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CONTENTS

ARTICLE

Neuropathic pain: current definition and review of drug treatment

Bridin P Murnion
Senior clinical lecturer
University of Sydney
Senior staff specialist
Drug Health Services
Concord Repatriation General Hospital
Sydney

Keywords
anticonvulsants, antidepressants, cannabinoids, neuropathic pain, opioids

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SUMMARY

Neuropathic pain is relatively common and often poorly treated.

Management options include tricyclic antidepressants or serotonin and noradrenaline reuptake inhibitors in the first instance, followed by pregabalin or gabapentin.

Tramadol or topical lidocaine (lignocaine) could be considered as second line. Stronger opioids have been relegated to third line.

It is important to remember that opioids and gabapentinoids have abuse potential.

Fibromyalgia and chronic low back pain without radiculopathy do not meet the current criteria for the definition of neuropathic pain.

Introduction

Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7–8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain.[1]

The management of neuropathic pain can be challenging and, as with all pain, should be approached with a biopsychosocial framework. There are several options for drug treatment as part of an overall approach to improve patients' quality of life and function.[2]

International guidelines have clarified the definition of neuropathic pain and updated their recommendations for drug treatment based on evidence from a systematic review and meta-analysis.[3,4] Being aware of these changes is important in the clinical assessment and treatment.

A new definition for neuropathic pain

Neuropathic pain is now defined by the International Association for the Study of Pain (IASP) as 'pain caused by a lesion or disease of the somatosensory nervous system'.[3] This replaces the older definition of 'pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system'.

The definition was reviewed and updated because the term dysfunction in the old definition was thought to be over-inclusive and did not reflect the pathophysiology. Additionally, neuropathic pain is not one disease entity but a number of diseases or lesions with a cluster of symptoms and signs, where understanding of pathophysiology is evolving.[5]

Proponents of the change believe it has greater scientific rigour. It removes confusion around pain arising as a result of disease within the nervous system but outside the somatosensory system, for example pain from muscle spasticity. It now excludes syndromes where pathophysiology is unclear, such as fibromyalgia or complex regional pain syndrome, which is controversial and has been perceived by some to be overly restrictive.[6]

Primary disease management

The primary disease management of neuropathic pain needs to consider the individual as a whole. For instance, in patients with diabetic neuropathy, erratic glycaemic control worsens symptoms and improving glycaemic control may reduce progression of neuropathy. However, there is increased mortality with intensive insulin regimens in patients with established diabetic neuropathy compared to patients without neuropathy.[7] HIV-associated neuropathy presents an even more complex picture – starting antiretrovirals may initially improve symptoms although nerve damage may progress. Some antiretrovirals can cause neuropathy, and neurotoxicity may be a feature of concomitant medicines such as isoniazid for tuberculosis.[8,9]

Drugs for neuropathic pain

The IASP's Neuropathic Pain Special Interest Group (NeuPSIG) has recently undertaken a systematic review of medicines for neuropathic pain (Table).[4] Fibromyalgia, atypical facial pain, complex regional pain syndrome and chronic low back pain without radiculopathy were not included in the review as they do not meet the current criteria for the definition of neuropathic pain.

The review included tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs, opioids, topical lidocaine (lignocaine), capsaicin high-concentration patches and oromucosal cannabinoids. A number of overarching themes were identified:

- most studies were conducted in diabetic neuropathy or postherpetic neuralgia
- publication bias accounted for approximately 10% of the treatment effect
- placebo effect was large
- drug effects were modest[4]
- data did not identify that one particular drug or drug class was superior in any particular neuropathic pain syndrome
- the majority of studies were for 12 weeks or less
- data were limited to non-cancer pain in adults.

Antidepressants

Tricyclic antidepressants and SNRIs were effective in reducing pain. Amitriptyline was the most studied tricyclic antidepressant (daily doses 25–150 mg) and did not show a dose-response effect. Seven of nine studies with duloxetine 20–120 mg were positive, while two of four studies identified efficacy with venlafaxine 150–225 mg daily. The negative venlafaxine studies were at lower doses.

Antiepileptics

Most trials with pregabalin (18/25) showed improvement in neuropathic pain, and the effect was greater with larger doses. Pregabalin in HIV neuropathy was no better than placebo. However, the placebo was very effective. Gabapentin was also found to be effective, although no dose response was identified. The number needed to harm was 13.9 for pregabalin and 25.6 for gabapentin. Other antiepileptic drugs had minimal evidence of efficacy, and topiramate, carbamazepine and oxcarbazepine had a poor safety profile.

Tramadol, tapentadol and opioids

Tramadol consistently showed efficacy, while tapentadol had very limited supporting data. With morphine or oxycodone, 10 of 13 trials showed benefit, with no benefit in increasing the dose beyond 180 mg daily oral morphine equivalents.

Topical treatments

There were some limited data suggesting the efficacy of lidocaine (lignocaine) 5% patches, with good safety and tolerability. Although registered, this product is not available on the Pharmaceutical Benefits Scheme (PBS)[10] so may be prohibitively expensive for patients.

Table **Drug treatment for neuropathic pain – updated recommendations from the International Association for the Study of Pain**

Recommendation	Drugs
First-line	SNRI – duloxetine, venlafaxine
	Tricyclic antidepressants
	Gabapentin, pregabalin
Second-line	Capsaicin 8% patches
	Lidocaine (lignocaine) patches
	Tramadol
Third-line	Strong opioids

SNRI serotonin noradrenaline reuptake inhibitors
Adapted from reference 4

For postherpetic neuralgia and HIV neuropathy, a high-concentration (8%) capsaicin patch demonstrated efficacy over a low-dose (0.04%) patch. Unfortunately the high-dose patch is not available in Australia.

Oromucosal cannabinoids

The meta-analysis identified mostly negative data for a fixed-dose combination of cannabidiol and 9-tetrahydrocannabinol (nabiximols) in reducing pain in multiple sclerosis.[4] A statement by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists on medicinal cannabis identifies no role for the use of cannabinoids in neuropathic pain, but notes pain and spasticity related to multiple sclerosis may be an exception.[11]

Trigeminal neuralgia

Trigeminal neuralgia is the only condition in which a specific drug class has shown superior efficacy. Carbamazepine and oxcarbazepine are first line for pharmacological pain management.[12]

It is currently recommended that Asian people of non-Japanese origin are tested for the HLA-B*1502 allele as this confers an increased risk of cutaneous drug reactions with carbamazepine.[13]

Interventional modalities

Local nerve blocks, spinal or epidural medicines, and neuro-ablative, neuromodulatory and neurosurgical procedures are also used for neuropathic pain.[14]

Updated recommendations for treatment

As a result of the meta-analysis, NeuPSIG has updated its recommendations for the treatment of non-cancer associated neuropathic pain in adults. With the exception of trigeminal neuralgia, there were no data identifying that any particular drug was superior to another in any particular disease state.[4]

The guidelines recommend tricyclic antidepressants, gabapentin or pregabalin, and the SNRIs venlafaxine or duloxetine as first line.[4]

Second-line treatments include tramadol. Topical lidocaine (lignocaine) or high-concentration capsaicin may be considered for neuropathic pain when there is a presumed local generator.[4]

The consensus is that opioids can no longer be recommended as first-line treatment, and there is general agreement that they should only be considered as third line, with appropriate monitoring for safety and efficacy.[4] It is increasingly recognised that the harms of opioids, in particular addiction, cannot be adequately identified in short-term studies. Also, these short-term studies could not identify if any benefit persists or is lost as tolerance develops.

A pragmatic approach to drug therapy

Choose a tricyclic antidepressant or SNRI with consideration of the patient's comorbidities, potential drug interactions and adverse effects, and consider pregabalin or gabapentin next before tramadol. There is a paucity of guidance on duration of treatment. Again, a pragmatic approach may be to try a therapy for 12 weeks as this is the maximum duration of most of the trials. Monitor for efficacy (using multidimensional tools for pain intensity, quality of life and patient function) and safety, and stop if the treatment is not working.

The PBS listing for pregabalin in neuropathic pain is that 'the condition must be refractory to treatment with other drugs'. Cost of treatment is significant. In 2016–17, more than 3.5 million PBS scripts for pregabalin were issued at a cost of over $190 million.[15] Gabapentinoids have neurocognitive adverse effects, can cause weight gain and are associated with an increased risk of falls. They are anxiolytic, and there is emerging evidence of significant pregabalin abuse.[16]

Any consideration of psychotropic drugs including gabapentinoids or opioids (tramadol or stronger opioids) should involve:

- assessing the risk of abuse, including history of psychiatric, personality or substance use disorder
- ongoing monitoring for development of abuse
- multidimensional assessment of efficacy.

A plan to stop therapy should be discussed with the patient before treatment starts, and daily opioid doses should not exceed 60 mg oral morphine equivalents without specialist review.[17]

Conclusion

A well-conducted meta-analysis reviewing drug treatment of neuropathic pain provides clear recommendations. Tricyclic antidepressants and SNRIs should be trialled first. If they are ineffective, consider a trial of a gabapentinoid then tramadol. This should be accompanied by multidimensional assessment of efficacy, review for harms associated with treatment and a plan for stopping treatment if there is no benefit. <

Conflict of interest: none declared

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LETTERS

Letters to the Editor

Maintaining milk supply as the baby grows

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The article on drugs affecting milk supply during lactation states that babies drink 150 mL/kg/day.[1] This calculation is used for newborns and for formula-fed babies, but is not applicable to breastfed babies past the early days. Research from the Hartmann Human Lactation Research Group at the University of Western Australia showed that from one month until six months of age, babies drink on average 800 mL/day.[2] The amount varies only minimally with age and weight, contrary to previous belief, although the average intake from baby to baby can vary from 500 mL to 1350 mL/day. At six months when solid foods are normally introduced, this amount gradually reduces.

It is misleading to report that mothers in general need to produce 1350 mL/day, when this is at the very upper limit determined from the Hartmann study and a volume that would be consumed by very few babies.

Please could you correct this information? Fully referenced amounts are available on the Australian Breastfeeding Association website.[3]

Kerry Smith
Breastfeeding mother
Perth

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Thank you for the article on drugs affecting milk supply in lactation.[1] This area is of particular interest to me as a community pharmacist and a breastfeeding mother myself. I enjoyed the article and it was relevant to many of the situations that I come across in the community.

I did notice that some of the information about milk supply differs from the current Australian Breastfeeding Association guidelines. The article states that maintaining the milk supply may be problematic as the baby grows. An infant typically requires 150 mL/kg/day. So, to feed a 9 kg versus a 3 kg baby daily (1350 mL vs 450 mL) can be a physiological challenge for some women. While I have seen references to 150 mL/kg/day used, most conclude that milk intake of exclusively breastfed infants averages 750–800 mL/day, but can vary from less than 500 mL to more than 1000 mL/day.

My current understanding is that the volume of breastmilk consumed is typically consistent from one to six months of age.[2] I would also add that in my experience, it is extremely uncommon for mothers to successfully establish breastfeeding then be physiologically challenged to produce enough milk as their baby grows, if they have been advised to feed according to their baby's needs without supplementing with formula or solid food.

Is there a reference to support mothers being physiologically challenged as their babies get older?

Kylie Hulkes
Community pharmacist
Karratha, WA

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Treasure McGuire, the author of the article, comments:

Thank you to Kerry and Kylie for commenting on my article. The 150 mL/kg/day figure originated from a breastfeeding counselling training course by the World Health Organization.[1] It remains widely used in calculations for the amount of medication transferred from a breastfeeding mother to her infant. It is also often used to calculate the amount of expressed breast milk or infant formula infants require.

