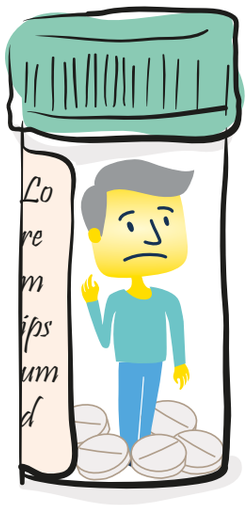
September 2019

circuit

clinical initiatives, research and current updates in treatment



Reducing Opioid Harm

Jasneet Biri, Epic Pharmacy Brisbane Private Hospital

Opioid use is on the rise in Australia, with opioid prescriptions increasing by 24% between 2010-2011 and 2014-15.[1] Pharmaceutical opioids are commonly indicated in the treatment of either acute or chronic pain and include medications such as codeine, fentanyl, morphine, oxycodone and tapentadol.[2] Opioids provide analgesia by dampening and modifying the central nervous system, altering the messages transmitted between the brain and body.[3]

Opioids are considered "high-risk" medicines due to their extensive side effect profile, which includes sedation and potentially fatal respiratory depression. If used in combination with alcohol and/or other sedatives, the risk and potential severity of these adverse effects is increased.[1] Other common side effects include constipation, nausea, vomiting, and dizziness. Long-term opioid use can impair cognitive function and precipitate dependency and addiction.[1]

Opioid dependence is recognised as a mental and behavioural disorder that stems from repeated and prolonged usage.[1] It may present as a strong desire for the medication, difficulty in controlling its use despite harmful repercussions, increased tolerance, withdrawals or prioritising the drug over other activities and obligations.[1]

In Australia, pharmaceutical opioid induced side effects are responsible for more deaths and hospitalisations than illegal opioids (such as heroin) resulting in almost 150 hospitalisations and 14 emergency department presentations daily.[4] Over the past 10 years, the incidence of opioid induced death has almost doubled, increasing from 3.8 to 6.6 deaths per 100,000 Australians between 2007 and 2016.[8] Opioids are now responsible for more drug-related deaths than any other drug category, with an average of 3 people dying from opioids every day.[4]

Opioids initially prescribed in a hospital setting, often following surgery, have been identified as a key risk for ongoing use and dependence.[1] Studies have found opioid harm largely originates from iatrogenic dependence, meaning it may inadvertently develop after treatment for a genuine condition.[1] A systematic review found one-third of adults receiving long-term opioid therapy were initially prescribed an opioid by their surgeon.[5] Following surgery, many patients have the unrealistic expectation that taking prescribed medication should allow them to be pain free, whereas a more reasonable aim is for patients to experience a tolerable or functional pain level.[6] This unrealistic expectation often results in patients taking more opioids than recommended, increasing the risk of toxicity and dependence.[5]

The dose and quantity of opioids prescribed on discharge have both been identified as risk factors for long term use, with each additional week of opioid supply being associated with a 44% increase in the rate of misuse by the patient.[7] In addition to the individual risk, the practice of supplying unnecessary quantities of opioids can also result in opioids being inappropriately stored in the home, shared, or diverted for illicit use.[8] Sustained release opioids have a greater risk of harm compared to immediate release (24.5% versus 3.5%).[9]

Australia's peak body for hospital pharmacy, the Society of Hospital Pharmacists of Australia (SHPA), surveyed pharmacies at 135 Australian public and private hospitals in 2018 to gain insight on the role and activities of hospital pharmacists in the care of patients receiving opioids in hospital following surgery.[1]

The survey highlighted many key issues associated with both the prescribing and dispensing of opioids. More than 70% of patients were prescribed and supplied opioids for discharge "just in case" even though their pain had not required opioid analgesia in the 48 hours prior.[1] See Figure 1

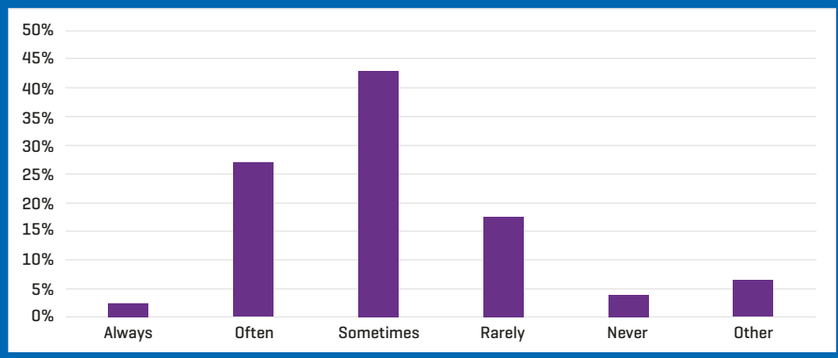


Figure -1: If opioid analgesics were not administered in the 48 hours prior to discharge, are opioid analgesic supplied on discharge "just in case" a patient might need them?

