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CONTENTS

ARTICLE

Medical management of malignant melanoma

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Key words
dabrafenib, dacarbazine, ipilimumab, melanoma, trametinib, vemurafenib

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SUMMARY

The treatment and outcomes for people with metastatic melanoma have changed considerably in the past few years with the introduction of targeted anticancer drugs.

About half of the patients with metastatic melanoma will have activating mutations in the BRAF gene. These people may benefit from a BRAF inhibitor (vemurafenib or dabrafenib) or a MEK inhibitor (trametinib).

Addition of a MEK inhibitor to a BRAF inhibitor improves progression-free survival and alters the adverse effect profile.

Ipilimumab is another drug indicated for metastatic melanoma. It works by altering the patient's own immune response to the tumour.

Toxicities are common with these drugs and include arthralgias, fatigue, photosensitivity, squamous cell carcinomas, fever, diarrhoea, pruritus and immune-related adverse effects.

Introduction

Metastatic melanoma is the fourth most common cancer diagnosed in Australia and the most common malignancy among 15–24 year-olds.[1,2] Metastatic disease is incurable and results in a significant loss of life – for example, 365 deaths from metastatic melanoma were registered in Queensland in 2010.[1,3]

The most commonly used drugs in melanoma were dacarbazine and fotemustine. These have been trialled extensively and have complete and partial response rates* of around 10%. They do not prolong survival.

Until 2010, there were no significant advances in improving survival for metastatic melanoma – the median overall survival of nine months had not changed in 30 years. However, the introduction of targeted anticancer drugs has substantially altered the treatment and outcomes for patients with melanoma.

Melanoma mutations

Systemic therapy options for metastatic melanoma currently depend on whether the patient's tumour expresses the BRAF mutation. These mutations occur in the mitogen-activated protein (MAP) kinase pathway (see Fig.). Acquired BRAF mutations lead to the expression of an abnormal protein kinase that mediates continuous cell growth and malignant transformation.

BRAF mutations were found to be frequent in melanoma in 2002.[4] About 40–60% of patients have an activating BRAF mutation in their metastatic

* A complete response is defined as the disappearance of all lesions on imaging, and a partial response is defined as a 30% reduction in the size of target lesions.

From the Editor

Many new drugs, including those Victoria Atkinson reviews in the article on medical management of malignant melanoma, are expensive. While there is an expectation that money will be found to fund new therapies, millions of dollars are being wasted. Phillip Bergen and colleagues have found that Australians return more than 600 tonnes of unwanted medicines every year.

Antibiotics are among the most commonly discarded drugs. This could contribute to increased antibiotic resistance. Brendan McMullan and Mona Mostaghim also warn against unfettered prescribing of azithromycin because of the risk of macrolide resistance.

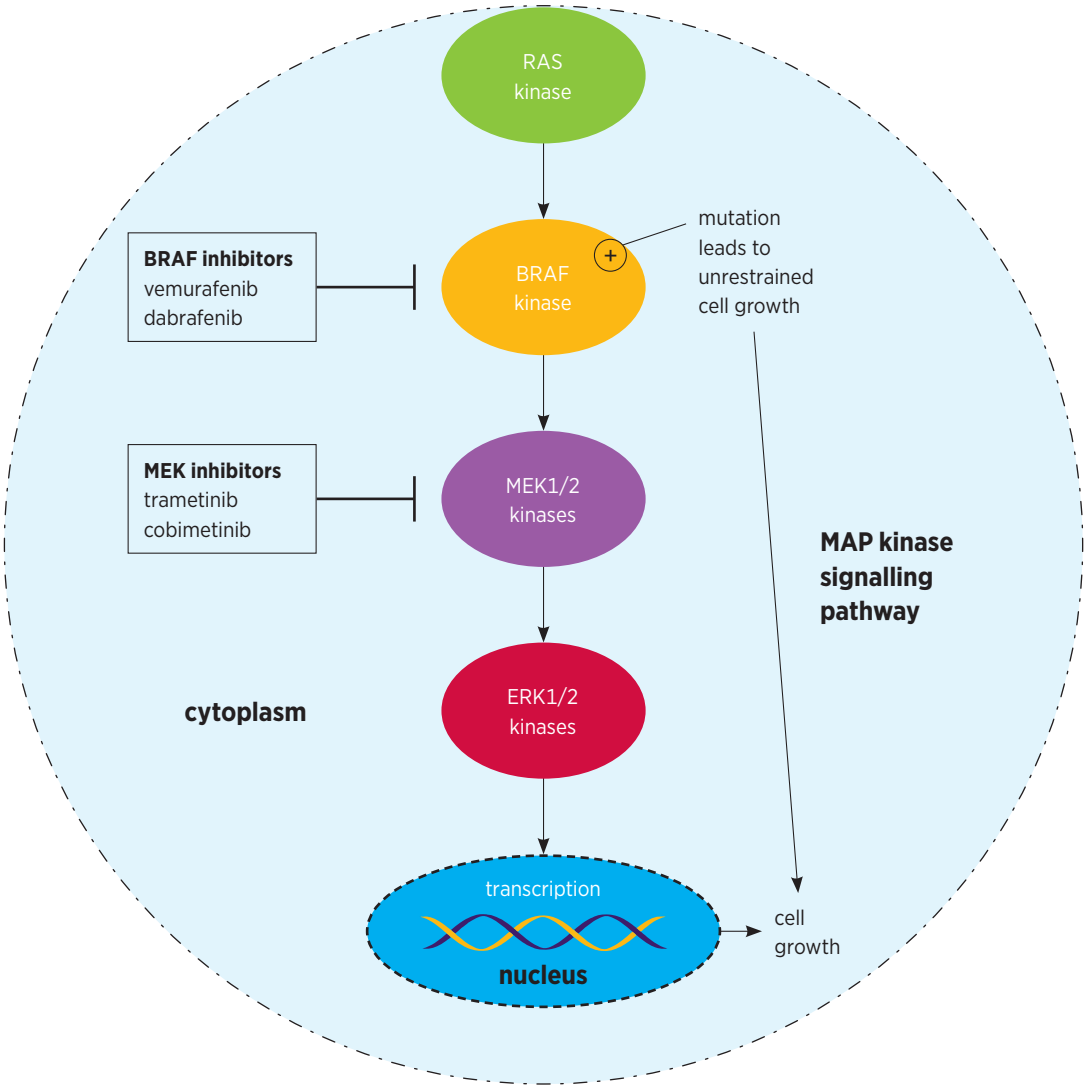
Another drug that requires careful prescribing is quetiapine. Jonathan Brett says the concerns about quetiapine are mainly due to its off-label use. Greta Palmer tells us there is also a lack of evidence for many of the drugs used to treat complex regional pain syndrome.