There is evidence suggesting that the intake for most (but not all) breastfed infants who are growing well is relatively constant from one to six months of age with a mean intake of approximately 800 mL, but with a wide range in milk volume.[2-4] However, limitations to the 2006 Hartmann study were that milk samples were collected over a single 24-hour

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period and total milk volumes were not stratified by infant age.[3] A more recent longitudinal study by Hartmann's group also found a wide range in milk volume (463–1370 mL), but with only six mothers in the 'milk production during exclusive breastfeeding' arm.[4] Further longitudinal research with larger participant numbers is needed in this area.

A 9 kg infant would be a large six-month-old and so was not the best example to use in any calculations. However, these figures are not essential for the main content of the article and were used to illustrate the point that some women have difficulty maintaining an adequate milk supply. Often this is due to suboptimal breastfeeding management, but for others there are physiological (including hormonal) or anatomical reasons why they have difficulty with their milk supply, especially as the infant grows. These women may benefit from the galactagogues that are discussed in the article.

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LETTERS

Adverse effects of herbs as galactogogues

Aust Prescr 2018;41:66
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In the article on drugs affecting milk supply during lactation, the author states that Shatavari (*Asparagus racemosus*) has possible teratogenicity so it should be avoided in pregnancy.[1]

Shatavari is an ingredient in most herbal teas which are recommended to be taken during pregnancy and breastfeeding.

Can the author give an explanation of why Shatavari is considered a teratogen when it is widely used in readily available teas?

Judith Gallagher
Retired pharmacist
Melbourne

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Treasure McGuire, the author of the article, comments:

For a drug to be considered teratogenic, it must demonstrate a dose-related disturbance on embryo or fetus development, producing an irreversible defect present at birth, with a temporal relationship to organ formation.

Shatavari contains steroidal saponins (shatavarins). In ayurvedic medicine, the root is considered a reproductive tonic, with adaptogenic and hormonal activity. Despite long traditional use, data on reproductive use in humans are limited. When Shatavari root was given orally in a therapeutic human equivalent dose (20 g/day) adjusted for body weight (30 mg/100 g/day) to rats, guinea pigs and rabbits, it produced oestrogenic effects on mammary glands and genital organs, and a competitive blockade of oxytocin-induced contractions.[1,2] In a randomised study of pregnant rats given Shatavari root 10 mg/100 g/day or a control treatment for 60 days, there was an increased resorption of fetuses, and pups showed teratogenic disorders, gross malformations (e.g. swelling in legs) and intrauterine growth retardation. Live pups showed a significant decrease in body weight and developmental delay. The investigators concluded that the herb be used cautiously in pregnancy, as its exposure during that period may cause damage to the offspring.[3]

Herbal teas often contain a mix of herbs and doses tend to be much lower than amounts used therapeutically. However, until there is clearer evidence of doses that are safe in pregnant women, it seems prudent to avoid Shatavari in the first trimester (during organogenesis). This does not preclude use in later trimesters or during breastfeeding.

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ARTICLE

Common eye infections

SUMMARY

Not all red eyes are due to infections. Not all eye infections respond to antibiotic eye drops.

Conjunctivitis is the most common eye infection. Most cases are viral and do not require antibiotic eye drops.

Infectious keratitis is a cause of blindness. It is an emergency that requires specialist treatment.

Infectious endophthalmitis is an emergency that has become more frequent with the use of intravitreal injections. Intravitreal antibiotics are needed to try and prevent visual loss.

Stephanie Watson
Professor

Maria Cabrera-Aguas
Clinical research officer

Pauline Khoo
Clinical research officer

Save Sight Institute
University of Sydney

Keywords
conjunctivitis, endophthalmitis, eye infection, keratitis

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Introduction

Eye infections are a common presenting problem in primary care. 'Red eye', 'conjunctivitis' and 'corneal ulcer/keratitis' were among the top five problems most commonly referred to two ophthalmology departments in Brisbane.[1]

To ensure a good visual outcome for the patient, the practitioner should make a prompt diagnosis and start appropriate treatment. Conjunctivitis typically does not threaten vision, but infections of the cornea or inside the eye are serious threats and require immediate referral to an ophthalmologist.

Infectious conjunctivitis

Conjunctivitis is a common condition that causes dilation of the conjunctival blood vessels and results in inflammation. Figure 1 is an algorithmic approach to diagnosing and treating conjunctivitis, based on signs and symptoms.[2]

Both viral and bacterial conjunctivitis (Fig. 2) present with a red eye and are highly contagious. Assessment should include checking visual acuity and examination with a torch or slit lamp. Fluorescein drops should be instilled in the conjunctival sac and the eye viewed with the cobalt blue light of the slit lamp or fundoscope, to rule out any signs of corneal ulceration or infection (Fig. 3). A history of cold sores or shingles should be sought and the patient examined for cold sores or a vesicular rash in case the infection is due to herpes simplex or zoster virus.

Viral conjunctivitis

Viral conjunctivitis is the most common cause of infectious conjunctivitis. This infection is more common in adults than in children. Around 65–90% of cases are caused by adenovirus. Occasionally, herpes simplex or zoster virus is responsible.

Patients can generally be advised that viral conjunctivitis is self-limiting and, as there are no specific treatments, for comfort they can use cold compresses, artificial tears or topical antihistamines.[2,3] Antibiotics are not needed, are costly and may increase antibiotic resistance. If there is evidence of herpes simplex or zoster virus then antivirals should be prescribed, such as aciclovir ointment or ganciclovir gel.

When viral conjunctivitis is severe or the patient experiences symptoms after its resolution, the patient should be referred to an ophthalmologist. This is to consider topical steroids and to exclude an immune 'post-viral' keratitis.

Bacterial conjunctivitis

Bacterial conjunctivitis, although a less frequent cause of conjunctivitis, is more common in children. The most common bacteria are *Haemophilus influenza*, *Streptococcus pneumoniae* and *Staphylococcus aureus*.[4]

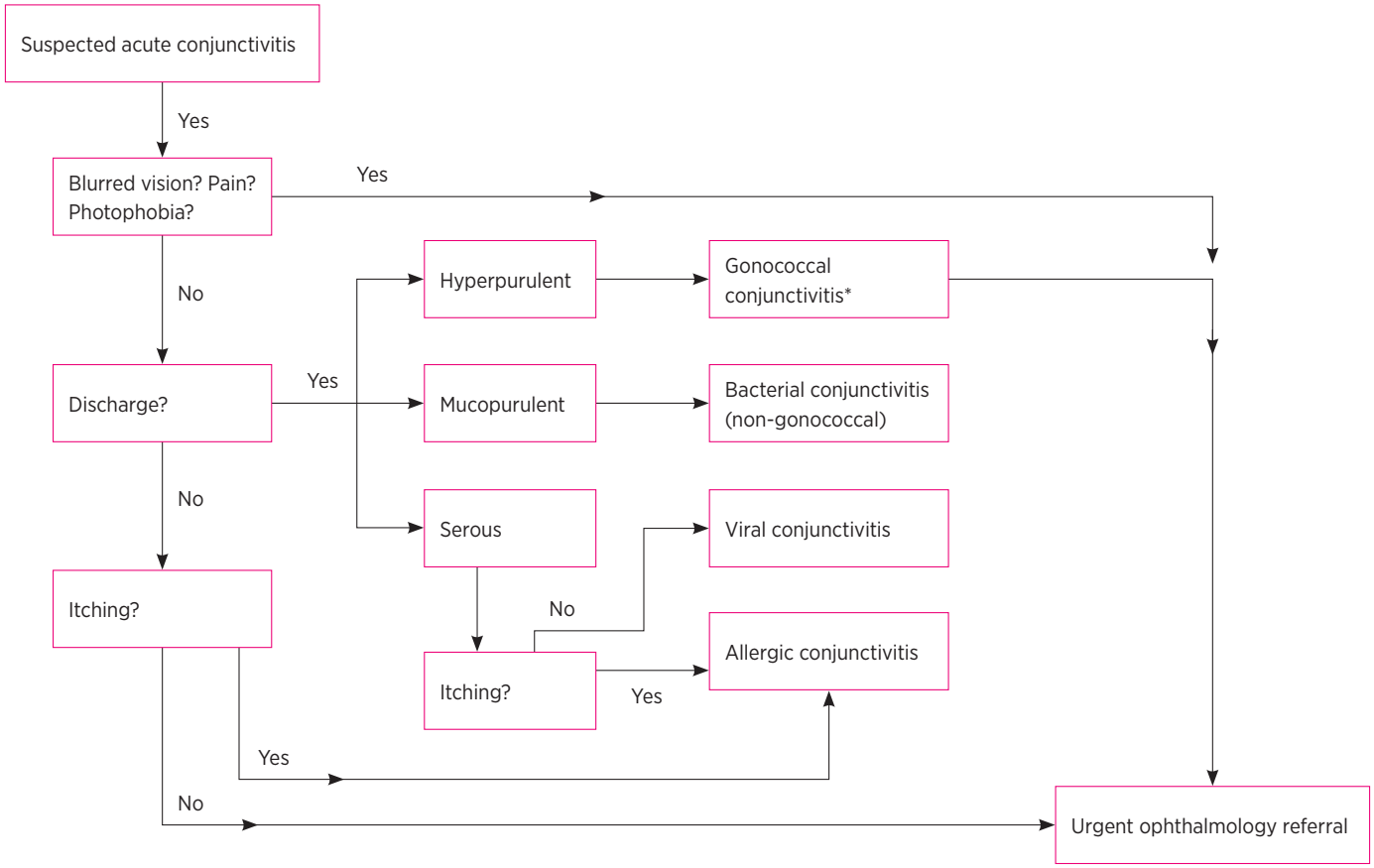
Compared to placebo, the use of antibiotic eye drops is associated with improved rates of clinical and microbiological remission.[4] A broad-spectrum topical antibiotic is recommended. The practitioner can select the most convenient or least expensive option, as there is no clinical evidence suggesting the superiority of any particular antibiotic.[3,4]

The initial treatment recommended by Therapeutic Guidelines: Antibiotic[5] is:

- chloramphenicol 0.5% eye drops, one to two drops every two hours for the first 24 hours, decreasing to six-hourly until the discharge resolves, for up to seven days
- framycetin sulfate 0.5% eye drops, 1–2 drops every 1–2 hours for the first 24 hours, decreasing to eight-hourly until discharge resolves for up to seven days.

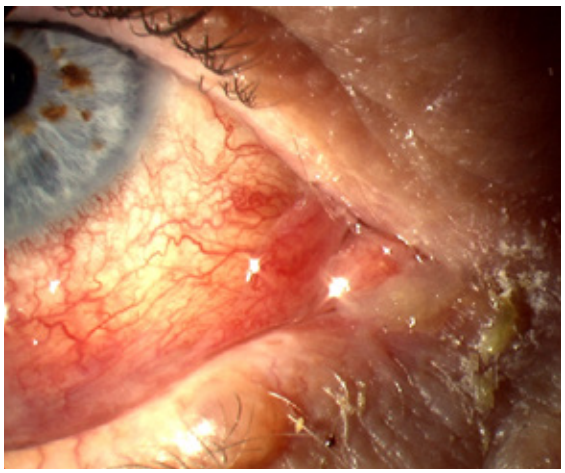
Chloramphenicol 1% eye ointment may be used at bedtime. Gentamicin, tobramycin and quinolone eye drops are not recommended for empiric treatment. If the condition does not improve within five days, the patient should be immediately referred to an ophthalmologist.

Fig. 1 **Suggested procedure for clinical approach to suspected acute conjunctivitis**



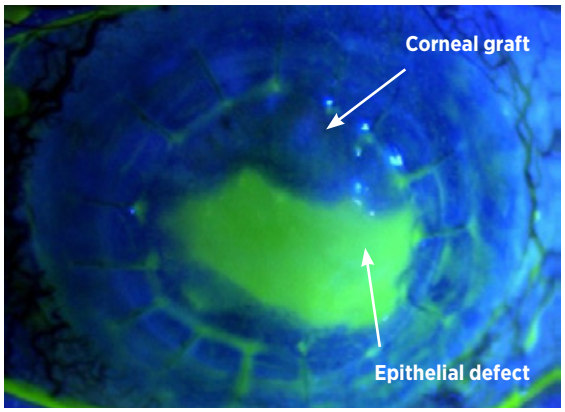
* Gonococcal conjunctivitis is mainly seen in neonates

Fig. 2 **Conjunctivitis**



Note discharge at medial canthus.