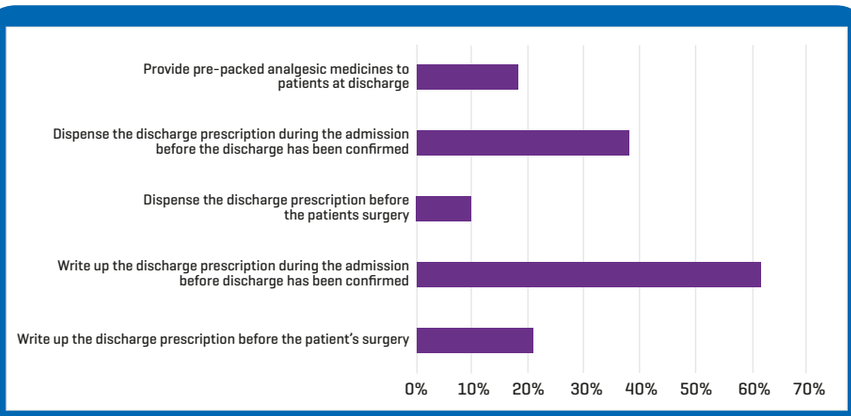


Figure 2: To improve patient flow and bed availability, does your hospital site undertake any of the following?

Also identified in the survey was that in an attempt to increase overall efficiency, a patient's discharge prescriptions are often prescribed and dispensed prior to the discharge being confirmed.[1] In addition, 18% of respondents stated pre-packed analgesics were provided to patients at discharge.[1] See Figure 2.

Based on these survey results and a subsequent forum of pharmacist experts from across the country, the SHPA identified numerous potential strategies to minimise opioid-related harm among patients, published in their November 2018 landmark paper, "Reducing Opioid Harm".[1] Painaustralia (the peak body representing health, medical, research and consumer organisations) has also since published the National Strategic Action Plan for Pain Management. Whilst a more broadly scoped consumer-centred publication for all healthcare settings, it reiterates some of the same recommendations.[6]

Recommendations to reduce opioid harm include: [1,6]

Multidisciplinary team work

- Implement a collaborative approach between the patient, medical, nursing, pharmacy, and allied health staff for the management of post-surgical pain
- Ensure a patient-centred interdisciplinary approach, whereby the health and well-being of the whole individual patient is considered

Health practitioner education

- Establish systems and evidence-based guidelines for the prescribing and supply of post-surgical analgesics
- Improve the understanding and implementation of both pharmacological and non-pharmacological pain management interventions

Engaging and empowering patients

- Provide patients with education, counselling and a clear plan of opioid use on discharge, thereby eliminating the guesswork associated with administration
- Challenge attitudes towards pain and its management, changing the expectation that medication should allow patients to be "pain-free" following surgery, to experiencing "tolerable pain" or medications providing "functional analgesia"
- Improve patients' health literacy: Replace the term "pain killers" with "medicines for reducing pain" to assist in managing patient expectations
- Advise on correct medicine disposal methods to reduce the risk of diversion and/or inappropriate use or storage
- Ensure the availability of user-friendly information and support programs for all patients, carers and families

Managing medication supply

- Encourage the adoption of digital solutions across all states and territories which enable real-time prescription monitoring systems, whereby data can be used to guide prescribing and dispensing behaviour
- Support the prescribing and supply of the smallest quantity of opioids appropriate for the patient, including the supply of partial packs when required
- Encourage the pharmaceutical companies to produce a greater variety of pack sizes for opioids i.e. packs of 5, 10 or 20. Note: a pack of oxycodone 5mg x 10 immediate-release capsules labelled as "Short Course" will be marketed from August for surgical analgesia discharge supplies
- Advocate to government and regulatory authorities for increased information on opioid manufacturers packs related to the risk of long-term use and overdose

Supporting opioid stewardship

- Encourage the establishment and implementation of an opioid stewardship program in all healthcare facilities
- Advocate for the inclusion of opioid stewardship in appropriate healthcare standards, namely the National Safety and Quality Health Service Standard 4: Medication Safety
- Support the creation of a National Opioid Utilisation Surveillance Program for healthcare facilities to monitor opioid usage and enable benchmarking between similar sites, i.e. similar to the existing National Antimicrobial Utilisation Surveillance Program (NAUSP)
- Review healthcare facilities medication formulary and governance systems to minimise the risk or diversion and misuse of opioids
- Evaluate the quality use of opioid medicines and benchmark across the health system

Community education

- Implement national advertising campaigns on medicines for reducing pain and disseminate the "Choosing Wisely Australia" principles to prompt conversations with patients on opioid related harm
- Support the development of patient-centred tools for self-assessment and pain management to reset community expectations of pain and use of medicines for reducing pain

