option in several malignancies.

Renal Immune-Related Adverse Events

The use of ICIs has led to a broad spectrum of irAEs, which can affect various organ systems at different time points of treatment. While mechanisms remain incompletely understood, irAEs are broadly attributed to loss of peripheral tolerance beyond the tumour microenvironment, triggering immune responses against self-peptides and non-tumour antigens. Potential sources of non-tumour antigens include dietary components, environmental chemicals, viral infections, and concomitant medications.[1]

Renal irAEs, while less commonly occurring than toxicities affecting other organs, are a recognised complication of ICI therapy. In a large retrospective study, the overall incidence of AKI among ICI-treated patients was 17%, though only 3% were directly attributed to ICIs. Clinical trials have reported ICI-associated AKI rates of between 2.2% and 5%. The risk is higher with combination therapy (e.g., ipilimumab + nivolumab), with reported AKI rates of 4.9%, compared to monotherapy (2% for ipilimumab, 1.9% for nivolumab, and 1.4% for pembrolizumab).[2] The most common type of kidney injury observed on histology is AIN (Figure 1), although glomerular disease has also been reported.[3]

A significant proportion of patients who develop ICI-associated AIN have concurrent exposure to AIN-associated medications at the time of injury, with proton pump inhibitors (PPIs) being the most frequently implicated. Studies have linked PPI use to a higher likelihood and earlier onset of ICI-related AKI. Continued PPI use may also increase the risk of AKI recurrence if ICIs are rechallenged.[4] The consistent findings across studies, albeit observational in nature, highlight the need to review PPI use and monitor kidney function in this patient group.

The underlying mechanisms of ICI-associated AIN remain under investigation, but several immune-mediated pathways have been proposed. These include loss of tolerance to kidney antigens, activation of drug-specific T cells, and cytokine-driven inflammation. Although the direct contribution of PPIs is not yet fully understood, there is evidence suggesting that PPIs may act as triggers by engaging drug-specific T cells, particularly when immune tolerance is already compromised by checkpoint inhibition.[5] Anecdotal reports of AIN recurrence after PPI re-exposure, including the current case, further support this hypothesis.

Local situation

As at 1 August 2025, HSA has received 27 suspected reports of renal AEs following the use of ICIs, including the case above (latency nine to 253 days, median 31 days). These were reported with the use of pembrolizumab (n=13), atezolizumab (n=4), nivolumab (n=4), nivolumab and ipilimumab (n=3), durvalumab and tremelimumab (n=1), ipilimumab (n=1) and durvalumab (n=1). Of these, 18 described acute kidney injury, nephritis, renal failure or renal impairment with limited information or with confounders present (e.g., sepsis, underlying disease or diarrhoea). Eight cases reported AIN or acute tubulointerstitial nephritis (ATIN) attributed to ICI, of which six were biopsy-confirmed. The remaining case described AKI with clinical presentation highly suggestive of glomerulonephritis, postulated to be related to ICI use.

Of the 27 reports, two reported the use of PPIs, including the above case. The second was an 84-year-old female with colorectal cancer who developed KDIGO stage 2, non-oligouric AKI four months after starting pembrolizumab.[6] She was taking PPI, but not NSAIDs or antibiotics. She was treated with empiric prednisolone for suspected ICI-AIN and remained off immunotherapy for the next five months. However, upon restarting PPI for dyspepsia, she developed AKI four weeks later. ATIN was confirmed on kidney biopsy. She was treated with prednisolone with improvement and switched to vonoprazan for her dyspepsia.

Management

Recognition of ICI-AIN and timely initiation of immunosuppression (e.g., corticosteroids) are key to achieving optimal renal outcomes. ICIs should be temporarily withheld during the acute episode. Medications that are known to trigger AIN, such as PPIs, NSAIDs, and selected antibiotics (e.g., co-trimoxazole), should ideally be avoided during treatment of irAE.[7] Rechallenge with ICIs can be considered following renal recovery, based on a multi-disciplinary evaluation.