Fig. 3 **Epithelial defect in a corneal graft viewed with fluorescein drops and cobalt blue light**



The epithelial defect is stained green.

Gonococcal conjunctivitis

Conjunctivitis caused by *Neisseria gonorrhoeae* is uncommon but should be considered in neonates and sexually active young adults. If suspected, the practitioner should take conjunctival swabs for Gram staining and special culture for *Neisseria* species.[6] Patients should be referred immediately to an ophthalmologist. Antibiotic therapy is the recommended treatment and ceftriaxone is the drug of choice.[3] Additionally, patients should lavage the infected eye with saline and add therapy to cover chlamydia.[2]

Chlamydial conjunctivitis

Most cases of chlamydial conjunctivitis are unilateral and have concurrent genital infection. Symptoms usually include conjunctival hyperemia, mucopurulent discharge and lymphoid follicle formation.[6] Patients with symptoms should be referred immediately to an ophthalmologist. Oral antibiotics such as azithromycin or doxycycline are effective treatments.[7]

Infectious keratitis

Infection of the cornea (microbial keratitis) is an ophthalmic emergency requiring immediate attention as it can progress rapidly. It is a significant cause of corneal blindness[8] and is one of the most common causes of visual impairment in working age adults.[9] In the USA, about 30 000 cases of microbial keratitis are reported annually.[10]

If infectious keratitis is suspected, the practitioner should take a history to look for risk factors such as contact lenses, corneal abrasions, physical and chemical trauma, refractive surgery, diabetes, immunosuppressive diseases and topical steroids.[10,11] The type of infecting organism varies according to the climate and geographical region and the patient's risk factors.

Bacterial keratitis

Bacterial infection is the most common cause of infectious keratitis. Common causal bacteria include *S. aureus*, coagulase-negative staphylococci, *S. pneumoniae* and *Pseudomonas aeruginosa*.[10,11] *P. aeruginosa* is the most common microorganism implicated in bacterial keratitis among contact lens wearers. Less commonly, fungi or acanthamoeba can be responsible.[12] Fungi should be suspected when there is trauma particularly with vegetative matter and is more common in rural environments. Suspect acanthamoeba if a patient has been swimming or in a spa while wearing contact lenses. Specific antifungal or anti-acanthamoebal therapy is needed and treatment may take some months.[13-15]

The signs and symptoms of bacterial keratitis are shown in the Table and Fig. 4.[16] Patients with pain, photophobia, blurred vision, corneal opacity or hypopyon (pus inside eye), or contact lens wearers with red eye or increasing pain, should be referred promptly to an ophthalmologist for a slit lamp

Table **Clinical features of keratitis and endophthalmitis**

Condition	Common symptoms	Common signs	History
Bacterial keratitis	Pain Photophobia Tearing Decreased or blurred vision	Redness Discharge Corneal ulcer Corneal infiltrates Hypopyon	Contact lens wear Trauma
Herpes simplex virus keratitis	Pain Decreased or blurred vision Tearing Itching Photophobia	Redness Discharge Epithelial: • Dendritic ulcer Stromal: • Stromal haze/opacity with or without ulceration • Scarring • Vascularisation Endothelial: • Stromal oedema • Keratitic precipitates	Labial cold sores Prior keratitis
Endophthalmitis	Pain Decreased vision	Redness Hypopyon	Recent ocular surgery Intravitreal injections Trauma Intravenous drug use

examination and corneal scraping. These scrapings are sent for Gram stain and culture to identify the organism. To begin, treatment has to be empiric because the results can take over 48 hours, and the condition can progress rapidly with loss of vision or even the eye if treatment is not started.

Topical antibiotics are the mainstay of treatment and options include monotherapy with fluoroquinolones (ciprofloxacin 0.3% or ofloxacin 0.3% 1–2 drops hourly for 48 hours, then every 4 hours until healed) or fortified aminoglycoside/cephalosporin combinations (fortified cefalotin 5% plus gentamicin 0.9% 1–2 drops hourly for 48 hours, then reduce frequency according to treatment response).[5] These regimens have similar effectiveness but fluoroquinolones reduce the risk of chemical conjunctivitis and ocular discomfort. Compared to ofloxacin, ciprofloxacin increases the risk of white corneal precipitates.[17] Occasionally, corneal grafting may be needed to eradicate the organism or repair damage.

Chloramphenicol is the most common first-line antibiotic prescribed for red eye. It is a bacteriostatic broad-spectrum antibiotic but lacks activity against *P. aeruginosa*.[18] Primary healthcare providers should not prescribe chloramphenicol when microbial keratitis is suspected as this delays appropriate treatment, with the risk of the patient losing vision or the eye.[18,19]

Herpes simplex keratitis

Keratitis caused by herpes simplex virus is an important cause of infectious blindness in developed countries. The global incidence of herpes simplex keratitis was calculated at approximately 1.5 million with 40 000 new cases of severe monocular visual impairment or blindness per year.[20] Herpes simplex keratitis can be classified as epithelial, stromal, endothelial or mixed, depending on which layer of the cornea is involved (Fig. 5). It may also be considered as primary or recurrent depending on whether it is the patient's first episode. If suspected, the practitioner should ask about a history of cold sores or previous viral keratitis as this can be the first clue to the diagnosis. The clinical features of herpes simplex virus keratitis (Table) can be identified on slit lamp examination.[21,22]

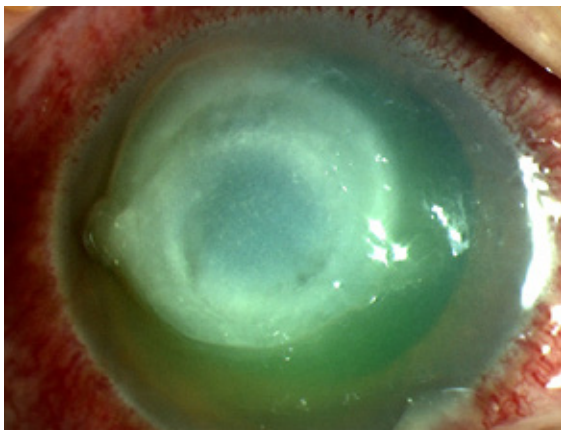
Epithelial herpes simplex keratitis typically manifests as a dendritic ulcer. To visualise the ulcer, fluorescein staining and a cobalt blue light are needed (Fig. 5).[21] The treatment is aciclovir ointment five times daily for 14 days.[23-25]

Stromal herpes simplex keratitis presents with haze or opacity of the stroma, with or without ulceration, scarring or vascularisation. Endothelial keratitis is characterised by keratitic precipitates on the endothelium and corneal oedema.[23] Management of stromal and endothelial keratitis involves referral to an ophthalmologist for oral antivirals (aciclovir or valaciclovir), topical steroids[25] and follow-up until the episode has resolved.

Infectious endophthalmitis

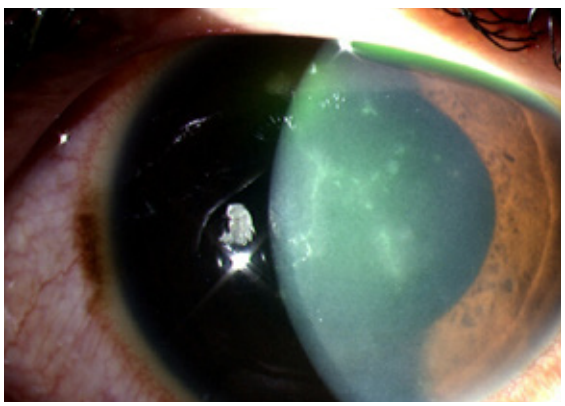
Endophthalmitis is an inflammation inside the eye that can be caused by infection with microbes, including bacteria or fungi (Fig. 6). The Table lists the clinical features. Endophthalmitis is an ocular emergency, requiring urgent referral to an ophthalmologist to prevent permanent loss of vision. It is a rare condition and its incidence depends on the cause. Risk factors for endophthalmitis include cataract surgery, intravitreal injections (for age-related macular

Fig. 4 **Bacterial keratitis**



The central cornea has a white opacity known as an 'inflitrate' with an epithelial defect and conjunctival injection.

Fig. 5 **Herpes simplex virus dendritic ulcer**



This photograph illustrates an epithelial dendrite from herpes simplex keratitis seen with fluorescein staining and a cobalt blue light.

degeneration), trauma, filtering bleb (for glaucoma), corneal infection, bacteraemia or fungemia. Endophthalmitis due to systemic infection may be associated with intravenous drug use.

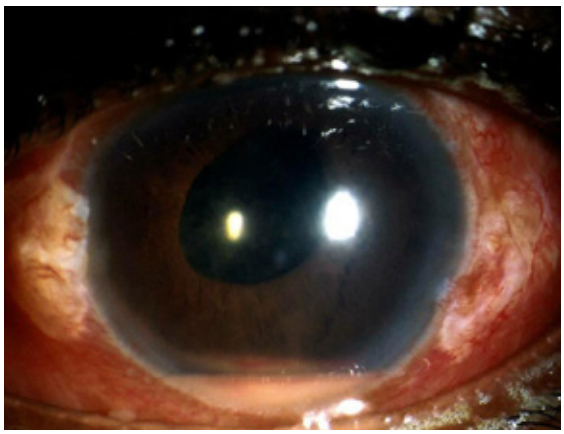
Worldwide, cataract surgery is the most common cause of endophthalmitis, occurring in around 1 in 1000 cases.[26] It typically presents within seven days of the surgery and is most often caused by bacteria.

The incidence of endophthalmitis following intravitreal injections is increasing along with the widespread use of intravitreal antivascular endothelial growth factors for managing neovascular age-related macular degeneration and diabetic retinopathy. The risk of endophthalmitis is 0.05% per injection and, with injections often given monthly, the risk is cumulative. Typically, patients present within five days of the injection with decreased vision and pain. The most common microorganisms involved are coagulase-negative staphylococci, *S. aureus*, streptococci and Gram-negative bacilli. A minor procedure is needed to obtain samples of vitreous and aqueous humour to isolate the organism.

Urgent treatment is needed with intravitreal antibiotics such as ceftazidime or vancomycin injected by an ophthalmologist. In some cases vitrectomy may be beneficial to avoid loss of vision.[5,27] If there is a delay in administering intravitreal treatment, give single doses of:

- oral ciprofloxacin 750 mg (child: 20 mg/kg up to 750 mg) plus intravenous vancomycin (adult and child 15 mg/kg)
- gentamicin (adult and child 5 mg/kg) intravenous plus intravenous cefazolin 2 g (child: 50 mg/kg up to 2 g).[5]

Fig. 6 **Endophthalmitis**



In this photograph of a patient's eye with endophthalmitis a pus level inside the front of the eye, known as a hypopyon, can be seen.