While the diagnosis of complex regional pain syndrome is clinical, laboratory tests may be needed to exclude other conditions. These could include investigation of inflammation. Michael Harrison discusses the role of measurements of erythrocyte sedimentation rate and C-reactive protein.

The role of oxygen as a drug is reviewed by Janine Pilcher and Richard Beasley. They call for a major change in the acute use of oxygen therapy.

Many other drugs have a role in acute medical conditions. The Editorial Executive Committee hopes the new Australian Prescriber mobile phone app will support health professionals when they are determining the dose of the emergency drugs supplied through the Pharmaceutical Benefits Scheme.

Fig. **Action of BRAF and MEK inhibitors in the MAP kinase signalling pathway**



melanoma cells.[5] The most common mutation is V600E, then V600K.[6] There are less common mutations including R and D.

Other cellular mutations can be tested for, but are still being investigated in clinical trials. These include NRAS and c-kit mutations. Tumours that do not harbour a BRAF or NRAS mutation are called BRAF wild type.

BRAF inhibitors

Drugs that block the abnormal BRAF protein kinase aim to slow the growth of melanoma cells (see Fig.).

Vemurafenib [7]

The first published report of BRAF inhibitors in metastatic melanoma was in 2010.[5] This phase I dose escalation study looked at vemurafenib in patients with V600E-mutated melanoma. With treatment, 81% of patients had a complete or partial response.

A phase III trial reported in 2011 compared vemurafenib to dacarbazine in 675 randomised patients. Vemurafenib improved both overall and progression-free survival, with an improvement in median survival from 9 to 13.6 months.[8] A phase II trial in 2012 in patients who had had one previous therapy confirmed the survival benefit. The median overall response rate (complete and partial response) was 53% and median overall survival was 16 months.[9]

Vemurafenib is well tolerated, with the most common adverse events being arthralgias, fatigue and photosensitivity. Keratoacanthoma or squamous cell carcinomas developed in 18% of patients. These were usually managed with simple excision.[8]

In early 2012, patients were accessing therapy through compassionate access schemes or clinical trials. Vemurafenib was only approved by the Therapeutic Goods Administration (TGA) in May 2012, but is not

currently reimbursed on the Pharmaceutical Benefits Scheme (PBS).

Dabrafenib [10]

Phase II and III trials of dabrafenib in patients with V600E and V600K-mutated metastatic melanoma found similar results to the trials with vemurafenib.[11,12] The response rate to treatment was 50% and median overall survival improved from 9 to 18 months. The adverse effect profile was similar to vemurafenib apart from an increased incidence of fever, and less photosensitivity.

Dabrafenib was listed on the PBS for selected patients in December 2013 and is currently the only reimbursed BRAF inhibitor in Australia.

MEK inhibitors

MEK1 and MEK2 are enzymes downstream of BRAF in the MAP kinase pathway (see Fig.). In preclinical models, adding a MEK inhibitor to a BRAF inhibitor reduced some resistance to BRAF inhibition.

Trametinib

Trametinib is the first MEK inhibitor to be approved in Australia. It has been shown to improve response rates and progression-free survival compared to chemotherapy.[13] However, the benefits were not of the same magnitude as those of BRAF inhibitors.

A phase III randomised trial of dabrafenib and trametinib versus dabrafenib found improved progression-free survival and response rates for the combination arm (see Table 1).[14] Adding trametinib to dabrafenib reduces the incidence of cutaneous squamous cell carcinomas.[13] These appear because unopposed BRAF inhibition causes paradoxical activation of the MAP kinase pathway.[15]

Dabrafenib combined with trametinib has also been compared to vemurafenib. Improved overall survival has been observed with combination therapy (see Table 1).[16]

These findings establish that combination therapy is a new standard of care for BRAF mutation-positive metastatic melanoma. Combination therapy with dabrafenib and trametinib was approved by the TGA in March 2014. Trametinib is currently being accessed through a compassionate access program from the supplier.

Adding trametinib does however increase the risk of dabrafenib-induced fever. This is manageable and may require low-dose corticosteroids or dose reduction.

Cobimetinib

Cobimetinib is another MEK inhibitor tested in phase III trials. The superiority of combination therapy was confirmed in a phase III trial of vemurafenib and cobimetinib versus vemurafenib (see Table 1).[17]

Immunotherapy

Given that only about half of people with metastatic melanoma express the BRAF mutation, other treatment options are needed. Immunotherapies have been shown to improve overall survival for patients with metastatic melanoma. They aim to modulate the patient's own immune response to the tumour cells.

Ipilimumab

Targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has been trialled as an anticancer strategy.[18] It is present on immune cells and is a negative regulator of T cells. Blocking the interaction of CTLA-4 on antigen-presenting cells with cytotoxic T cells leads to ongoing proliferation of T cells, with the hope that these will then target and destroy the melanoma cells.

Ipilimumab is a fully humanised monoclonal antibody that blocks CTLA-4. A phase III trial compared a melanoma vaccine plus ipilimumab (3 mg/kg) to ipilimumab alone and vaccine alone. Median overall survival for both of the ipilimumab arms was around 10 months compared with 6.4 months in the vaccine arm.[19] It must be noted that the median overall survival of 6.4 months in the vaccine arm was shorter than the expected median survival of untreated patients with metastatic melanoma.