Supporting transitions of care

- Ensure medication reconciliation, counselling and transition of care management for all surgical patients. Prioritise medication reconciliation for long term opioid users, as evidence surrounding chronic use is lacking
- Harness technology to expand access and communication to multiple health services, including primary care services and pain management specialists

Research

- Provide national support for pain research through a network of pain research specialists
- Identify gaps in knowledge and practice
- Translate and disseminate research into practice, policy and guidelines
- Communicate research findings to the community

Regulatory Interventions [11]

In late August, the Therapeutic Goods Administration announced further regulatory reforms to support appropriate opioid prescribing, supply, and consumer education: https://www.tga.gov.au/alert/prescription-opioids

With recent statistics highlighting the extent of patient harm caused by opioid misuse, the above recommendations should be considered (and regulatory reforms welcomed) to minimise the potential for harm.

References are available on request.

Revisiting Penicillin Allergy

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Introduction

Approximately 10% of the Australian population report an allergy to penicillin, making it the most commonly reported medication allergy.[1-3] A drug allergy is a hypersensitivity reaction mediated by a patient's immunologic response to a drug.[1] Although patients frequently report a penicillin allergy, very few have a true allergy and many can still safely use penicillin.[2,3]

Poorly documented or false reporting of a penicillin allergy on patient records is a significant health care issue and is associated with the following risks:[1]

- Inferior patient clinical outcomes (i.e. treatment failure, increased readmission, mortality)
- Increased use of more powerful and restricted antibiotics
- Increased risk of adverse events (i.e. clostridium difficile)
- Increased risk of antibiotic resistance
- Increased cost (i.e. increased length of hospital stay, works days absent)

It is important to remember that penicillins are still among the leading causes of drug-induced anaphylaxis and a true penicillin allergy can result in a fatal reaction.[1,2,4]

Therefore, a systematic approach to improve the detail and accuracy of penicillin allergy labelling is required.

1. Clinical history

It is important to gather detailed documentation of a patient's adverse reaction to ensure penicillin treatment is not avoided unnecessarily.[2] Hypersensitivity is usually diagnosed on the basis of clinical history. Thus the nature and timing of the reaction, concurrent illnesses, concurrent drugs, the history of other antibiotics used and the outcome are important details to source from the patient or clinician (see Table 1).[1,3,7]

2. Defining the allergy

Adverse drug reactions are defined as any undesirable reaction to medication and can be both allergic and non-allergic reactions.[2]

Examples of non-allergic reactions to penicillins are non-immune mediated adverse drug reactions consistent with a known drug side effect (i.e. gastrointestinal upset).[2]

Non-allergic reactions do not indicate hypersensitivity and do not specify the need to avoid penicillins if they are required.[1,2]

A drug allergy or hypersensitivity can be broadly classified as either an immediate or delayed response.[1-3]

Immediate allergic reactions occur rapidly after drug administration, typically within 1 hour, but can be longer if the drug is administered with food, and are mostly immunoglobulin (Ig) E mediated. Some clinical manifestations include urticaria, angioedema, bronchospasm or anaphylaxis.[2-3]

Patients with a clear history of an IgE mediated reaction should not be administered penicillin again without appropriate precautions (i.e. de-sensitisation).[1-5]

Delayed hypersensitivity reactions occur later, typically more than 1 hour after drug administration, and are most commonly caused by T-cell-mediated reactions.[2,3] Examples of delayed T cell-mediated reactions can include a benign reaction such as maculopapular exanthema (MPE) or a life threatening reaction, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), severe cutaneous adverse reactions (SCAR), erythema multiforme (EM) and toxic epidermal necrolysis (TEN).[1,3,7]

Patients with a life-threatening T-cell response should not receive penicillins again under any circumstances and are not applicable for de-sensitisation.[1-5]

3. Timing

It is also important to establish the time elapsed since the patient last experienced a penicillin hypersensitivity reaction. Penicillin-specific IgE antibodies decrease over time, consequently patients with recent reactions are more likely to be allergic than patients with distant reactions.[2,3] It is reported that approximately 80% of people with IgE-mediated penicillin allergy lose the sensitivity reaction after approximately 10 years.[3,4]

4. Determining the risk of cross reactivity

Penicillins, cephalosporins, carbapenems and monobactams all belong to the beta-lactam antibiotic class.[5] Prevalence of cross-reactivity between beta-lactam antibiotics can vary according to similarity of drug structure and is mainly caused by the R-chain side groups, not the beta lactam ring, as was previously thought.[1, 5]