Adverse effects of topical antibiotics

Bacterial infections are typically treated with antibiotic drops which may cause systemic adverse effects. The volume of commercial dispensers (25–50 microlitres) exceeds the capacity of the conjunctival sac (10 microlitres), therefore a large volume of the liquid drains out of the eye. This liquid may be systemically absorbed through different pathways including conjunctiva, nose, lacrimal drainage, pharynx, gastrointestinal tract, aqueous humour, lids, cheeks and inner ocular tissues. However, the risk of systemic absorption is low since ocular drug bioavailability is 5–10% and the corneal epithelium and conjunctival epithelium act as natural barriers limiting absorption.[28] Some adverse effects include skin irritation, itching or rash with sulfonamide, sulfacetamide and neomycin.[28] Fluoroquinolones can cause local irritation, stinging, chemosis, conjunctival hyperaemia, corneal precipitations and alteration of taste.[29]

A minimal dose and concentration of the antibiotic must be used in pregnancy to limit systemic absorption. Patients must be advised of punctal occlusion, nasolacrimal pressure and wiping away extra liquid to prevent systemic absorption.[30] Practitioners should refer to the ABCD pregnancy category before prescribing antibiotics to pregnant women. Antibiotics and antivirals such as chloramphenicol, tobramycin, fluoroquinolones and topical aciclovir are considered safe to use during pregnancy.[31]

Conclusion

Patients with eye infections typically present with pain, blurred vision and a red eye. Conjunctivitis is the most common eye infection to present to primary healthcare providers and rarely threatens vision. Corneal infection (keratitis) and endophthalmitis are less common but pose a serious risk to vision. If the patient has a history of blurred vision, pain, photophobia, corneal opacity or hypopyon, specialist assessment is urgently needed.

Primary healthcare providers should avoid prescribing topical antibiotics for an eye infection unless the patient has bacterial conjunctivitis. Viral conjunctivitis is common and self-limiting. Urgent referral to an ophthalmologist for microbiological samples and treatment is needed for infectious keratitis and endophthalmitis. ≺

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Q:

SELF-TEST QUESTIONS

True or false?

1. Chloramphenicol eye drops should not be used to treat bacterial keratitis.
2. In adults, most infectious conjunctivitis is caused by a virus.

Answers on page 95

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ARTICLE

Reducing medication errors at transitions of care is everyone's business

SUMMARY

Medication errors are a common and significant problem, particularly when patients transition between healthcare providers. Discrepancies are especially prevalent on hospital admission and discharge.

People with complex medication regimens, older people, those with mental health problems, people who are poor or have low literacy, and Aboriginal and Torres Strait Islander and migrant populations are particularly at risk of medication discrepancies.

A patient-centred approach is a necessary shift towards reducing medication discrepancies and errors. The patient is the one 'constant' as they progress through GP and ancillary primary care services, hospital services, and specialist outpatient and private clinics. Patients and their carers need to be involved as active participants in this process.

Maintaining an accurate, comprehensive and up-to-date medicines list that follows the patient, reduces serious medication error. Pivotal to this record is a medicines reconciliation review at error-prone transition points.

Multiple health professionals involved in a patient's journey through healthcare services need to embrace accountability for medicines-related outcomes. Emerging technologies for communication between primary care and specialist or secondary services will facilitate this, but importantly, there needs to be commitment from each health professional to undertake this approach.

Amanda J Wheeler
Professor of Mental Health
Menzies Health Institute Queensland
Griffith University
Brisbane

Shane Scahill
Senior lecturer
Health Services Management and Entrepreneurship
School of Management
Massey University
New Zealand

David Hopcroft
General practitioner
Auckland
New Zealand

Helen Stapleton
Student support and Research educator
Mater Education
Brisbane

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Introduction

As patients move between health providers and settings, discrepancies and miscommunication in clinical records are common and lead to serious medication errors.[1,2] Hospital admissions and discharges, interdepartmental transfers, or care shared between a specialist and a GP, are often dangerous times for patients, especially those with long-term conditions or taking multiple medicines.[3]

A 2017 report by the World Health Organization on medication safety emphasised that improving communication at transition points is vital to avoiding medication-related harm.[4] Also, a recent commentary has highlighted the need for better transitional care in Australia to reduce the significant costs of medication mismanagement, including avoidable hospital (re)admissions.[3] For example, poor medication management during or immediately after hospital admission increased the risk of readmission in the next month by 28%.[5]

The size of the problem

Discrepancies in medicine records can occur at every level of care. There are significant discrepancies between the medicines people take at home, the medicines GPs think they are taking at home, medicines listed in GP referral letters, medicines people obtain from pharmacies, the medicines recorded when they are admitted to hospital, and when they leave hospital, and the medicines detailed in their official discharge summary. These discrepancies often relate to medicine omissions.[6–8]

In mental health community care, medication discrepancies cause particular problems. Psychiatrists often remain involved in prescribing and reviewing psychotropic medicines, while GPs are expected to manage medicines related to other conditions. Patients may take a number of medicines in complex regimens so there is a high potential for drug interactions, particularly given the substantial comorbidity and mortality rates in this population.[9,10] Recent research on clozapine has shown that discrepancies with concomitant medications can have potentially fatal outcomes (see Box).[11,12]

Indigenous or migrant people, and those who are socially disadvantaged or have low literacy, experience health outcomes that reflect their difficulties when navigating the healthcare system.[13–16] Culturally appropriate delivery of health services is crucial to effective engagement and uptake, and this may be challenging to do well.

Box Medication discrepancies with clozapine in a shared-care program

Clozapine is the most effective antipsychotic for treatment-resistant schizophrenia. However, its use is restricted because of potentially fatal adverse effects (including agranulocytosis, myocarditis, gastrointestinal hypomotility and severe constipation) and the requirement for mandatory monitoring. Pharmacokinetic and dynamic interactions can alter clozapine levels and cause additive adverse effects (e.g. concomitant medicines that cause constipation, such as codeine, can cause fatal bowel obstruction[12]). Clozapine prescribing is commonly restricted to psychiatrists and dispensed by a hospital pharmacy.

In a shared-care model with the specialist, a GP may prescribe maintenance treatment. The mandatory 4-weekly well-being and haematological monitoring is undertaken by the GP who instructs the hospital pharmacy to dispense the prescription and arrange delivery to the local community pharmacy for the consumer to pick up. The psychiatrist reviews the patient quarterly, which reduces the number of hospital appointments and associated time and cost burdens. This model also promotes primary care relationships and physical health management.

However, the very high rates of medication discrepancies identified across shared-care medication records in a Queensland service are of significant concern.[11] Overall, 32/35 patients had at least one medication discrepancy, mostly omissions, with an average of 4.9 per consumer. Specialist records had the highest number of discrepancies (74%), followed by GP records (70%) and community pharmacy (62.5%).[11]

People with chronic conditions and multiple medications from multiple prescribers, particularly older people, are another group who are likely to have incomplete or incorrect medicine lists. It is important to focus on these vulnerable groups if we are to reduce medication errors.

Patient-centred approaches lead to patient-centred outcomes

The key to reducing serious medication errors and patient harm is to ensure timely, accurate handover of medicines at all transition points in care. Smooth transitions require competent and coordinated responses from health professionals focused on the individual's needs.[3,4,6] The one person who remains constant is the patient, who has the most to lose in a disconnected health system. Patients and their carers need to be actively involved in the management of their medicines and transfer of information.

Improving medicines communication during transitions

In Australia, strategies to improve communication at transition points have been trialled. They include medication reconciliation and discharge planning in hospital settings, electronic prescribing, personal electronic health records (My Health Record) and collaborative medicines review in the community.[6]

Medicines reconciliation

Medicines reconciliation involves matching the medicines the person should be prescribed to those they are actually prescribed.[17] The verified information must include reasons for changes made to medicines during an episode of care, which must be shared with the next care provider. It is commonly undertaken during inpatient visits and studies have shown it significantly reduces medication error[18,19] and improves patient outcomes.[20] Patients are integral to the process by providing their current medicine list (on paper, as a photo or on a smartphone app such as MedicineWise), or the medicines themselves. They also need to be provided with education and an updated list at discharge or whenever medicines are changed.

The reconciliation process helps to identify problems such as drug interactions and risk of adverse events.[18] Ideally, it should occur at each episode of care and upon transfer to the next care provider, and patients and their carers should be fully involved.

While hospital pharmacists have played a leading role,[6] medicines reconciliation is everybody's business and training is needed for the whole clinical team.[2,19,21-24]

Discharge planning

It is just as important to ensure accurate and timely transfer of information at hospital discharge as it is on admission. Providing a Pharmaceutical Benefits Scheme (PBS) prescription on discharge for one month's supply should be reconciled by a pharmacist against the Discharge Medication Record, to ensure that patients have access to any new or changed medicines and an adequate supply of continuing medicines. The hospital pharmacist can liaise with the patient's community pharmacist to organise dispensing in the community, particularly if a dose administration aid is needed. It also allows the pharmacist to provide the consumer with information to manage their medicines (e.g. with their own copy of the Discharge Medication Record). This process allows time for the discharge summary communicating the current medication plan to reach the GP before a new prescription is needed. However, effective discharge planning requires cooperation between doctors, pharmacists and nurses in the hospital and community.

Electronic prescribing

As part of electronic medication management systems, e-prescribing can enhance safety and quality by ensuring complete and legible orders, and reducing medication errors and adverse reactions. However, e-prescribing systems can introduce new types of errors such as incorrect selection of medicines from drop-down menus.[25] They need to be integrated with other systems to provide clinical decision support and easy exchange of patient data between GPs, secondary or specialist care and shared personal health records. These systems

need to ensure medication selection processes are safe, for example provide warnings if a medicine is contraindicated, or when a medicine is similar in name to another, or dosing is potentially harmful. Warnings also need to be prioritised so they are not ignored. With many different e-prescribing systems available, national standards to ensure safety and quality criteria are vital.[26,27]

Personal electronic health records

Stronger linkages between primary and secondary care, particularly for people transitioning between outpatient specialists and GPs, are needed (see Box). Linked and controlled electronic patient management systems are a partial solution, and My Health Record is a step toward this notion of integration. This will be the main conduit in Australia for an integrated system. As it will become an opt-out model, significant uptake in the national roll-out is expected.[28] Clearly, appropriate controls governing security, access and privacy are paramount but these are manageable. Such systems are operational in other developed countries (such as New Zealand) where security and privacy are managed through automated security detection which highlights when patient files have been accessed by those practitioners (or other health workers) who should not have access. When notified files have been inappropriately accessed, review and due process are undertaken by the relevant agency.

With My Health Record, access and privacy are driven by the consumer.[29] They can set a record access code which they give to their healthcare providers to allow them to view their records. This prevents other healthcare providers from access unless in an emergency. Consumers can also flag specific documents in their record as 'limited access', and control who can view these documents.

My Health Record is an online summary of a person's individual real-time health information. Primary digital health records will still be maintained at source, including general practices and hospitals. Medicines information, including PBS dispensing information (from the last two years), GP electronic prescriptions, pharmacy dispensing records, electronic hospital discharge summaries and specialist letters will be available from multiple sources in a Medicines Information view.[30]

While ease of access to medicines information for consumers moving between multiple prescribers is a significant step forward, information may be incomplete. For example, medicines that have been stopped, or doses changed, may not be reflected in prescription or dispensing records. Practitioners' notes may not have been uploaded and made available via the Medicines Information view. Also, consumers may have removed prescription and dispensing information in their record.[31] The vital element in all transitions of care is accurate and timely communication between patients, their carers, and health practitioners. This helps to confirm and validate information contained in the shared electronic health record.

Medicines reviews

Home Medicines Reviews (and Residential Medication Management Reviews conducted in aged-care facilities) are additional avenues to improve medicines reconciliation in primary care.[6,32] The GP, patient and an accredited pharmacist collaborate to identify and resolve medication-related problems, particularly following hospital discharge or significant changes to a patient's condition or medicine regimen.[33] Studies report improvements in prescribing and health outcomes (including costs) by reducing medication-related problems. Reviews undertaken shortly after hospital discharge have also been shown to reduce adverse events and provide an opportunity for medicines reconciliation.[32] Although research has shown that Home Medicines Reviews reduce hospital admissions for people on high-risk medicines, the current funding cap and referral pathways restrict access to the program.[16] This is particularly notable for Aboriginal and Torres Strait Islander people who experience multiple barriers to accessing existing medicines review programs.[34] Over the next two years a study in nine Aboriginal Health Services will assess the feasibility of community pharmacists delivering an individualised, culturally appropriate medicines review to resolve medication-related problems and reduce hospitalisations.[35]

Another avenue to improve medicines reconciliation in primary care is currently being trialled in Queensland.[36] A non-dispensing pharmacist based within a general practice will conduct a review within a week of discharge, reconciling any differences between the discharge summary and the practice medical records. A pharmacist consultation with the patient will be followed directly by a GP appointment, and any anomalies clarified. The aim of this study is to reduce unplanned readmissions to hospital.