Minimising unnecessary PPI exposure may help reduce the risk of renal irAEs. Compared to other AIN-associated medications, PPIs are more frequently used inappropriately or for prolonged durations. Emphasising indication-based, time-limited use offers a practical strategy for mitigating risk.[8] In specific high-risk scenarios, such as ICI rechallenge following a renal irAE, a stricter avoidance of PPIs and other AIN-associated medications (where feasible) may be warranted. PPI use in patients on ICIs could be regularly reviewed, with necessary use limited to the lowest effective dose and shortest duration. Alternatives such as famotidine may be considered where appropriate.

Conclusion

Renal irAEs arising from ICI use may be potentiated with the use of PPIs. The following clinical considerations could mitigate the risk of these AEs:

- **Review necessity** of PPI therapy in patients starting ICIs
- **Avoid unnecessary PPI use**, especially in patients without a clear indication
- **Monitor renal function** closely during ICI therapy, particularly if PPIs are co-prescribed
- **Reassess PPI continuation** if AKI occurs or if rechallenging with ICIs after kidney injury

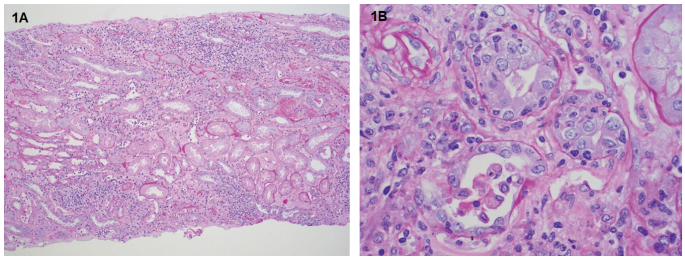

Figure 1. Images from patient's kidney biopsy during first episode of ICI-AIN. 1A. A diffuse tubulo-interstitial mononuclear inflammatory infiltrate is noted, comprising lymphocytes, histiocytes and some plasma cells, without tissue eosinophilia. No well-formed interstitial or intratubular granulomas are present. Periodic acid-Schiff, original magnification x100. 1B. Lymphocytic tubulitis. Periodic acid-Schiff, original magnification x600.

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Answer to AE Case in Focus 2: Test Yourself

Although the patient's visual hallucinations started only 20 years after initiation of propranolol to treat her hypertension, her doctors suspected that propranolol could be the culprit and requested her general practitioner to switch her propranolol to another anti-hypertensive agent. The patient's hallucinations decreased dramatically in frequency from multiple times daily to approximately once a fortnight shortly after propranolol was substituted with atenolol 50 mg once daily, with all other medications unchanged. Additionally, the nature of the remaining hallucinations became less distressing. The significant improvement in symptoms following the medication switch confirmed that propranolol was the causative agent for the patient's visual hallucinations. Although atenolol can also cause hallucinations, the patient chose to continue with it as she was satisfied with the marked reduction in frequency and severity of her symptoms.

Drug-induced hallucinations associated with beta-blockers

Neuropsychiatric adverse events (AEs) including sleep disturbances, hallucinations and nightmares have been reported to occur rarely with beta-blockers, particularly with moderately and highly lipophilic agents such as metoprolol and propranolol which readily cross the blood brain barrier.[2-4] This was investigated in a double-blind crossover study which compared the hydrophilic beta-blocker atenolol with lipophilic agents metoprolol and propranolol in 14 patients with a previous history of nightmares or hallucinations when treated with lipophilic beta-blockers.[2] All patients receiving lipophilic beta-blockers reported nightmares or hallucinations compared to three patients on atenolol. The total number of episodes was significantly lower for patients receiving