Table 1 **Phase III trials of combination BRAF and MEK inhibitors for melanoma**

Trial	**Study arms** (patients)	Objective response rate	Median progression-free survival
COMBI-D[14]	dabrafenib + placebo (n=212)	51%	8.8 months
	dabrafenib + trametinib (n=212)	67%	9.3 months
COMBI-V[16]	dabrafenib + trametinib (n=352)	64%	11.4 months
	vemurafenib (n=352)	51%	7.3 months
Co-BRIM[17]	vemurafenib + placebo (n=248)	45%	6.2 months
	vemurafenib + cobimetinib (n=247)	68%	9.9 months

Another phase III trial compared a higher dose of ipilimumab (10 mg/kg) combined with dacarbazine, to dacarbazine alone. Median overall survival improved from 9 months in the dacarbazine arm to 11 months when ipilimumab was added. There were no treatment-related deaths in this trial, but elevated liver enzymes were more common with ipilimumab.[20] It is not certain whether this is related to the higher dose of ipilimumab or the addition of dacarbazine.

Objective response rates to ipilimumab were only 10.9%[19] and 15.2%[20] in the phase III trials. However, in the second trial the patients in the ipilimumab arm had a 20.8% chance of being alive at three years compared with 12.2% in the dacarbazine arm.[20] A trial comparing ipilimumab 3 mg/kg and 10 mg/kg has been completed and should be reported this year.

The mechanism of action of ipilimumab leads to unrestrained T cell activation and accounts for the serious (grade 3–4) immune-related adverse events observed in 10–15% patients. The most common events were diarrhoea (27–31%), pruritus (17–24%) and other endocrine insufficiency disorders. Of the deaths in this study, 2.1% were thought to be due to the study drug.[19] Adverse events with ipilimumab can be managed with the appropriate treatment algorithms in clinical practice.

Ipilimumab 3 mg/kg was listed on the PBS for unresectable stage 3C and stage 4 melanoma in August 2013.

Other immunotherapies

Studies of ipilimumab have shown that the immune system can be manipulated to improve survival in melanoma. Antibodies to other molecules such as programmed death 1 (PD-1) and programmed death ligand (PD-L1) are also being developed and have shown promising phase I results.

Programmed death ligand is a key inhibitory receptor expressed by activated T and B cells. When this receptor binds to tumours that express PD-L1 this leads to T cell downregulation[21] or 'exhaustion'. PD-1 antibodies interfere with this interaction, allowing for ongoing activation of the activated T cells.

Comparative phase III trials of PD-1 antibody (e.g. nivolumab and MK3475) alone or in combination with other therapies are underway. Recruitment to both of these trials was completed in early 2014.

Nivolumab was recently compared to dacarbazine in BRAF wild-type metastatic melanoma (see Table 2). Trials found a significant improvement in response rates and progression-free survival in the nivolumab arm, with fewer adverse events than dacarbazine.[22,23] The most common adverse event with nivolumab was pruritus.

MK3475 and nivolumab are currently available for limited compassionate access use in Australia for patients who meet the eligibility criteria. Patients are encouraged to discuss whether they are eligible with their oncologist.

Conclusion

The landscape for metastatic melanoma has changed significantly in the last few years with novel drugs that have been shown to prevent progression and improve overall survival. This has reinvigorated research efforts on new targets for drug development and offers hope for further improvement for patients with metastatic melanoma. ◁

The author has received travel grants from Roche and Bristol-Myers Squibb, and is on advisory boards for Roche, Bristol-Myers Squibb and MSD.

Table 2 **Phase III trials of nivolumab for melanoma**

Trial	**Study arms** (patients)	**Overall response rate**	**Median progression-free survival**
CheckMate066 (treatment naïve)[22]	nivolumab (n=210)	40%	5.1 months
	dacarbazine (n=208)	13.9%	2.2 months
CheckMate037 (progression after previous therapy)[23]	nivolumab (n=268)	32%	5.3 months
	chemotherapy (n=102)	11%	2 months

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FURTHER READING

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Letters to the Editor

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Pharmaceuticals, pharmacists and profits

I am writing in response to the editorials on Pharmaceuticals, pharmacists and profits (Aust Prescr 2014;37:146-7 and 148-9). I enjoyed reading the Pharmacy Guild's perspective on troubles facing the industry. However, the editorial failed to mention the financial troubles facing community pharmacists who are not pharmacy owners.

Few people, including those studying to become pharmacists, are aware that the award rate for a full-time pharmacist in charge is $27.16/hour (equivalent to $53 674 annual salary).[1] Note that pharmacist interns, pharmacists and experienced pharmacists are all paid less than this. To compare, an unqualified experienced retail employee may earn up to $44 787.[2] Pharmacists' wages are significantly below the average Australian wage of $76 804 before tax.[3]

From this wage, a pharmacist must pay to be registered for insurance and course fees for 40 hours of continuing professional development per year. Debt from university fees must also be paid. There is a current oversupply of pharmacists, and jobs for salaried pharmacists are not easy to obtain.

I understand that some pharmacies are currently experiencing a period of hardship. But should salaried pharmacists be the ones to subsidise the industry by being forced to accept these low rates of pay?

Michelle Edwards
Pharmacist
Narrabeen

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Conflict of interest in medical journals

I would like to thank John Dowden for summarising this important issue so well in his editorial (Aust Prescr 2015;38:2-3). Simply reporting a conflict of interest is pointless because it does not seem to change the interpretation or impact of the information presented. Clinical practice is largely determined by opinion leaders. With respect to publishing restrictions, this is the group we need to target, particularly because of their financial conflicts which are the most concerning.

These people write the most influential literature such as reviews, editorials, meta-analyses, guidelines and position statements. A contemporary example is the literature around the efficacy of stroke thrombolysis, which has polarised clinicians worldwide. This controversy is complicated by the fact that virtually all the interpretative literature supporting the therapy has been written by people with financial conflicts.

What we need is a policy that prohibits the involvement of authors with financial conflicts in these interpretative types of articles. This is achievable, and in the long run will discourage clinicians from accepting money from industry for fear of limiting their academic careers.