Health service delivery: structure and agency

A focus on avoiding costly hospital admissions and providing high-quality, patient-centred care in the community is challenging, particularly in light of an ageing and expanding population of people with multiple long-term conditions. An OECD Health Care Quality Review found that Australia needs to strengthen its primary care system to better coordinate consumer care. It emphasises the role

of GPs and promotes a system that enables people to access care from a multidisciplinary team of health professionals.[37]

Any service reconfigurations centred on improving medication safety must consider the complexities associated with prescribing and supply. The physical (structure) and human aspects (agency) of health service delivery are equally important when it comes to service design and delivery. Physical elements focus on the geographical location of healthcare providers. Co-location of the GP, pharmacy and specialists generally improves communication and teamwork in primary care.[38] Australia started two-year trials of Health Care Homes in general practices in July 2017.[39]

Patient care pathways must be integrated through the health sectors. Electronically shared records would facilitate easy transfer of correct, real-time information.

In order to improve Australia's fragmented health system, the OECD recommended devolving responsibility for delivering primary care to the states and territories.[37] For example, building on the primary care collaboratives[40] and practice incentives program,[37,41] Primary Health Networks could have greater responsibility in creating more effective and efficient systems in their regions which are tailored to local needs, with accountability for reducing hospital admissions.[42] This should be underpinned by seamless integration of care between healthcare professionals and the use of technology. Clinical records and a single medication record should follow the patient.

At the clinical professional level (i.e. agency), a culture of teamwork and shared accountability needs to be actively promoted. Professional boundaries and competition, among health professionals and between health practitioners and managers, need to be dissolved.[43] In hospitals, practitioners work largely in multidisciplinary teams. However, in primary care, and at the interface between primary and specialist or secondary care, this level of collaboration and trust is often more difficult to initiate and sustain.

Conclusion

Medication discrepancies and errors arising from lack of care coordination for healthcare consumers seeing multiple prescribers is a very real problem. A patient-centred approach is key to improvement, along with strategies including integrated care pathways facilitated by technology and shared accountability. All healthcare providers need to commit to the consumer being central to the goal of medications accuracy. ≺

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ARTICLE

Returning unwanted medicines to pharmacies: prescribing to reduce waste

Emilie Bettington
Research fellow[1,2]

Jean Spinks
Research fellow[1,2]

Fiona Kelly
Senior lecturer[2,3]

Amanda J Wheeler
Professor of Mental Health[2]

[1] Centre for Applied Health Economics
School of Medicine
Griffith University
Brisbane

[2] Menzies Health Institute Queensland
Griffith University
Brisbane

[3] School of Pharmacy
Griffith University
Gold Coast
Queensland

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SUMMARY

The Return Unwanted Medicines Project is a free and safe way for consumers to dispose of unwanted medicines at pharmacies.

In 2016 the Project collected over 704 tonnes of unwanted medicines. An audit found that the most commonly returned medicines were unexpired opened packets of medicines for the treatment of acute conditions. They included paracetamol, salbutamol and glyceryl trinitrate.

Doctors, pharmacists, nurses and consumers should be more aware of which repeat prescriptions of 'if required' medicines are needed.

In making decisions about the quantity of medicine to supply, prescribers need to consider patient access, adherence and cost.

It is the responsibility of all health professionals to encourage consumers to return unwanted medicines to their community pharmacy.

Introduction

The accumulation of unwanted medicines at home can result in accidental ingestion, or lead to confusion, and out-of-date medicines can become toxic or ineffective.[1] Disposal of these medicines in general household waste means they can end up in landfill or contaminate waterways and affect animal and plant life and potentially human life.[2-5]

The collection and disposal of unwanted medicines is an important public health issue and is part of the Australian National Medicines Policy.[6] The Return Unwanted Medicines (RUM) Project is a subsidised national scheme that allows unwanted medicines to be collected by any community pharmacy and disposed of by high-temperature incineration.[7]

In 2016, the RUM Project was audited by Griffith University. The aim was to identify the types and quantities of medicines being discarded, including prescription, pharmacist and pharmacy-only medicines (Schedules 4, 3 and 2 respectively), controlled medicines (Schedule 8), complementary medicines, unscheduled medicines and dose administration aids. This allows health professionals to better understand consumer behaviour and provides a starting point for discussions around quality use of medicines[8] and prescribing practices.

Why are some medicines prescribed but not used?

There are various reasons why someone may obtain a medicine but not use all of it. Medicines often require titration or adjustment, antibiotic courses may not be finished, a medicine may not work, or it may cause an adverse effect and need to be stopped. Sometimes the pack size prescribed might be more than is required, especially for acute conditions such as pain or nausea and vomiting. In addition, people may keep spare medicines, such as a salbutamol inhaler at their work, which expire before they are fully used.

Audit of unwanted medicines

The 2016 audit assessed the types and amounts of medicines returned via the RUM Project at the three national incineration sites (Brisbane, Perth and Melbourne). On average, 13 000 RUM bins per month are collected for incineration.[7] The audit aimed to examine the contents of a nationally representative sample of 423 RUM bins.[9] This represented approximately 0.26% of the total number of bins collected between July 2015 and June 2016.[7]

In total, 452 bins were assessed in terms of percentage filled, proportion of loose tablets and whether they contained inappropriate items. Twenty-nine bins were excluded from the audit as

they were less than 50% full (4 bins), contained a high proportion of general waste (7 bins), contained more than 50% loose tablets (5 bins) or contained unsafe waste, such as liquids, sharps or biological waste (9 bins).

What is being returned?

In total, 30 422 different medicine items were counted. This included prescription medicines, dose administration aids (which may include multiple medicines), over-the-counter medicines and complementary medicines (see Box). These were in the form of unopened or opened packs, including loose countable forms of medicines e.g. a blister strip of tablets, but not loose tablets and capsules. For each item, the number of individual tablets and capsules or nebules was counted. For dose administration aids, creams, liquids and aerosols, the proportion returned was estimated.

Box **Types of medicines returned in a 2016 Return Unwanted Medicines Project audit**

60% of the returned items were PBS medicines:

- 55% were prescription only (Schedule 4)
- 1% were controlled drugs (Schedule 8)
- 4% were pharmacist-only medicines (Schedule 3 – these were assumed to be PBS medicines).

10% of items were over-the-counter medicines (Schedule 2).

14% were dose administration aids.

11% were unscheduled medicines.

4% were complementary medicines.

1% were international, and unknown schedule medicines.

PBS Pharmaceutical Benefits Scheme

The Table lists the 20 most commonly returned Pharmaceutical Benefits Scheme (PBS)-listed medicines identified in the 2016 audit and compares these to the most commonly dispensed PBS medicines in 2015–16 and to the results of a 2013 RUM Project audit.[9-12]

Not surprisingly, 10 of the most commonly prescribed PBS medicines in 2015–16 were included in the list of the 20 most commonly returned PBS-listed medicines in the 2016 audit. Six of the most commonly returned PBS medicines in 2016 are used for chronic conditions, and three – atorvastatin, simvastatin and metformin – were in the top 20 most prescribed PBS medicines (Table).

In comparing the 2016 and the 2013 RUM Project audit results, 11 PBS-listed medicines appear on both lists (Table). Salbutamol and glyceryl trinitrate appear in the top five of both audits. In 2013, 13 of the most commonly returned PBS medicines were 'if required' medicines. These were defined as items used for acute conditions such as nausea, acute infections, asthma or angina attacks, medicines that required regular dose adjustments (e.g. prednisolone, warfarin), and analgesics. Analgesics were included because, although pain can be acute or chronic, there are often dose adjustments and medicine changes for people with chronic pain conditions. The results revealed that in 2016 the top six were 'if required', as well as 14 of the 20 most commonly returned PBS-listed medicines.

Just over a third (36%) of all medicines returned in 2016 were expired, compared with 51% in the 2013 audit. Approximately 10% of the PBS-listed medicines were expired and approximately 10% were unopened.

The 2016 audit attempted to calculate a cost to the PBS of wasted medicines. PBS waste was assumed to consist of all dispensed (i.e. had a dispensing label) and unopened PBS-listed medicines, irrespective of expiry. If a medicine had been opened and at least one dose taken, it was not considered as waste as it could have been discarded for valid reasons, including adverse events or poor efficacy. Using this definition, and assuming that the sample was representative of the total number of bins collected annually, the estimated cost of wasted medicines discarded via the RUM Project is approximately $11.6 million a year.

Is the system working?

Yes, the RUM Project is working. It collected potentially dangerous medicines from consumers and prevented over 704 tonnes of expired or unwanted medicines ending up in landfill and the waterways in 2016.[7] However, awareness of the RUM Project within the general population is low. As part of the 2016 audit, we conducted a survey of 4 302 people and found that less than 18% had heard of it and most people dispose of unwanted medicines in the household rubbish or into the sewerage.[1]

It appears that the RUM Project is being used appropriately by community pharmacy staff. Liquid cytotoxic agents, Schedule 8 items (without evidence of destruction in some states and without exception in other states) and sharps should not be disposed of in RUM bins.[7] No liquid cytotoxic agents were found in the bins and only a small number of Schedule 8 items (1.6%) were found.

Although 29 bins were excluded from the audit, only seven of 452 bins (1.5%) were excluded because they

Table **The most commonly dispensed and returned PBS-listed medicines in Australia**

Rank	2015–16 PBS prescription counts [10]	2016 audit of returned medicines [9]	2013 audit of returned medicines *[11,12]
1	Atorvastatin	Paracetamol †	Salbutamol †
2	Rosuvastatin	Salbutamol †	Insulin ‡
3	Esomeprazole	Glyceryl trinitrate †	Furosemide (frusemide)
4	Paracetamol †	Cefalexin †	Prednisolone/prednisone †
5	Pantoprazole	Metoclopramide †	Glyceryl trinitrate †
6	Perindopril	Doxycycline †	Telmisartan/amlodipine
7	Metformin	Furosemide (frusemide)	Fluticasone/salmeterol
8	Pregabalin	Simvastatin	Paracetamol †
9	Fluticasone/salmeterol	Atorvastatin	Metoclopramide †
10	Salbutamol †	Aspirin	Warfarin †
11	Irbesartan	Warfarin †	Influenza vaccine
12	Cefalexin †	Tramadol †	Perindopril
13	Atenolol	Oxycodone †	Metoprolol
14	Simvastatin	Pregabalin †	Paracetamol/codeine †
15	Oxycodone †	Pantoprazole †	Atorvastatin
16	Amoxicillin †	Amoxicillin †	Amoxicillin †
17	Amlodipine	Metformin	Betamethasone †
18	Paracetamol/codeine †	Prednisolone †	Oxycodone †
19	Amoxicillin/clavulanic acid †	Valproate	Cefalexin †
20	Ramipril	Amoxicillin/clavulanic acid †	Ipratropium †

PBS Pharmaceutical Benefits Scheme RUM Return of Unwanted Medicines

* The 2013 audit was of 377 RUM bins. Although the processes were similar in the 2016 audit, the 2013 audit considered any quantity of a returned medicine as a full pack (i.e. the full dispensed amount). In the 2016 audit, the exact quantity of each medicine returned was counted.

