

TITLE: Pharmacist-initiated management of a suspected case of risperidone-induced Neuroleptic Malignant Syndrome in an aged-care resident. The role of Residential Medication Management Reviews in medication safety.

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ABSTRACT:

A 70-year-old female aged-care resident was referred by her general practitioner for a residential medication management review after nurses reported difficulties with swallowing, episodes of hyperthermia, elevated blood pressure and tachycardia. These symptoms were accompanied by increasing confusion and drowsiness. Risperidone had recently been prescribed to treat behavioural and psychological symptoms of dementia. This case-study describes the pharmacist-initiated management of the symptoms through a national medication review program. It demonstrates the valuable role collaborative medication reviews play in managing adverse drug events in aged-care.

INTRODUCTION:

Neuroleptic malignant syndrome or NMS is a rare and potentially fatal recognised adverse drug effect associated with the use of typical and atypical antipsychotic medication (1-3). NMS is an idiosyncratic reaction characterised by a set of symptoms including hyperthermia, muscle rigidity, altered mental status and autonomic instability (1-3). NMS often occurs within months after the initiation of neuroleptic treatment, or after dose increases (3). Associated risk factors include exposure to multiple antipsychotics, dehydration and multiple co-morbidities (3). Once the syndrome begins, it usually evolves over 24-72 hours. No laboratory test is diagnostic for NMS. Laboratory studies are used to assess severity and complications or rule out other diagnostic possibilities (3).

The estimated incidence of NMS ranges from 0.02% to 0.16% depending on the source of information used (3). The most prevalent complications reported are rhabdomyolysis and acute kidney injury (1). Mortality is reported to range from 3.3 to 27.7% with a decreasing trend in the past decade which may be attributable to improved recognition and clinical management of the syndrome (1). Clinical management is mainly supportive and includes withdrawal of the offending medication, cooling the

patient, correcting fluid and electrolyte imbalances and management of blood pressure (e.g. calcium channel blockers) (3). In most cases, symptoms will resolve in 1-2 weeks (4).

Antipsychotics are widely used 'off' and on-label for the treatment of behavioural and psychological symptoms of dementia (BPSD) (5, 6). In Australia risperidone is approved for the short-term management of BPSD in Alzheimer's disease (7). Over 50% of Australian aged-care residents have a diagnosis of dementia with the prevalence of use of antipsychotics estimated to be 22% (6, 8).

In Australia, aged-care residents are eligible for a federally funded residential medication management review (RMMR) every two years or when there is a clinical need (9). A general practitioner (GP) must initiate the referral and reviewing pharmacists are required to be accredited which involves training and assessment with annual accreditation requirements (10). Upon referral, the accredited pharmacist visits the aged care resident in their facility and takes a medical history including all medications (regular and 'as required' (prn or pro re nata)), clinical investigations, observations and relevant progress notes. In addition, the pharmacist communicates with relevant staff when appropriate. The pharmacist prepares a report and submits this to the referring GP which includes recommendations for starting, stopping or changing medications to improve the clinical care and quality of life of the resident (11). RMMRs have been shown to decrease medication burden in aged care residents (12). For example, a retrospective analysis of 500 RMMR reports showed a statistically significant reduction in exposure to medications included in the Drug Burden Index (DBI) (13). High DBI scores have been associated with a decline in physical and cognitive functioning in the older population (13).

The following case study describes the results of an RMMR after nurses noted changes in a resident's clinical status following initiation of risperidone to control BPSD. Given the high prevalence of dementia in Australian aged care and the frequent use of antipsychotics in this population, this case

presents a timely reminder of a rare but serious adverse drug reaction. It also highlights the significant clinical input accredited pharmacists can contribute to the collaborative management of aged care residents.

Consent was obtained for publication of this study.

CASE PRESENTATION:

A 70-year-old female resident was referred by her regular GP for an earlier than routine RMMR due to increased difficulty in swallowing and general clinical decline. Her medical history included advanced dementia, depression, hypertension and gastro-oesophageal reflux disease (GORD). The resident had no known allergies. Her regular and 'as required' medications are listed in Table 1.

Risperidone was the most recent addition to her medication profile, initiated ten days prior to the RMMR due to aggressive behaviour associated with dementia (BPSD). Eight doses of risperidone were administered over four days immediately prior to symptoms emerging.

The reviewing pharmacist noted the temporal relationship between risperidone commencement and the clinical deterioration of the resident. The resident was unable to take her oral medications due to difficulty with swallowing. In addition, carers had noted elevated blood pressure, episodes of hyperthermia, tachycardia and increasing drowsiness and confusion. Table 2 below shows the vital signs recorded during the clinical episode.

After reviewing the resident's medications and medical notes in addition to consultation with facility staff, the pharmacist made a preliminary diagnosis of NMS due to risperidone and contacted the GP immediately for further instructions.