Chris Johnstone
Director, Emergency Medicine
Caboolture Hospital, Qld

Yes, readers are informed when a conflict of interest is declared. But no reader knows how to adjust the take-home messages from such articles to compensate for possible bias.[1] Declaring a conflict of interest shifts the responsibility of dealing with potential bias from the writer, through the editor, to the reader. Is this fair?

The author asks how hard will it be to find non-conflicted authors in Australia. Do we need someone who has done the primary research when any cardiologist with information-literacy skills could evaluate new antihypertensive drugs? In the age of evidence-based medicine, writing these articles is mostly literature reviewing. For opinion-based parts of an article, why is the opinion of someone less deeply involved less valuable than one likely to be influenced inappropriately?

You don't need to refuse to deal with people with a conflict of interest. Could you get a non-conflicted author to write the article, then ask your conflicted reviewer to edit it and give the final say to the writer? Or you could get the conflicted author to write the complicated physiology part, and another author to write the diagnostic or therapeutic sections?

No, we shouldn't be concerned about authors funded by the National Health and Medical Research Council (NHMRC) because the aim of NHMRC aligns with doctors' duty of care to their patients. In contrast, profit-seeking drug makers' primary obligations are to their shareholders. If those don't align with patients' interests we have a problem.

Lastly, is *Australian Prescriber* complicit if doctors are flouting the medical board requirement to not accept gifts of more than trivial value,[2] when authors report funding from drug makers for conference attendances?

Peter Grant
Retired health professional

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We read a very good editorial on conflict of interest by John Dowden, but we find that it deserves comment. We think that all authors who submit a manuscript of any type should disclose their financial and personal relationships that might bias or be perceived to bias an article's content. Therefore, when the editor of a journal writes an editorial, he also should report the conflict of interest, like some used to do.[1] The editorial board should vote to approve the editorial without participation of the editor.

However, if an editorial focuses on therapeutics, other treatments or potential advice for medical practice, the editorial should be reviewed by external referees who report no conflict of interest. This is in addition to the author declaring any conflict of interests.[2] Thus, when the editor is the author, they should also disclose their conflict of interest, as all other authors,[3] for editorials that will be published in the journal.

Editors should not publish other types of articles such as research or review papers in their own

LETTERS

journal. Perhaps the editor may publish information related to the journal or historic articles in the journal, provided it is peer-reviewed. However, the situation of editing and publishing in small and developing countries often makes the peer-review process difficult due to various restraints. Fortunately, Australia is not this type of country.

Liljana Sokolova
Hygiene specialist
Institute of Public Health
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Rajko Igić
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John Stroger Hospital of Cook County
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Rajko Igić accepted travel and local living expenses while Editor-in-Chief of the Scripta Medica, Banja Luka (2010 to 2013).

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While I believe that we should be on guard against the promotional activities of the drug companies, I often wonder if we might be throwing the baby out with the bathwater. I do believe that many of the past developments in health care have been assisted by close association with the providers of our therapeutic armamentarium. Examples include the early association with a good apothecary, the development of the syringe, right up to Ian Frazer and the human papillomavirus vaccine, and Fiona Woods and spray-on skin.

The practice of denying all access to industry is rather akin to the army introducing a new assault rifle without talking to the soldiers about their requirements or gaining feedback on its problems after its introduction. It has been suggested that generic manufacturers have added fuel to this discussion as they do not develop new drugs or technologies and therefore have no need to educate the users or hear their feedback.

What John Dowden and others, who may occasionally suckle at the government teat, consistently fail to mention is how devastating it would be to their career or their position on a government panel if they were to spout a line of doctrine that was diametrically opposed to the government or their academic institution. I have never seen mention of this in any article. Surely the loss of income from not towing the line is just as persuasive as a plate of soggy salad sandwiches?

For example in the February 2015 issue of Medical Journal of Australia, an article concluded that cancer patients achieved better outcomes if they were treated in a major cancer institute.[1] The contact details for that author showed that his employment was at a major cancer institute. Are academics so beyond reproach that they don't feel the need to at least state the obvious?

I welcome continued discussion on the issue of the pervasive influence of company marketing on medical decision making, but I feel that a little perspective on this issue is warranted.

Peter McLaren
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Peter McLaren hosts clinical meetings that may have industry-sponsored catering.

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John Dowden, the Editor of Australian Prescriber *and the author of the editorial, comments:*

All of the new drug comments and most of the articles published in *Australian Prescriber* are written by authors without financial conflicts of interest. While some authors may declare such conflicts, the Editorial Executive Committee believes that the journal's editorial processes reduce the risk of bias. We have confidence in those processes and believe it is not unreasonable for readers to be able to make their own assessments. This is why it is important to publish any relevant conflicts of interest that have been declared.

The response of readers to conflicts of interest has been studied. A randomised trial involving BMJ readers found that their views of an article were more sceptical if conflicts of interest were declared.[1] As Dr Grant suggests, readers are more concerned if the author of the article is an employee of a company, rather than the recipient of a research grant.[2]

Professor Igić, Dr Sokolova and Dr McLaren raise the question of whether an author's employment should

be declared as a conflict of interest. Our Editorial Executive Committee will consider this, but it would mean duplicating the author's details given at the start of every article.

The authors of articles in *Australian Prescriber* do not have to be involved in primary research, but sometimes those who have participated in clinical trials know more about the problems of a new drug than the published literature might reveal. As Dr Johnstone points out, opinion leaders are influential and they can be used by the pharmaceutical industry for promotional purposes.[3]

The industry is moving towards greater transparency regarding the payments made to health professionals.[4] Once this information is available, perhaps it will help the Medical Board of Australia to define what constitutes 'trivial value'.

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ARTICLE

Complex regional pain syndrome

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Key words
analgesics, anticonvulsants, antidepressants, complex regional pain syndromes

Aust Prescr 2015;38:82–6

SUMMARY

Complex regional pain syndrome is an uncommon chronic pain condition. It develops spontaneously or following an injury.

The features are limb pain, allodynia, hypersensitivity, hyperalgesia, abnormalities of the vasomotor, sudomotor and motor systems, and trophic changes, with reduced use of the affected limb. The diagnosis is clinical and one of exclusion.