† Items that could be considered 'if required' (i.e. medicines for acute or short-term conditions, chronic conditions with unpredictable flare-ups, or medicines that require regular dose adjustments).

‡ 'Insulin' in the 2013 audit included all types of insulins. In the 2016 audit, each type of insulin was counted separately. If all insulins were grouped together in the 2016 audit, 'insulin' would have been the third most commonly returned PBS-listed item.

contained inappropriate waste (over 50% of general waste). Approximately 11% of bins contained sharps which included unused needles, syringes, lancets and blades.

What could be improved?

There is never going to be a situation when there are no wasted medicines, and, in fact, the return of medicines via the Project should be considered positive. For example, the return of any unused oxycodone and tramadol removes these potentially dangerous medicines from households.[13]

Based on the proportions of medicines returned, it could be argued that some 'if required' medicines – for example, analgesics for acute pain – are being prescribed in excessive quantities. A recent study found that 42–71% of opioid tablets prescribed after surgery were unused.[13] While prescribing smaller quantities is often proposed as a way to reduce wastage, this may have negative impacts on consumer access and adherence to medicines, and may increase costs because of the need for more frequent prescribing and dispensing. Although it was beyond the scope of the 2016 audit, this could be an area of future research and economic analysis.

Awareness of the RUM Project could be improved. When provided with information about the Project, over 90% of survey respondents who were previously unaware of the Project stated that they would now use it.[1]

Although the proportion of general waste, liquid cytotoxics and Schedule 8 medicines was low, sharps were found in approximately 11% of RUM bins. This suggests that education of pharmacists and pharmacy staff about the correct disposal of sharps could be improved.

Conclusion

It is everyone's responsibility to reduce medicine waste and to be aware of which regular and 'if required' medicines are needed at the time of prescribing and dispensing. Education is critical to ensure that practices to minimise wastage are implemented. Prescription quantities need to be balanced with access, adherence and overall cost. However, despite our best efforts to minimise medicine waste, it will occur. The RUM Project is therefore a vital public service that provides a safe, easy and free way for consumers to dispose of unwanted medicines and it should be promoted by all health professionals. ◀

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ARTICLE

Observational studies and their utility for practice

Julia FM Gilmartin-Thomas
NHMRC-ARC* Dementia research development fellow[1]

Honorary senior research associate[2]

Danny Liew
Professor of Clinical Outcomes Research and Co-Director of the Centre of Cardiovascular Research and Education in Therapeutics[1]

Ingrid Hopper
NHMRC Early career fellow and Head of Drug and Device Registries[1]

[1] Department of Epidemiology and Preventive Medicine School of Public Health and Preventive Medicine Monash University Melbourne

[2] Research Department of Practice and Policy University College London School of Pharmacy London

* National Health and Medical Research Council – Australian Research Council

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SUMMARY

Randomised controlled clinical trials are the best source of evidence for assessing the efficacy of drugs. Observational studies provide critical descriptive data and information on long-term efficacy and safety that clinical trials cannot provide, at generally much less expense.

Observational studies include case reports and case series, ecological studies, cross-sectional studies, case-control studies and cohort studies. New and ongoing developments in data and analytical technology, such as data linkage and propensity score matching, offer a promising future for observational studies. However, no study design or statistical method can account for confounders and bias in the way that randomised controlled trials can.

Clinical registries are gaining importance as a method to monitor and improve the quality of care in Australia. Although registries are a form of cohort study, clinical trials can be incorporated into them to exploit the routine follow-up of patients to capture relevant outcomes.

Introduction

Observational studies involve the study of participants without any forced change to their circumstances, that is, without any intervention.[1] Although the participants' behaviour may change under observation, the intent of observational studies is to investigate the 'natural' state of risk factors, diseases or outcomes. For drug therapy, a group of people taking the drug can be compared to people not taking the drug.

The main types of observational studies used in health research, their purpose and main strengths and limitations are shown in the Table.[2-8] Their purpose may be descriptive, analytical or both.

- Descriptive studies are primarily designed to describe the characteristics of a studied population.
- Analytical studies seek to address cause-and-effect questions.

Case reports and case series

Case reports and case series are strictly speaking not studies. However, they serve a useful role in describing new or notable events in detail. These events often warrant further formal investigation. Examples include reports of unexpected benefits or adverse events, such as a case report describing the use of high-dose quetiapine in treatment-resistant schizophrenia after intolerance to clozapine developed[9] and a case report of a medication error involving lookalike packaging.[10]

Ecological studies

Ecological studies are based on analysis of aggregated data at group levels (for example populations), and do not involve data on individuals. These data can be analysed descriptively, but not definitively for causation. Typical examples include studies that examine patterns of drug use over time. One example is the comparison of the use of non-steroidal anti-inflammatory drugs and COX-2 inhibitors in Australia and Canada.[11] Sometimes ecological studies describe associations between drugs and outcomes, such as changes in the rates of upper gastrointestinal haemorrhage after the introduction of COX-2 inhibitors.[12] However, because individual-level data are not presented, causality is at best only implied in ecological studies. The 'ecological fallacy' refers to the error of assuming that associations observed in ecological studies are causal when they are not.

Cross-sectional studies

Cross-sectional studies collect data at a single point in time for each single individual, but the actual data collection may take place over a period of time or on more than one occasion. There is no longitudinal follow-up of individuals. Cross-sectional studies represent the archetypal descriptive study.[1] Typically, they provide a profile of a population of interest, which may be broad, like the Australian Health Survey undertaken intermittently by the Australian Bureau of Statistics,[13] or focused on specific populations, such as older Australians.[14]

Table **Summary of observational studies used in health research**

Study type	Purpose	Strengths	Limitations
Case reports and case series	Descriptive Usually first report of a notable issue[2,3]	Easy to undertake Can provide detailed information to assist hypothesis generation	Not generalisible
Ecological studies	Descriptive Data at group/population level[4]	Relatively easy to undertake Routinely collected data can be used	No data on individuals
Cross-sectional studies	Descriptive Profiling of a population or outcome of interest at a single time point[5]	Relatively easy to undertake	Need for representative data
Case-control studies	Analytical Identify risk factors for a defined outcome (disease or condition)[5,6]	Can be used to explore rare outcomes	Limited to a single outcome
Cohort studies	Descriptive and analytical Estimate the incidence of outcomes of interest as well as their determinants[5,7,8]	Longitudinal Can be used to study multiple outcomes and multiple risk factors	Relatively difficult and expensive

Case-control studies

Case-control studies focus on determining risk factors for an outcome of interest (such as a disease or a drug's adverse effect) that has already occurred.[5]

First, two groups of participants are assembled:

- those who already have the outcome (cases)
- those who do not have the outcome (controls), who are often matched to the cases to make them similar and reduce bias.

Second, data on previous exposure to selected risk factors are collected and compared to see if these risk factors are more (or less) common among cases versus controls. Case-control studies are useful for studying the risk factors of rare outcomes, as there is no need to wait for these to occur. Multiple risk factors can be studied, but each case-control study can involve only one outcome.[5] One example explored the relationship between the use of antiplatelet and anticoagulant drugs (risk factor) and the risk of hospitalisation for bleeding (outcome) in older people with a history of stroke.[15] Another case-control study explored the risk factors for the development of flucloxacillin-associated jaundice (outcome).[16]

Cohort studies

Cohort studies compare outcomes between or among subgroups of participants defined on the basis of whether or not they are exposed to a particular risk or protective factor (defined as an exposure). They provide information on how these exposures are associated with changes in the risk of particular downstream outcomes. Compared to case-control studies, cohort studies take individuals with exposures and look for outcomes, rather than taking those with outcomes and looking for exposures. Cohort studies are longitudinal, that is they involve follow-up of a cohort of participants over time. This follow-up can be prospective or retrospective. Retrospective cohort studies are those for which follow-up has already occurred. They are typically used to estimate the incidence of outcomes of interest, including the adverse effects of drugs.

Cohort studies provide a higher level of evidence of causality than case-control studies because temporality (the explicit time relationship between exposures and outcomes) is preserved. They also have the advantage of not being limited to a single outcome of interest. Their main disadvantage, compared to case-control studies, has been that longitudinal data are more expensive and time-consuming to collect. However, with the availability of electronic data, it has become easier to collect longitudinal data.

One prospective cohort study explored the relationship between the continuous use of antipsychotic drugs (exposure) and mortality (outcome) and hospitalisation (outcome) in older people.[17] In another older cohort, a retrospective study was used to explore the relationship between long-term treatment adherence (exposure) and hospital readmission (outcome).[18]

Observational studies versus randomised controlled trials

Compared to randomised controlled trials, observational studies are relatively quick, inexpensive and easy to undertake. Observational studies can be much larger than randomised controlled trials so they can explore a rare outcome. They can be

undertaken when a randomised controlled trial would be unethical. However, observational studies cannot control for bias and confounding to the extent that clinical trials can. Randomisation in clinical trials remains the best way to control for confounding by ensuring that potential confounders (such as age, sex and comorbidities) are evenly matched between the groups being compared. In observational studies, adjustment for potential confounders can be undertaken, but only for a limited number of confounders, and only those that are known. Randomisation in clinical trials also minimises selection bias, while blinding (masking) controls for information bias. Hence, for questions regarding drug efficacy, randomised controlled trials provide the most robust evidence.

New and upcoming developments

New methods of analysis and advances in technology are changing the way observational studies are performed.

Clinical registries

Clinical registries are essentially cohort studies, and are gaining importance as a method to monitor and improve the quality of care.[19] These registries systematically collect a uniform longitudinal dataset to evaluate specific outcomes for a population that is identified by a specific disease, condition or exposure. This allows for the identification of variations in clinical practice[20] and benchmarking across practitioners or institutions. These data can then be used to develop initiatives to improve evidence-based care and patient outcomes.[21]

An example of a clinical registry in Australia is the Australian Rheumatology Association Database,[22] which collects data on the biologic disease-modifying antirheumatic drugs used for inflammatory arthritis. Clinical data from treating specialists are combined with patient-reported quality of life data and linked to national databases such as Medicare and the National Death Index. This registry has provided insight into the safety and efficacy of drugs and their effect on quality of life. It was used by the Pharmaceutical Benefits Advisory Committee to assess cost-effectiveness of these drugs.[23]

Another example is the Haemostasis Registry. It was used to determine the thromboembolic adverse effects of off-label use of recombinant factor VII.[24]

Clinical registries can also be used to undertake clinical trials which are nested within the registry architecture. Patients within a registry are randomised to interventions and comparators of interest. Their outcome data are then collected as part of the routine operation of the registry. The key advantages are convenience, reduced costs and greater representativeness of registry populations as opposed to those of traditional clinical trials.

One of the first registry-based trials was nested within the SWEDEHEART registry.[25] This prospectively examined manual aspiration of thrombus at the time of percutaneous coronary intervention in over 7000 patients.[26] The primary endpoint of all-cause mortality was ascertained through linkage to another Swedish registry. The cost of the trial was estimated to be US$400 000, which was a fraction of the many millions that a randomised controlled trial would have cost.

Propensity score matching

Even without randomising people within cohorts, methods have emerged in recent years that allow for less biased comparisons of two or more subgroups. Propensity score matching is a way to assemble two or more groups for comparison so that they appear like they had been randomised to an intervention or a comparator.[27] In short, the method involves logistic regression analyses to determine the likelihood (propensity) of each person within a cohort being on the intervention, and then matching people who were on the intervention to those who were not on the basis of propensity scores. Outcomes are then compared between the groups. Propensity score analysis of a large cohort of patients with relapsing remitting multiple sclerosis found that natalizumab was superior to interferon beta and glatiramer acetate in terms of improved outcomes.[28]

Data technology

Increasing sophistication in techniques for data collection will lead to ongoing improvements in the capacity to undertake observational studies (and also clinical trials). Data linkage already offers a convenient way to capture outcomes, including retrospectively. However, ethical considerations must be taken into account, such as the possibility that informed consent might be required before linking data. Machine learning will soon allow for easy analyses of unstructured text (such as free text entries in an electronic prescription).[29] Patient-reported outcome measures are important and in future will be greatly facilitated by standardised, secure hardware and software platforms that allow for their capture, processing and analyses.