Differential diagnoses in this case included (1) respiratory infection due to oropharyngeal dystonia and aspiration which could present with fever, autonomic instability and increased confusion (2) other infection (e.g. urinary tract infection) and (3) pain.

Outcome and follow-up:

The GP agreed that NMS, secondary to risperidone, was a possible reason for the clinical deterioration of the resident. The GP attended the resident and checked vital signs and ordered urine and electrolyte screening. Differential diagnoses were discounted after clinical review with a 'watch and wait' approach.

The GP ceased both the risperidone and regular oxazepam (to reduce medication burden). Recommendations to support the resident included cooling of the resident (tepid sponge baths), volume replacement (preferably oral), antipyretics and monitoring of electrolytes. Prior to and over the clinical course no doses of oxazepam or metoclopramide were administered to the patient (per medication chart review).

The GP also ordered palliative care in-case of further deterioration over the week end. Palliative care included morphine 2.5-5mg every four hours (subcutaneously) for pain, midazolam 1-2mg every four hours (subcutaneously) for agitation and soluble paracetamol 1g three times daily (oral) for pain and fever.

After the risperidone was ceased, the resident was able to maintain normal fluid and electrolyte balance through oral intake and her temperature returned to normal. No other supportive interventions were required. Palliative care interventions were also not required. The monthly holistic report written 25 days after cessation of risperidone, stated that the resident had slowly returned to her pre-morbid state since ceasing the risperidone (all other medications remained stable). The nurse

in charge of the resident's section confirmed with the reviewing pharmacist that the resident had starting to eat normally with no episodes of refusal of medication or swallowing difficulties. The resident had become more mobile since ceasing the risperidone.

DISCUSSION:

This case study has shown that a collaborative relationship fostered through a national RMMR program has identified and managed a potentially life-threatening adverse drug reaction. Another positive outcome of this study is the timely and successful management of the resident's symptoms within the aged care environment without the need for transfer to hospital. For aged care residents, transfer to an acute health care setting has been associated with significant morbidity such as increased delirium (14). Most importantly, the resident returned to base-line functioning without re-emergence of BPSD.

The clinical evidence presented in this case study suggests that risperidone was the cause of the resident's clinical decline. The probability of causation was assessed according to the Naranjo criteria (15). The Naranjo scale is a standardised and validated scale for assessment of causality of all types of suspected drug-induced reactions including those occurring in clinical trials. A Naranjo score of 7 was generated when using a conservative approach to the known clinical interventions and outcomes of this case-study (see appendix A). This score translates into risperidone being a 'probable' cause of the neuroleptic malignant symptoms experienced by the resident (16). However, we cannot claim a 'definite' causation due to lack of sufficient and timely clinical observations.

This case study highlights limitations of the current RMMR program. The Australian RMMR program was introduced in 2001 to address known medication-related issues in residential aged care including managing adverse drug events (12). The program has taken several forms since inception and currently provides federal government funding for a review biennially which includes a report to the

resident's GP. More frequent reviews may be undertaken when there is a clinical need, however this is up to the discretion of the GP (9). Therefore, the RMMR program is limited with respect to ongoing clinical pharmacist support. There is currently no pathway or remuneration for pharmacists to have a continuous clinical relationship with residents and this limits the opportunity to follow-up recommendations made in the report to the GP. Knowledge regarding the acceptance and impact of recommendations on a resident's health outcomes is scarce. Small retrospective studies have shown high GP acceptance rates of pharmacist's recommendations made in RMMR reports, however there are no studies demonstrating the impact these recommendations have on resident health outcomes (12).

The success of the RMMR program relies on strong interprofessional relationships between pharmacists and general practitioners (12). Due to the service delivery restrictions in the current RMMR program, maintaining strong interprofessional relationships is challenging. In this case study, due to the dedication of the pharmacist, GP and nurses involved, communication was ongoing to ensure the best outcome for the resident, regardless of remuneration restrictions.

Creating a pathway within the current model to support clinical pharmacists to establish continuous collaborative relationships with residents and their health care providers may be an avenue for managing adverse drug events in this vulnerable population. As demonstrated in this case study, potential benefits include improvement of resident health outcomes and avoidance of admission to hospital.

Whilst case studies are ranked low in terms of scientific evidence (level four on the National Health and Medical Research Council research hierarchy), they can provide signals for drug safety and address evidence-practice gaps (17). This case-study describes the successful management of a known but rare

adverse drug reaction in the aged care setting. In addition, it addresses an evidence-practice gap by demonstrating the significant impact an RMMR can have on improving health outcomes.

CONCLUSION: This case study demonstrates the significant impact collaborative medication reviews can have on resident health outcomes. Future development of the national medication review program should include pathways for ongoing clinical pharmacist support to residents and their health care providers.