The emphasis of therapy is graded rehabilitation and movement of the limb with physiotherapy and occupational therapy. Psychological therapies should be offered if a patient is making no or slow progress in the acute phase, and to all patients in the chronic phase as depression can occur.

The goal of pharmacotherapy is to assist functional improvement. The early phase may be managed with simple analgesia. Antineuropathic drugs including tricyclic antidepressants and antiepileptic drugs may be added. Other treatments with some evidence of effectiveness include corticosteroids, calcitonin and bisphosphonates.

Vitamin C has been used for primary prevention after wrist fracture and upper and lower limb surgery. There is no evidence that it is effective for treating established complex regional pain syndrome.

Introduction

Complex regional pain syndrome is a painful debilitating condition in a limb. It is associated with abnormalities in skin, bone, and the autonomic, sensory and motor nerves.[1,2]

In complex regional pain syndrome type I there is no evidence of nerve damage. This was formerly called reflex sympathetic dystrophy or Sudeck's atrophy. In complex regional pain syndrome type II there is a history of nerve injury. This was formerly called causalgia.

The syndrome occurs spontaneously or is triggered by injury, such as a strain or sprain, a distal fracture or surgery.[1-3] The upper limb is affected more in adults[2] and the lower limb in children.[4] Usually, the pain is out of proportion to any preceding injury.

Epidemiology

Complex regional pain syndrome accounts for approximately 2–5% of adult and up to 20% of paediatric pain clinic patients. The prevalence in Australia is unknown. It affects females more, in a 3.5:1 ratio in adults[2] and 9:1 in children.[4] The prevalence is highest in Caucasians.[3]

Pathophysiology

The pathophysiology of complex regional pain syndrome is debated and there are possibly multiple mechanisms. Suggestions include inflammation and changes in the brain and sympathetic, peripheral and spinal nervous systems, aggravated by immobility.[1,5-7] Research using functional imaging and electroencephalogram mapping is providing more information, with demonstrated topographical shrinkage in cortical activation, for example of the hand region of the motor cortex, and reduction in the size of the somatosensory homunculus (reduced face-to-hand distance).[5,6] Altered neurological processing occurs with development of neglect, spatial perception change and reduced two-point discrimination.[5,6,8]

Clinical features

The clinical course varies. The pain spreads regionally, beyond a single dermatome, for example from hand to forearm. It is commonly described as burning, shooting or sharp. Patients may be unable to tolerate clothes, bedding, wind or water touching their limb (allodynia). Sleep disturbance and avoiding using the limb are common. A 'hot florid' phase of variable duration usually occurs early with a red, warm, sweaty limb, later progressing to a 'blue cold' atrophic phase. Some patients have the blue cold phase from the outset.[6] Swelling occurs in both phases and fluctuates (mild to extreme). Motor manifestations vary and include stiffness and impaired coordination.[6]

The natural history of complex regional pain syndrome is variable. Some patients' symptoms spontaneously resolve in weeks or months, while other patients have persistent pain and allodynia with

stiffness. A few develop a wasted, contractured, shiny limb.[1-3,9] The prognosis in children is better, as more patients achieve full recovery.[4] Relapses[3] and spread to other limbs can occur.[9]

Diagnosis

The diagnosis is clinical.[1] Investigations are only performed to exclude other diagnoses. Diagnostic features include symptoms and signs that have no other cause, in several categories:

- sensory – allodynia (pain sensed with a non-painful stimulus), hyperalgesia (increased pain sensed with a painful stimulus), hyperaesthesia (increased sensitivity felt with a stimulus)
- vasomotor – changes in skin colour and temperature
- sudomotor – oedema, sweating
- motor – weakness, tremor, dystonia
- trophic – changes in skin, hair or nails.

Prevention

Complex regional pain syndrome can be difficult to treat, so there is interest in preventing it or recognising it early in its clinical course. Earlier multimodal intervention may positively influence outcome. While there is limited evidence about prevention, providing good analgesia after trauma or surgery seems appropriate. There is no physical or psychological profile to identify which patients warrant prophylactic intervention in the setting of limb injury or surgery and immobilisation (splinting/casting), or early treatment for complex regional pain syndrome.

There is some evidence that vitamin C 500–1000 mg daily for 50 days reduces complex regional pain syndrome after wrist fracture and limb surgery (4 studies, 1065 patients).[10] Perioperatively, strategies used for primary prevention and prevention of recurrence include:

- regional, sympathetic or epidural block or infusion
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAIDs) such as cyclo-oxygenase (COX-2) inhibitors
- clonidine, ketamine or lignocaine infusions.

To date, none of these perioperative strategies has specific clinical trial evidence to support their use.

When to refer

Clinicians are often faced with the quandary of an anxious, distressed patient seeking a diagnosis or physical explanation for their ongoing pain that can then be repaired or treated. Other investigations may be required to rule out infection, non-union, or a missed bony or soft tissue injury.

The instruction to move a painful (often swollen) limb is counterintuitive to the first-aid principle to immobilise and rest following acute injury. Patients may not accept this advice.

If complex regional pain syndrome is suspected, then early referral is encouraged. High initial pain scores, high levels of emotional distress, anxiety or catastrophisation, and moderate to high opioid requirements beyond the first week are possible flags. As spontaneous remission can occur, patients can be given encouragement.

Treatment

There is little evidence to guide therapy because of the difficulties in studying specific interventions in complex regional pain syndrome.[1-3,11] These difficulties include the need for multidisciplinary treatments, limited numbers of patients, differing diagnostic criteria, the varying nature and duration of the clinical manifestations, and knowing whether recovery is due to treatment or spontaneous remission.

Treatments are often based on expert opinion and what works in other neuropathic pain conditions. It is difficult to prepare guidelines[1,11] or advice[12] for treatment because of the limited number of trials. One approach is a mixture of several drugs and other interventions according to the symptomatology and comorbidities present. Having an agreed treatment plan can help with management.