Conclusion

While clinical trials remain the best source of evidence regarding the efficacy of drugs, observational studies provide critical descriptive data. Observational studies

ARTICLE

can also provide information on long-term efficacy and safety that is usually lacking in clinical trials. New and ongoing developments in data and analytical technology offer a promising future for observational studies in pharmaceutical research. ≺

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Q:

SELF-TEST QUESTIONS

True or false?

3. Cohort studies cannot be retrospective.

4. Patients in clinical registries cannot be randomised to receive or not receive an intervention.

Answers on page 95

ARTICLE

Prescribing wellness: comprehensive pain management outside specialist services

Simon Holliday
Staff specialist[1]
General practitioner[2]

Chris Hayes
Specialist pain medicine physician[3]

Lester Jones
Pain educator and PhD candidate[4]

Jill Gordon
Associate professor in medical education (retired)[5]
General practitioner[6]

Newman Harris
Consultant psychiatrist and Specialist pain medicine physician[7]
Clinical senior lecturer[8]

Michael Nicholas
Clinical psychologist[7]
Professor and Director, Pain Education Unit[8]

[1] Drug and Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, NSW
[2] Albert St Medical Centre Taree, NSW
[3] Hunter Integrated Pain Service, John Hunter Hospital, Newcastle, NSW
[4] Discipline of Physiotherapy, Judith Lumley Centre, La Trobe University, Melbourne
[5] University of Sydney
[6] Lindfield, NSW
[7] Royal North Shore Hospital, Sydney
[8] Pain Management Research Institute, Northern Clinical School, University of Sydney

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SUMMARY

Opioids have important roles in the time-limited treatment of acute and cancer pain, end-of-life pain or dyspnoea, and in opioid dependency.

Maintaining focus on biomedical treatments, including drugs, has limited success in chronic pain.

Active self-management and healthy lifestyle choices are fundamental to addressing multisystem complexity and harnessing neuroplasticity in chronic pain.

Addressing psychosocial maladaptations and physical deconditioning requires a variety of approaches, frequently involving multiple care providers.

In practice, most pain care is delivered outside specialist centres by GPs and other non-pain specialists. Although they are well placed to provide multimodal care, they often lack training and confidence in delivering this care.

Introduction

Codeine rescheduling in February 2018 prevented consumers accessing over-the-counter opioids without a prescription.[1] This presents a major challenge because of the number of patients involved – over 15 million packs of over-the-counter opioid analgesics were purchased in Australia in 2013, accounting for 36.6% of total opioid pack sales.[2]

Chronic pain is defined as pain lasting beyond the time of tissue healing or for over three months.[3] Almost half of GP consultations involve some discussion of pain, usually relegated behind comorbidities such as obesity and diabetes or psychiatric and substance-use disorders.[4,5] Chronic pain challenges classic models of diagnosis and treatment.

Trials indicate that the best care for chronic pain involves self-management by the patient and a multidisciplinary approach through a pain centre rather than GP 'treatment as usual'.[6-9] However, a large US outpatient study found that only 0.12% of chronic pain consultations involved pain specialists.[10] While less expensive, GP care does not become cost effective until it addresses physical disability alongside pain-related thoughts, emotions and behaviours.[11] However, GPs have the advantage of capacity, accessibility (geographical and financial) and the potential to provide longitudinal, holistic and opportunistic care.[7] For this reason, it is important GPs do not feel that treating chronic pain simply requires a choice between prescribing opioids or referring to specialist care.

Multimodal, multidisciplinary chronic pain care can be translated into time-poor primary care settings. Practice policies, holistic assessment then drug and non-drug approaches need to be explored.

Practice policies

A proactive pain management approach that begins at the reception desk can encourage optimum care. Suitable practice policies include refusing phone scripts, ensuring continuity of care with one doctor, displaying a sign about the opioid policy, and using Medicare items that support complex and collaborative care.

Ongoing holistic assessment

Even in acute pain, standard care is enhanced by a broad, 'whole person' assessment. The psychosocial dimension includes assessment of mood, cognitions, trauma, suicide risk and the social context of the presenting problems (e.g. workers' compensation, family issues). Additional components incorporate physical activity, sleep patterns, nutrition, and past or current use of addictive substances including prescription drugs. Practice nurses can play a role in implementing time-efficient assessments of chronic pain.

Practical steps for assessment include:

- Regular use of validated brief outcome tools. Just asking patients how bad their pain is out of 10 is simplistic in chronic pain and tends to elicit default opioid prescriptions.[12] The three-item PEG scale allows a broader and readily repeatable assessment and only requires a few extra seconds.[13]
- Assessing cognitive aspects. Identify psychosocial risks early using a tool such as the ten-item Örebro Musculoskeletal Pain Screening Questionnaire.[14] Ask what the patient is concerned about or fears the most regarding their pain. This will guide targeted reassurance.[15]
- Assessing physical activity. Use the Five Times Sit to Stand Test (taking over 15 seconds correlates with an increased risk of falls).[16] The patient should be encouraged to do the best they can without significantly flaring their pain.

Why opioids are no longer first line

Guidelines for using opioids to treat pain have changed markedly, with prescription now being recommended only for acute pain, active cancer pain or palliative care. There is evidence to support long-term opioids as substitution therapy to minimise harm from dependency in opioid use disorders.

Prescribing opioids for over a week for acute pain doubles the risk of long-term use at one year (6% to 13%) and this risk doubles again (to 29.9%) if the initial prescription lasts a month.[17] Dispensing in Australia increased 15-fold between 1992 and 2012, predominantly reflecting long-term opioid provision for chronic pain.[18]

The absence of long-term efficacy data has finally been addressed in a landmark randomised controlled trial of long-term opioids compared to non-opioid medicines for chronic musculoskeletal pain. During a year of collaborative care, the initiation of opioids failed to improve function, but caused more adverse effects and marginally worse pain intensity.[19]

Adverse effects include opioid-induced hyperalgesia and tolerance which cause a perceived increase in pain and need for dose escalation. Recent animal and human studies indicate that opioids may actually contribute directly to chronic pain. This toxicity may commence after brief exposure and leave a vulnerability to increased pain responses that may be of indefinite duration.[20] Other long-term opioid toxicities include depression, sleep interference, hypogonadism, prolonged disability and delayed return to work.[21-23]

Suggested strategies to mitigate the risk of addiction (i.e. universal precautions) resemble an assortment of opioid substitution therapy approaches. However, these strategies fail to reliably predict or identify abusers or mitigate risks,[3,6] and are rarely implemented by GPs.[24] When initiated with dose reduction, risk mitigation strategies do not worsen pain control or quality of life.[25]

Tapering or stopping opioids

In general, introducing multimodal chronic pain care will facilitate opioid tapering or cessation and so improve pain outcomes and lower opioid-related risks both to patients and, when diverted, to their social network.[26] GPs need to first estimate total opioid dose in morphine equivalents using conversion tables.[27] Starting at a lower equivalent dose when rotating or simplifying regimens will reduce the risk of overdose. The deprescribing process may prove challenging – gradual weaning may be derailed by an abstinence syndrome involving insomnia, emotional blunting, deficits in executive control and the exacerbation or re-emergence of comorbid psychiatric disorders.[28] If an attempt at deprescribing has been unsuccessful, it may be wise to plan a slower taper or consider opioid substitution therapy.

It is unwise to assume that new patients already taking opioids have a continuing need for opioid prescription. Difficult conversations may follow as doctors explain why opioids are no longer recommended for chronic pain. The requirement to comply with relevant state or territory regulations is protective in this setting.[29] In some cases, providing limited dispensing and 'methadone-style' supervision may help to minimise harms such as abuse or overdose. It is important to consider safety strategies such as take-home naloxone for patients and families,[30] fentanyl patch exchanges[6] and the avoidance of benzodiazepine co-prescription.[3,6]

Non-opioid medicines

Patients consider meaningful chronic pain relief equates to at least 50% reduction in pain intensity. A systematic review found medicines, opioids or otherwise, do not achieve this for most patients.[31] This finding was endorsed recently by a Canadian review of the limited evidence for non-opioid analgesics which included non-steroidal anti-inflammatory drugs, antidepressants and antiepileptics such as pregabalin and gabapentin.[6]

As well as practising evidence-based medicine, doctors should identify and stop harmful or ineffective therapies. Regular pain reviews facilitate the early deprescribing of ineffective medicines.[31]

More effective approaches

Recent concepts of pain look past any nociceptive (damaged tissue) or neuropathic (damaged nerve) contributors, to the role of brain interpretation, central sensitisation, descending modulation and immune and endocrine activation.[32-34] The interpretation of pain by the brain involves encoding of signals from multiple sources and is more likely to occur when the person perceives a threat or danger. The pain experience is dampened or amplified by the dopamine (reward) system and the limbic system (emotions, motivations, learning and memory). Current theorists conceptualise pain as a warning system that consciously or unconsciously selects which behaviours will ensure the survival of the individual or their tribe.[35]

We need to educate patients that, just as their chronic pain is not a simple readout of the severity of tissue damage, their pain management must move beyond a narrow sensory focus. Education allows patients to reframe their treatment needs away from solely tissue-focused and passively received interventions. Explaining the neuroscience of pain has actually been shown to improve pain, movement and fear-avoidance,[36] especially when provided with active strategies such as encouraging the patient to gradually resume normal activities in a paced manner and assistance with sleep disturbance.

Ultimately, non-drug interventions have the potential to improve outcomes for chronic pain and comorbidities[4] and tend to be low-tech, low-cost and low-risk. GPs can deliver multimodal care themselves in micro-interventions over multiple consultations.[7,37] They can supplement their patient care with workbook and online programs (see Box) or may collaborate with or refer to allied health providers.

Physical treatment

Establishing safe, consistent patterns of movement can calm nervous system arousal and reduce central sensitisation.[38,39] This can be facilitated by negotiating treatment goals that reflect meaningful and enjoyable activities, not just pain relief. Goals should be achievable and measurable with activities starting well below what the patient can do before gradually building their functional capacity. For example, sit-to-stand exercises can be used as the basis of a simple home-based strength program, starting from a raised seat height to reduce effort. Activity pacing and graded exercise avoids the 'boom then bust' trap and helps reduce pain, fatigue and depression.[4]

Pacing encourages patients to maintain relatively constant daily activity despite their pain levels. This means capping activity at the daily goal when pain is mild and using self-management strategies to increase activity to the daily goal when pain is more severe. Rotating time-limited activities decreases the frequency and often the intensity of pain flare-ups and potential recourse to opioids.[40] Behavioural activation, delivered by clinicians without specialist training, may also improve depression as effectively as formal cognitive behavioural therapy.[41]

Psychological treatments

It is important to explore any cognitive, behavioural and affective factors contributing to pain and suffering. Clinicians can help patients to recognise and modify unhelpful cognitions such as catastrophising, 'black and white' thinking and beliefs that drive fear-avoidance behaviours.[15,42,43] It is critical to identify and treat depression or anxiety.[42] Treatments include encouraging the scheduling of pleasurable activities, relaxation and exercise based on pacing principles. Antidepressants that may have an impact on pain include duloxetine and low-dose amitriptyline. Relaxation strategies, mindfulness, self-awareness and non-judgemental acceptance can help to self-regulate distress in the presence of pain.[42] As well as directly supporting pain self-management, calming the nervous system and mind assists in alleviating insomnia and anxiety.