REFERENCES:

1. Modi S, Dharaiya D, Schulz L, Panayiotis V. Neuroleptic malignant syndrome: complications, outcomes and mortality. *Neurocritical care*. 2016;24(1):97-103.
2. Pileggi DJ, Cook AM. Neuroleptic malignant syndrome: focus on treatment and rechallenge. *Annals of pharmacotherapy*. 2016;50(11):973-81.
3. Tse L, Barr AM, Scarapicchia V, Vila-Rodriguez F. Neuroleptic malignant syndrome: a review from a clinically oriented perspective. *Current neuropharmacology*. 2015;13(3):395-406.
4. Reulbach U, Dütsch C, Biermann T, Sperling W, Thuerauf N, Kornhuber J, et al. Managing an effective treatment for neuroleptic malignant syndrome. *Critical Care*. 2007;11(1):R4-R.
5. Antai-Otong D. Pharmacological management of psychosis in Alzheimer's disease: clinical challenges associated with second-generation antipsychotic medications. *Perspectives in psychiatric care*. 2008;44(2):120-3.
6. Westbury J, Gee P, Ling T, Kitsos A, Peterson G. More action needed: psychotropic prescribing in Australian residential aged care. *Australian and New Zealand Journal of Psychiatry* [Internet]. 2018. Available from: journals.sagepub.com/doi/full/10.1177/0004867418758919.
7. Australian Government. Department of Health. The Pharmaceutical Benefits Scheme. [26/3/2018]. Available from: www.pbs.gov.au/medicine/item/3169T-8789N
8. Australian Institute of Health and Welfare 2011. Dementia among aged care residents: first information from the Aged Care Funding Instrument. Aged care statistics series no. 32 Cat. no. AGE 63. Canberra: AIHW.
9. Australian Association of Consultant Pharmacy (AACP). Fact sheet No. 2. The facts on remuneration for medicines reviews. 2006 [Available from: <https://aacp.com.au/wp-content/uploads/2016/02/No-2-Remuneration-for-MMRs-July-2016.pdf>].
10. Australian Association of Consultant Pharmacy (AACP). [28/3/2018]. Available from: <https://aacp.com.au>.
11. Australian Association of Consultant Pharmacy (AACP). What are MMRs 2017 [Available from: <https://aacp.com.au/what-are-mmrs/>].
12. Chen TF. Pharmacist-led home medicines review and residential medication management review: The Australian model. *Drugs and Aging*. 2016;33(3):199-204.
13. Nishtala PS, Hilmer SN, McLachlan AJ, Hannan PJ, Chen TF. Impact of residential medication management reviews on Drug Burden Index in aged care homes. *Drugs and Aging*. 2009;26(8):677-86.
14. Dwyer R, Gabbe B, Stoelwinder J, Lowthian J. A systematic review of outcomes following emergency transfer to hospital for residents of aged care. *Age and Ageing*. 2014;43(6):759-66.

15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics*. 1981;30(2):239-45.
16. National Institutes of Health. LiverTox: Clinical and research information on drug-induced liver injury. Bethesda, MD.: U.S. National Library of Medicine; 2017 [Available from: <https://livertox.nih.gov/Narajo.html>].
17. Frawley J, Finney-Brown T. Writing for publication: case studies. *Australian Journal of Herbal Medicine*. 2013;25(3):1-3.

TABLES:

Table 1: The resident's regular and 'as required' (prn) medications and associated indications.

Medication, dose and frequency	Indication
Regular medications (oral)	
Hyoscine butylbromide 20mg twice daily	Abdominal cramps
Docusate and senna 50/8mg every second day	Constipation
Risperidone 0.5mg twice daily	Behavioural and Psychiatric Symptoms of Dementia (BPSD)
Pantoprazole 40mg daily	Gastro oesophageal reflux disease (GORD)
Paracetamol (soluble) 1g three times daily	Pain (musculoskeletal and abdominal)
Perindopril 5mg daily	Hypertension
Oxazepam 15mg daily	Anxiety
Memantine 10mg daily	Alzheimer's Disease
As required (prn) medications (oral)	
Hyoscine butylbromide 10 to 20mg twice daily	Abdominal cramps
Metoclopramide 10mg three times daily (oral or IV)	Nausea and vomiting
Oxazepam 7.5mg twice daily	Agitation and restlessness
Loperamide 2mg twice daily	Episodes of diarrhoea
Docusate and senna 100/16mg twice daily	Episodes of constipation

Table 2: Vital sign observations in the week prior to RMMR.

Observation	Day 1	Day 3	Day 7
Blood pressure (mmHg)	210/95	132/86	166/96
Heart Rate (bpm)	110	96	---
Temperature (°C)	---	38	---

Appendix A

Naranjo Adverse Drug Reaction Probability Scale

Assessment of the probability that risperidone was the cause of the neuroleptic malignant syndrome symptoms in this case study.

Question	Yes	No	Do not know or not done	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued, or a specific agonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2 or Not appropriate	-1	0	2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	*0-2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total Score:				7-9

*Conservative score = 0. Investigations into other causes were undertaken, however not all results were available.

Score= probable to definite causation