Physical therapy

Physiotherapists and occupational therapists have a key role. Standard treatment includes desensitisation, contrast baths (ice-cold vs hot-warm water immersion), hydrotherapy, graded exercise/strengthening, gradual increase in weight loading of the limb (by using weights, or pushing down on a set of bathroom scales), sensory re-education/exposure therapy (placing limb in sand, use of tactile gloves and texture boxes) and oedema control (compressive garments).[1] The patient must move, exercise and reintegrate the limb into normal everyday activity.[11]

Graded motor imagery has evidence supporting its use.[6,8] This involves phased 'brain retraining' with left–right (laterality) discrimination training (photographs and mobile apps to identify limb side, improving accuracy and speed of response), proceeding to imagined and then mirrored movements.[7,13-16] Transcutaneous electrical stimulation has been used but without an evidence base to support it.

Psychological therapy

Psychological sequelae, including depression, anxiety, fear of movement and fear of harm/re-injury, are common due to ongoing pain, physical, emotional

and social losses.[16-19] Patient education about the pathophysiology, the negative effects of disuse and the reasons for resuming function, and the interplay of psychological and behavioural factors are important as for any chronic pain condition.[18] Physical therapists with experience in complex regional pain syndrome routinely use psychological strategies and psychoeducation incorporated with the physical intervention. If the patient fails to make progress (acute phase) or once the condition becomes chronic, a formal psychological assessment should be offered. Then, specific therapies can be considered and tailored for the patient as part of a 'whole person' approach.[1,20] These include learning, mindfulness and relaxation techniques, the adoption of active rather than passive coping strategies, cognitive behavioural therapy and, recently, acceptance and commitment therapy. Cognitive behavioural therapy (six sessions) in children has been added to outpatient physiotherapy, with positive effect.[1]

The psychological interventions attempt to address any external factors or incentives that can positively or negatively influence the patient's problems. For example, claims for compensation may add to the patient's stress.

Drug therapy

In addition to the lack of evidence for most treatments, few drugs have an indication for complex regional pain syndrome. The lack of subsidy by the Pharmaceutical Benefits Scheme (PBS) can result in significant out-of-pocket expenses for the patients.

The Table includes analgesics typically used in the community as first- to fourth-line therapies. Simple analgesia is used to address pain and stiffness to facilitate movement during exercise and to limit the use of opioids. Paracetamol has no specific evidence in complex regional pain syndrome, but is used.[1] NSAIDs, including COX-2 inhibitors, are used, particularly when oedema is present, alone[1] or added to paracetamol. Typically, opioids or tramadol have been started for acute pain management after the initial injury. Tramadol's efficacy is via noradrenaline and serotonin reuptake inhibition (parent compound) and opioid effects (metabolite). The former mechanism results in antineuropathic as well as somatic benefits. Tramadol is used second- to third-line, in some countries, in preference to opioids. The ongoing use of opioids when complex regional pain syndrome is suspected or formally diagnosed is controversial. Generally, if the use of an opioid assists physical gains or compliance with therapy, then continued use is acceptable as third- or fourth-line therapy.

Corticosteroids can be considered in the early inflammatory phase.[1,21] The optimal time for starting these and the duration of treatment is uncertain. A prednisolone dose of 30 mg/day can be gradually tapered off, but there is no evidence for any regimen.

As there is some evidence for vitamin C in prevention, it has been used as treatment early in the syndrome. However, there is no evidence to support this practice.

Patients may be prescribed an antidepressant often in combination with an antiepileptic drug, usually one of the gabapentinoids: gabapentin or pregabalin (Table). For sleep disturbance, tricyclic antidepressants are favoured. Giving a higher dose of gabapentin or pregabalin at night can also be tried.

Gabapentin is not subsidised by the PBS for this indication. Although it is more expensive, pregabalin is subsidised if other therapies for neuropathic pain have failed. A head-to-head trial of gabapentin and pregabalin in neuropathic pain has not been done. Their adverse effect profiles are similar (dizziness, altered concentration, sedation). Pregabalin has twice-daily dosing, while gabapentin is given three times a day.

When tricyclic antidepressants or gabapentinoids are poorly tolerated, rotation within the same drug class can be considered (e.g. amitriptyline to nortriptyline, or gabapentin to pregabalin) or to alternative antidepressants or antiepileptics, but there is no reported experience with these strategies (Table). If the patient has severe anxiety or depression and cannot tolerate tricyclics in antidepressant doses, or if their pain or mood is not improving, then alternative antidepressant drugs such as duloxetine can be considered. However, the evidence to support their use for complex regional pain syndrome is lacking. The dose of tricyclics used in complex regional pain syndrome is frequently too low to be effective for treating coexisting depression. Serotonin syndrome is a risk if doses of antidepressants are being escalated and the patient is also taking moderate to maximal doses of tramadol.

Antiepileptic drugs have been used with varying levels of supporting evidence (Table). The off-label use of newer antiepileptic drugs, such as topiramate, for complex regional pain syndrome is expensive.

Specialist interventions

If the patient fails to improve on optimised therapy, then the pain specialist will consider other interventions. Clonidine has low-grade evidence of effectiveness, but is cheap and is often used in Australia. Dimethyl sulfoxide cream has some evidence to support its use, but it is an organic solvent that can irritate the skin. It is available depending on the capacity of local hospital and community pharmacies. Other gels and creams are available but have

Table **Commonly used drugs for complex regional pain syndrome and levels of evidence** [1] *