atenolol than for those receiving lipophilic beta-blockers (n=8 vs n=54, p<0.01). It is postulated that lipophilic beta-blockers penetrate the brain at higher concentrations to block central norepinephrine receptors, although the exact site and mechanism in causing neuropsychiatric AEs remain unknown.[2,4] Some beta-blockers such as propranolol have also been found to bind to 5-hydroxytryptamine (serotonin) receptors, which may interfere with serotonergic transmission that regulates sleep and arousal.[5] Both auditory and visual hallucinations associated with beta-blockers have been reported in literature, mostly in case series and case reports, with acute to delayed onset ranging from within 24 hours to 20 years.[1,4,6] Most hallucinations caused by beta-blockers typically stop within a few days of drug discontinuation.[7] Use of a hydrophilic beta-blocker may be better tolerated in patients who experience such AEs with a lipophilic agent.[3,7]

Several factors can delay the recognition of beta-blocker-induced hallucinations, leading to reports of patients experiencing these AEs for years before a drug-induced cause is identified[1,3,6-8]:

- Patients may be reluctant to report hallucinations due to the fear that it may be confused with mental illness or substance abuse.
- The onset of hallucinations can be variable, sometimes occurring after prolonged use, making it challenging to connect the symptoms to the medication.
- Healthcare providers and patients may not readily associate these symptoms with beta-blocker therapy or consider them to be related to existing medical or psychiatric conditions.

Table 1. Routes of administration and characteristics of systemic beta-blockers registered locally

Active ingredient	Routes of administration (PO = oral, IV = intravenous)	Drug characteristics
Acebutolol	PO	Hydrophilic, β1-selective[9]
Atenolol	PO	Hydrophilic, β1-selective[3]
Betaxolol	PO	Highly lipophilic, β1-selective[10]
Bisoprolol	PO	Moderately lipophilic, β1-selective[11]
Carvedilol	PO	Highly lipophilic, selective α1 and non-selective β-blocker[12]
Labetalol	PO, IV	Moderately lipophilic, selective α1 and non-selective β-blocker[13]
Metoprolol	PO	Moderately lipophilic, β1-selective[3]
Nebivolol	PO	Moderately lipophilic, β1-selective[11]
Propranolol	PO	Highly lipophilic, non-selective β-blocker[3]
Sotalol	PO	Hydrophilic, non-selective β-blocker[3]

Local situation

Ten systemic beta-blockers are registered in Singapore (Table 1) for a variety of cardiovascular and non-cardiovascular conditions including hypertension, coronary artery disease, cardiac arrhythmias, chronic heart failure, hyperthyroidism, and essential tremor.

As at 1 August 2025, HSA has received only two other reports of hallucinations suspected to be associated with atenolol, since its registration in Singapore in 1988. One patient experienced visual hallucinations while the type of hallucination was unspecified in the second case. Both patients were in their 70s (one female, one male) with symptoms occurring more than nine and 12 months after starting atenolol respectively. Both patients did not have any other neurological or psychiatric conditions. One patient recovered after atenolol was stopped whereas the outcome was not reported for the other.

Other neuropsychiatric AE reports received with beta-blockers include 15 reports of sleep disturbances (insomnia, vivid dreams and nightmares). These were mostly with atenolol (n=7), followed by bisoprolol (n=4), propranolol (n=2), atenolol and metoprolol (n=1), and atenolol and bisoprolol (n=1). Three cases of depression were reported (atenolol (n=2), propranolol (n=1)). Isolated reports were received for memory loss and psychosis (in a patient with a background of depression) with atenolol, as well as individual reports of confusion, anxiety and restlessness with propranolol. Reports of lethargy, drowsiness, tiredness and giddiness were also received.

Conclusion

Beta-blocker-induced hallucinations, though rare, can significantly impact patients' quality of life. Healthcare professionals are encouraged to maintain a high index of suspicion for this AE, particularly in patients taking lipophilic beta-blockers who report hallucinations. Regular medication reviews, together with patient education and active questioning about neuropsychiatric symptoms, may help identify such AEs earlier.

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