Historically, cephalosporin cross-reactivity was thought to occur in approximately 10% of patients who were allergic to penicillin. However, recent studies have reported much lower rates (1%-2.5%) and cross-reactivity may largely be limited to cephalosporins with R-chain side groups similar to penicillin or amoxicillin.[1,5,8] Beta-lactam cross-reactivity is more likely in patients with amoxicillin or ampicillin allergy who receive cefalexin or cefaclor, due to their similar R1 side-chains.[5] Cefazolin has no common side-chains with other beta-lactams so is often tolerated in penicillin or cephalosporin allergy.[5]

Cross-reactivity between penicillins and carbapenems is low and is only reported in approximately 1% of cases.[1,5] There has been no demonstrated cross-reactivity between penicillin and monobactams.[1,5]

Cross-reactivity should not be used to guide treatment in patients with delayed severe penicillin hypersensitivity.[5]

Table 1 - Questions to establish a penicillin allergy

Clinical history analysis	
1	How many years ago did the reaction occur?
2	What was the antibiotic that caused the reaction? (i.e. amoxicillin or cephalexin not penicillin or cephalosporin)
3	Do you remember details of the reaction?
4	If a rash was present, can you describe the rash?
5	How long after taking the antibiotic did the reaction occur?
6	Did you have any concurrent illness?
7	Were you taking any other medicines?
8	How was the reaction managed? Did it require treatment or hospitilisation?
9	What antibiotics have you used and tolerated since?

Conclusion

Hypersensitivity to penicillins are the most commonly reported drug allergy.[1-3] Many of these allergies are not true allergies and the patient can safely use the medicine.[1-3] The high prevalence of penicillin allergy reporting can result in poorer patient clinical outcomes, increased risk of adverse events, increased risk of antibiotic resistance and increased cost.[1] Obtaining a comprehensive patient clinical history, classifying the type of penicillin reaction and determining the risk of antibiotic cross-reactivity can assist in accurate patient penicillin allergy labelling, influence treatment selection and reduce the use of more restricted antibiotic resources.

References are available on request.

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Venetoclax (Venclexta)
film-coated tablets 10mg, 50mg, 100mg

Justine Forbes, Epic Pharmacy Hollywood

Venetoclax is a new oral anti-cancer drug used in the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL), either in combination with rituximab or used alone. It can also be used for acute myeloid leukemia (AML) and lymphoma. Venetoclax is a novel B-cell lymphoma-2 (BCL2) protein inhibitor. BCL2 is a protein that prevents cell apoptosis, which helps tumour cells to survive. The drug acts as a pharmacological mimic of the protein that stimulates cell apoptosis, thus causing destruction of cancer cells which highly express BCL2.[1,2]

The most important side effect of venetoclax to note is tumour lysis syndrome (TLS). This is a set of side effects that result from a large number of cancer cells being destroyed at the same time. When destroyed, the cells release intracellular ions, proteins, nucleic acids and cell metabolites which can damage surrounding blood vessels and body tissue. Importantly, TLS can cause hyperuricaemia, hypercalcaemia, hyperkalaemia and hyperphosphataemia, which can lead to renal failure, cardiac arrhythmias, seizures and even death.[2,3] Reduced renal function further increases the risk of TLS. Due to the high risk of TLS, it is recommended that patients are monitored in hospital both in their first week of treatment, and at each dose increase. Venetoclax dosing usually starts at 20mg daily, and is titrated slowly over five weeks to the usual dosage of 400mg once daily. Patients should also be given adequate hydration during treatment and commence TLS prophylaxis with allopurinol two to three days prior to initiation of treatment.[3] Dose interruptions and modifications may need to be made if the patient is exhibiting any unwanted side effects or toxicities. In these instances, the drug can be withheld for a day or more, and restarted at a lower dose. Venetoclax can also cause neutropenia and thrombocytopenia, thus full blood counts must also be routinely monitored during treatment.[1]

Venetoclax should be swallowed whole, with a meal and a glass of water, at approximately the same time each day.[1] Grapefruit and its juice should be avoided while on this medication.[4] Venetoclax is classified as a hazardous medication and appropriate handling, administration and storage precautions should be adhered to. The patient should be counselled to self-monitor for signs of infection due to neutropenia (e.g. flu like symptoms) and to seek medical treatment if these occur.[3,4]

References are available on request.

next edition:

Our next edition will support World Antibiotic Awareness Week (AAW) which runs 18-24 November. Included in this edition will be a review of the latest Antimicrobial Use and Resistance in Australia (AURA) report. The AURA surveillance system was developed by the Australian Commission on Safety and Quality in Health Care (ACSQH) to support prevention and containment of antimicrobial resistance (AMR). AURA provides a comprehensive and integrated picture of patterns and trends of AMR and antimicrobial use across Australia.

coming soon:
the next edition of the Medication Safety Bulletin

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