Drug	When used	Dose	Evidence
Paracetamol	First-line analgesic	Usual doses but capped at the recommended maximum daily dose in chronic use	None
NSAIDs including COX-2 inhibitors	First-line analgesic particularly if muscle stiffness, oedema	Take regularly vs when required before physical therapy or exercise	Limited
Opioids	Third- to fourth-line in early phase. Use is 'acceptable' if it permits physical gain (opioids may have been started to manage initial injury) Controversial use in later phase so possibly restrict to short-term use for pain crisis	Avoid high doses and long-term use due to risks of death, dependency, tolerance, overdose, opioid-induced hyperalgesia, and long-term adverse effects	Debated
Tramadol	Second- to third-line	Usual doses; immediate and slow release	None
Antiepileptics	Either alone or in combination with antidepressants		
gabapentin		100–1200 mg 3 times daily	Level 4
pregabalin		25–300 mg 2 times daily	None
carbamazepine (oxcarbazepine)		200 mg 3 times daily	Level 2
phenytoin		Usual doses	None
others: • topiramate (appetite suppression can be a significant advantage) • valproate • lamotrigine		Usual doses	Anecdotal use, no trial evidence
Antidepressants	Either alone or in combination with antiepileptics		
Tricyclics • amitriptyline • nortriptyline	Particularly useful if sleep disturbance	Start low e.g. 10–25 mg and up-titrate to 1–2 mg/kg	None
SSRI/SNRI • paroxetine • duloxetine • venlafaxine • citalopram	May be preferable in overweight, somnolent patients or if unable to tolerate tricyclic antidepressants or have prominent anxiety/depression	Usual doses	Not studied

NSAIDs non-steroidal anti-inflammatory drugs COX cyclo-oxygenase
SSRI selective serotonin reuptake inhibitor SNRI serotonin and noradrenaline reuptake inhibitor

* According to National Health and Medical Research Council hierarchy

limited or no supporting evidence. These are often anecdotally effective for patients unable to tolerate oral drugs. They include single or combination drugs such as topical NSAIDs (available over the counter), local anaesthetics, ketamine (e.g. 2.5–5%) or clonidine (e.g. 0.01%) and amitriptyline/nortriptyline (e.g. 2%) gels. Capsaicin may be tried, but it is messy and painful and therefore invariably unpopular with patients. Patches of local anaesthetic, clonidine or capsaicin have also been used but are not always available.

Various regimens of ketamine and lignocaine infusions have become widely used, but patients need to be hospitalised and there is uncertainty regarding the optimal dose, duration and frequency of these treatments.

Calcitonin and bisphosphonates can reduce bone resorption and may have other actions. There is

evidence to support their use in complex regional pain syndrome.[1]

Invasive interventions

Sympathetic blockade (stellate ganglion block and lumbar sympathetic block) has been used extensively despite limited supporting evidence. The blocks are offered generally for the hot florid phase and for the blue cold phase, if there is prominent oedema. It is also unclear whether permanent sympathectomy is better than repeated temporary local anaesthetic blocks. Epidural block (providing sympathetic and somatic block) is sometimes used for inpatient treatment.

Implantable pumps (for lower limb) and stimulators (for lower or upper limb) have been used in severe or resistant complex regional pain syndrome. They require a rigorous selection process, significant expertise to insert, adjustment and ongoing supervision. The evidence to support these interventions is limited and they need further evaluation. The same is true for the experimental use of anti-inflammatories and immunomodulators in complex regional pain syndrome. Infliximab, intravenous immunoglobulin and thalidomide have been tried in very small case series.

Conclusion

Complex regional pain syndrome is an unusual neuropathic pain condition. Current therapy involves actual and simulated limb use facilitated by multimodal intervention and polypharmacy with drugs for neuropathic and inflammatory pain. Research is further delineating the pathophysiology and may eventually lead to the development of targeted therapy. Good-quality trials to support the use of drugs and other interventions are necessary. ◀

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ARTICLE

Prescribing azithromycin

SUMMARY

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and excellent tissue penetration.

It is primarily used for the treatment of respiratory, enteric and genitourinary infections and may be used in preference to other macrolides for some sexually transmitted and enteric infections.

Azithromycin has additional immunomodulatory effects and has been used in chronic respiratory inflammatory diseases for this purpose.

Potential major adverse effects include cardiovascular arrhythmias and hearing loss. Macrolide resistance is also a problem, as are interactions with commonly prescribed drugs.

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Key words
antibiotic resistance, azithromycin, immunomodulators, macrolide antibiotics

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Introduction

Azithromycin is a broad-spectrum macrolide antibiotic with bacteriostatic activity against many Gram-positive and Gram-negative bacteria including *Bordetella pertussis* and *Legionella* species. It also has activity against *Mycoplasma pneumoniae*, *Treponema pallidum*, *Chlamydia* species and *Mycobacterium avium* complex.[1]

Since the late 1990s, macrolide-resistant *Streptococcus pneumoniae* and *Staphylococcus aureus* infections have been increasing in Australia. Over 10% of *S. pneumoniae* infections and over 15% of *S. aureus* infections have been reported to be resistant to azithromycin.[2,3] *Haemophilus influenzae* is commonly susceptible to macrolides but resistance rates of 3–15% have been reported in Aboriginal and Torres Strait Islander children.[4]

Pharmacology

Azithromycin reversibly binds to the bacterial ribosome and inhibits protein synthesis.[5,6] The drug has an absolute oral bioavailability of 35–42% in healthy volunteers and people with cystic fibrosis[7,8] and a long half-life due to extensive uptake in tissue, particularly lung, tonsil and prostate. Tissue concentrations exceed the minimum inhibitory concentration that would inhibit 90% of likely pathogens (MIC90) after a single 500 mg oral dose. Mean concentrations in tissue are 10–100-fold higher than those reached in serum and persist for several days.[1] Azithromycin also accumulates in phagocytes, with levels up to 200 times greater than in serum,[1] but penetrates poorly into cerebrospinal fluid and peritoneal fluid.

Azithromycin is generally administered orally, but an intravenous formulation exists for patients unable to tolerate oral medications. Duration of treatment varies with indication and severity. Usually a single dose is recommended in some sexually transmitted infections. Several days of treatment is generally appropriate in respiratory tract infections and many months in mycobacterial infections. Guidelines should be consulted for detailed recommendations.[9]

Unlike clarithromycin, azithromycin does not interact significantly with cytochrome P450 3A4.[1] In comparison with erythromycin, it is more acid stable, which simplifies administration around food.