Patients frequently report using tobacco, cannabis and alcohol as a coping strategy.[22] Despite the perception of short-term relief, these substances retard function by disturbing learning, memory and sleep architecture.[22] For insomnia, first-line management involves cognitive behavioural strategies including sleep or bedtime restriction, avoiding screens before bedtime and other sleep hygiene measures.[44]

Social engagement

People typically feel safe when socially well connected and feel under threat when isolated. Meaningful positive social engagement at work or home is crucial for pain recovery. For example, the pain threshold is elevated when sharing a laugh with friends.[45] Partners may aid recovery by being goal-oriented and by avoiding being unreasonably critical or over-solicitous. When sexual intimacy has been lost, re-establishing it may require an adaptation of activity pacing known as sensate focusing.[46]

Nutrition

As with other chronic metabolic illnesses, obesity is frequently associated with chronic pain.[47] The gut microbial profile or microbiome has been hypothesised to be the nexus between the Western diet and the maladaptations in the nervous, immune and endocrine systems.[48] These may interlink with a low-grade inflammatory state (metaflammation).[34] Simple nutritional interventions for pain encourage consuming five serves of vegetables per day and two of fruit while reducing intake of sugary and processed foods.[34]

Conclusion

Long-term opioid therapy for analgesia is a surrogate for simplistic conceptualisations of pain and leads to inadequate pain management.[7] Effective care includes moving beyond a focus on pain relief and prescribing drugs. To do this, clinicians need to be familiar with the alternatives and become confident in their use so they can help patients to understand the benefits of deprescribing. However, some patients will require opioid substitution therapy.

A medical system that rewards rapid patient throughput, subsidises opioid analgesics, and focuses on 'quick fixes' will never untangle the many strands of suffering contributing to chronic pain. We need to give our patients hope for wellness and some sense of control over their adversity. Opioid deprescribing together with multimodal measures will improve individual and public health, and reduce chronic pain and associated comorbidities.[4,26]

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Box Pain management resources

Clinician resources

Australian Pain Management Association. Pacing activity. Brisbane: APMA; 2015. www.painmanagement.org.au/2014-09-11-13-35-53/2014-09-11-13-36-47/166-pacing.html [cited 2018 Mar 27]

Sleep restriction therapy. San Jose, CA: Kaiser Permanente; 2006. https://thrive.kaiserpermanente.org/care-near-you/northern-california/sanjose/wp-content/uploads/sites/7/2015/10/sleep-restriction-rev2_tcm28-557887.pdf [PDF] [cited 2018 Mar 27]

Pain intensity, Enjoyment of life, General activity (PEG) assessment tool. https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/page/PEG.pdf [PDF] [cited 2018 Mar 27]

[Example of a sign for the waiting room explaining the practice's opioid and benzodiazepine medication policy to patients] https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/page/GP%20Prescribing%20Practice%20Sign.pdf [PDF] [cited 2018 Mar 27]

Training

Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. Better pain management: pain education for professionals. [Twelve brief online education modules] https://www.betterpainmanagement.com [cited 2018 Mar 27]

Pain Management Research Institute, University of Sydney. Webinar skills training in pain management: putting cognitive behavioural therapy skills into practice. [Online, interactive webinars training in CGT skills for pain] http://sydney.edu.au/medicine/pmri/education/continuing/webinar.php [cited 2018 Mar 27]

Non-pharmacological management of chronic pain. Presented by the Black Dog Institute [recorded webinar]. https://medcast.com.au/courses/109 [cited 2018 Mar 27]

Books

Davies S, Cooke N, Sutton J. Rewire your pain: an evidence based approach to reduce chronic pain. Brisbane: Australian Pain Management Association; 2015.

Nicholas M, Molloy A, Tonkin L, Beeston L. Manage your pain: practical and positive ways of adapting to chronic pain. 3rd ed. Sydney: Harper Collins Publishers Australia; 2011.

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Pain Management Network. Sydney: Agency for Clinical Innovation; 2018. www.aci.health.nsw.gov.au/chronic-pain [cited 2018 Mar 27]

painHEALTH. Easing musculoskeletal pain. Perth: painHEALTH; 2017. https://painhealth.csse.uwa.edu.au [cited 2018 Mar 27]

Hunter New England Local Health District. Pain. Newcastle: Hunter Integrated Pain Service; 2016. www.hnehealth.nsw.gov.au/Pain/Pages/Pain.aspx [cited 2018 Mar 27]

Patient online training in cognitive behaviour therapy for pain

https://thiswayup.org.au. This program seeks to reproduce training provided at a multidisciplinary clinic. It costs $59 for eight lessons and participants may access it over a year. Participants need to be referred by a registered clinician who can then receive feedback about their patients' progress.

https://mindspot.org.au/pain-course. This program is free and is accessible without a referral. It provides five mental health self-help lessons over two months with weekly support from a therapist. A YouTube introduction is available.

www.cci.health.wa.gov.au/resources/consumers.cfm. Centre for Clinical Interventions. Consumer resources. Perth: Government of Western Australia Department of Health; 2016.

Brainman brief educational videos

Understanding pain in less than 5 minutes, and what to do about it! 2013 Jan 15. www.youtube.com/watch?v=C_3phB93rvI [cited 2018 Mar 27]

Understanding Pain: Brainman stops his opioids. 2014 Oct 3. www.youtube.com/watch?v=MI1myFQPdCE [cited 2017 Mar 27]

Understanding Pain: Brainman chooses. 2014 Oct 3. www.youtube.com/watch?v=jIwn9rC3rOI [cited 2017 Mar 27]

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NEW DRUGS

New drugs

Aust Prescr 2018;41:92–3
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First published 15 May 2018

Cabozantinib

Approved indication: renal cell carcinoma

Cabometyx (Ipsen)
20, 40 and 60 mg film-coated tablets
Australian Medicines Handbook section 14.2.4

Cabozantinib is a small molecule inhibitor of a number of tyrosine kinases that are thought to be involved in tumour growth and angiogenesis. It is indicated for patients with renal cell carcinoma that has progressed after being treated with a vascular endothelial growth factor receptor inhibitor such as sorafenib,[1] pazopanib[2] or axitinib.[3]

The approval of cabozantinib is based on an open-label phase III trial of 658 pre-treated patients with advanced disease. They were randomised to receive cabozantinib 60 mg or everolimus 10 mg once daily. Median progression-free survival (7.4 vs 3.9 months) and overall survival (21.4 vs 16.5 months) were longer with cabozantinib than with everolimus. The objective response rate (proportion of patients with a partial response) was also higher for cabozantinib (17% vs 3%) (see Table).[4,5]

The median duration of treatment with cabozantinib was 8.3 months. Dose reductions and interruptions were needed in 62% and 12% of patients.[5] Adverse events were very common – the most frequently reported were diarrhoea (74%), fatigue (56%), nausea (50%), anorexia (46%), palmar-plantar erythrodysaesthesia (42%), hypertension (39%), vomiting (32%), weight loss (31%) and constipation (25%). Over two-thirds of patients had a serious adverse event.[5] These included gastrointestinal perforation and fistulas, QT prolongation, haemorrhage and pulmonary embolism. Wound complications can also occur and cabozantinib should be stopped at least four weeks before scheduled surgery.

The recommended dose of cabozantinib is 60 mg once a day. This should be reduced to 40 mg once daily in patients with mild–moderate hepatic impairment. The drug should be used with caution in people with mild–moderate renal impairment and is not recommended for those with severe hepatic or renal impairment.

Patients should be advised not to eat for at least two hours before and one hour after taking cabozantinib. Following an oral dose, peak plasma concentrations are reached within 2–3 hours. The plasma half-life of cabozantinib is 99 hours and the drug and its metabolites are excreted in the faeces (54%) and urine (27%).

Cabozantinib is highly protein bound and there is a theoretical risk that it will displace concomitant warfarin so INR monitoring is recommended.

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 so co-administration of strong inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin) increase and decrease cabozantinib concentrations respectively. Caution is therefore urged and long-term use of inhibitors and inducers should be avoided. Cabozantinib also inhibits P-glycoprotein in vitro and may increase concentrations of co-administered substrates such as dabigatran, digoxin, maraviroc, saxagliptin and tolvaptan.

Cabozantinib offers another option for patients who have relapsed renal cell carcinoma. In the trial, it prolonged overall survival for up to five months longer than everolimus. However, serious adverse effects are very common with cabozantinib and are likely to limit treatment. The drug is also approved overseas for medullary thyroid cancer.

T manufacturer provided the product information

Table **Efficacy of cabozantinib in advanced renal cell carcinoma**

	Cabozantinib 60 mg/day (330 patients)	Everolimus 10 mg/day (328 patients)
Median progression-free survival	7.4 months	3.9 months
Objective response rate (proportion of patients with a partial response)	17%	3%
Median overall survival	21.4 months	16.5 months

Based on reference 5

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

NEW DRUGS

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Sonidegib

Approved indication: basal cell carcinoma

Odomzo (Sun)
200 mg capsules

Basal cell carcinoma is a common skin cancer. Usually it is slow growing and local treatment is effective. Sometimes the cancer becomes locally advanced and can metastasise. Sonidegib can be considered in these cases if patients cannot be managed with surgery or radiotherapy.

The development of basal cell carcinoma is thought to involve the hedgehog gene. Normally this has a role in regulating cell development, however abnormal activation of this signalling pathway can lead to the proliferation of cancer cells. Sonidegib is an antagonist of the hedgehog pathway to inhibit further signalling.

The drug is poorly absorbed and the capsules should be taken on an empty stomach. It takes about four months to reach a steady-state concentration. The concentration of sonidegib is higher in skin than in plasma. Sonidegib is partly metabolised by cytochrome P450 (CYP) 3A4 with most of the drug and its metabolites being excreted in the faeces. Strong inhibitors of CYP3A4, such as itraconazole and ritonavir, should not be given with sonidegib. Co-administration with strong inducers, such as carbamazepine and rifampicin, should also be avoided. No dose adjustment is recommended in hepatic or renal impairment.

The Australian approval of sonidegib appears to have been based mainly on one uncontrolled phase II trial. It randomised 79 patients to take sonidegib 200 mg and 151 to take 800 mg once daily. There were 194 patients with locally advanced disease and 36 with metastases. The Response Criteria In Solid Tumours (RECIST) were used to assess the effect of treatment. After a median follow-up of almost 14 months, 36% of the patients taking 200 mg and 34% of those taking 800 mg had responded. Apart from two patients with complete responses, these were all partial responses.[1]

A longer term analysis of the results (30 months after the last patient was randomised) reported higher response rates. For patients with locally advanced basal cell carcinoma, the response rate was 56.1% with 200 mg and 45.3% with 800 mg. The corresponding figures for metastatic disease were 7.7% and 17.4%.[2]

At the time of the 30-month analysis, 93% of the patients had stopped sonidegib. This was mainly because of adverse events, particularly with the 800 mg dose. The common adverse events were muscle spasm, alopecia, dysgeusia, nausea, decreased appetite and fatigue. Musculoskeletal problems are a class effect of hedgehog inhibitors.

In view of the risk of rhabdomyolysis, creatine kinase concentrations should be checked. The risk is likely to be increased if the patient is also taking a statin. Treatment may need to be stopped if creatine kinase is greatly elevated. Sonidegib is contraindicated in pregnancy and men should use condoms to avoid exposing their partners to the drug. Patients should not donate blood for at least 20 months after stopping sonidegib.

The recommended dose for clinical use is 200 mg daily as 800 mg is not more efficacious and causes more adverse effects. As basal cell carcinoma is slow growing, even after 30 months the median overall survival had not been reached. The estimated survival rate at two years in patients taking 200 mg was 93.2% for advanced disease and 69.3% for those with metastases, but there was no comparison with current managment.[2] Few patients had a complete response which suggests that more than the hedgehog pathway is involved in tumour growth. As some tumours may be resistant to treatment, the optimum use of sonidegib will require further investigation.

T T manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency.

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