Azithromycin is a pregnancy category B1 drug and is considered safe to use in pregnancy and breastfeeding. However, it may cause diarrhoea in breastfeeding infants.[9,10]

Indications

In Australia, azithromycin is subsidised by the Pharmaceutical Benefits Scheme (PBS) for a number of indications (see Table). It is also recommended for other infections by guidelines, but not specifically approved by the Therapeutic Goods Administration. Infections that may be treated with azithromycin include:

- community-acquired pneumonia
- specific respiratory infections, including pertussis and legionellosis
- sexually transmitted infections such as orchitis, pelvic inflammatory disease, chancroid and granuloma inguinale[9]
- bacterial enteritis due to *Campylobacter* and *Salmonella* species, cholera and travellers' diarrhoea, as well as enteric fever (caused by *Salmonella enterica* serovar Typhi and *S. enterica* serovar Paratyphi).

Other recommended uses of azithromycin include treatment of severe infection or persistent lymphadenopathy due to *Bartonella henselae* (cat-scratch disease), and some tick-borne infections such

Table **Pharmaceutical Benefits Scheme indications for azithromycin**

Schedule	Drug	Restriction	Repeats
General schedule	azithromycin 500 mg tablets (2/pack)	trachoma	2
		uncomplicated urethritis or cervicitis due to *Chlamydia trachomatis*	0
General schedule	azithromycin 200 mg/5 mL oral liquid (powder for 15 mL)	trachoma	0
Repatriation schedule	azithromycin 500 mg tablets (3/pack)	upper and lower respiratory tract infections	0
Highly specialised drugs (Section 100)	azithromycin 600 mg tablets (8/pack)	prevention of *Mycobacterium avium* complex in patients with HIV (CD4 counts <75/mm^3)	5

Based on www.pbs.gov.au [cited 2015 May 5].

as Australian tick typhus or scrub typhus. It is also used as part of combination therapy for *M. avium* complex infections.[9]

Azithromycin as an immunomodulator

In addition to their antimicrobial properties, there are in vitro and animal data on the immunomodulatory or anti-inflammatory effects of macrolides.[1] Effects in humans were initially reported in the treatment of diffuse panbronchiolitis, in which macrolides are associated with improved lung function and prognosis based largely on non-controlled trial data and retrospective studies.[1] In cystic fibrosis, treatment for six months is associated with improved respiratory function and reduced respiratory exacerbations.[11] Azithromycin produced a small increase in lung function (mean 8.8%) at seven months in patients treated for bronchiolitis obliterans syndrome after lung transplant,[12] but was no different compared to placebo for bronchiolitis obliterans syndrome after haematopoetic stem cell transplant.[13]

Azithromycin and other macrolides have also been proposed for use in sepsis and epidemic respiratory viral infections to prevent cytokine storm.[1] It has been used for various respiratory and non-respiratory inflammatory conditions. However, this use has been controversial due to limited direct clinical evidence for many conditions, and concerns about increased antimicrobial resistance.[1,14] New non-antibiotic macrolides may provide immunomodulatory benefits without contributing to antimicrobial resistance.[14]

Bronchiectasis

In non-cystic fibrosis bronchiectasis, three randomised, double-blind, placebo-controlled trials found that azithromycin reduced the number of exacerbations. In adults with bronchiectasis on CT scanning and at least one pulmonary exacerbation treated with antibiotics in the past year, the EMBRACE trial found a reduction in the rate of exacerbations (0.59 vs 1.57) with azithromycin three times weekly for six months compared to placebo.[15] The BAT trial found a reduced number of exacerbations (median 0 vs 2) in adults with radiologically confirmed bronchiectasis and at least three respiratory infections treated with antibiotics in the past year (daily azithromycin therapy over 12 months).[16] Finally, the Bronchiectasis Intervention Study investigated Australian and New Zealand indigenous children with non-cystic fibrosis bronchiectasis or chronic suppurative lung disease who had had at least one pulmonary exacerbation in the past 12 months. After once-weekly azithromycin for up to 24 months, the incidence of pulmonary exacerbations was half that observed in those given placebo. However, the authors noted a greater incidence of macrolide-resistant bacteria in children treated with azithromycin (46% vs 11%).[17]

Asthma and chronic obstructive pulmonary disease

Trials in children and adults with asthma and chronic obstructive pulmonary disease (COPD) have been small with heterogeneous outcomes, and the optimal regimens and subgroups are not yet established. Patients with neutrophilic asthma may benefit from macrolides, but further research is needed.[18]

A randomised controlled trial of daily azithromycin in patients with variable COPD severity, smoking status and medical management found that azithromycin prolonged time to exacerbation compared to placebo – median 266 days (95% CI* 227–313) versus 174 days (95% CI 143–215) (p<0.001). The rate of exacerbations was 1.48 per patient-year in the azithromycin group, compared with 1.83 in the placebo group (p=0.01). However, there was only a 7% increase in the proportion of people reporting clinically important improvements

* CI confidence interval

in quality of life with azithromycin as compared with placebo (43% vs 36%, p=0.03). Patients in the azithromycin arm experienced hearing decrements more frequently (25% vs 20%, p=0.04) and were more likely to be colonised with macrolide-resistant organisms (81% vs 41%, p<0.001). People with a prolonged QT interval were excluded from this study.[19]

Adverse effects

Azithromycin is generally well tolerated, but relatively common adverse effects (1–5% of patients) include gastrointestinal upset, headache and dizziness. Transient increases in transaminases have also been reported in 1.5% of patients.[5]

Hearing loss or impairment has also been reported with azithromycin, including in patients with COPD and normal hearing at baseline, and appeared to be irreversible in some patients.[19,20] Case reports of hearing loss after short-term use have also been published.[21]

Serious adverse effects include QT prolongation and torsades de pointes resulting in death. The US Food and Drug Administration issued a warning in 2012 to consider the risk of fatal heart rhythms in those:

- with a prolonged QT interval (including congenital long QT syndrome)
- taking medicines that are likely to prolong the QT interval
- with a history of torsades de pointes, arrhythmias or uncompensated heart failure.

This advice was primarily based on a large retrospective cohort study that suggested an increase in cardiovascular deaths, and death from any cause, in people treated with a five-day course of azithromycin compared to amoxycillin, ciprofloxacin, or no drug.[22]

At an individual and a population level, macrolides have been associated with antibiotic resistance in *Streptococcus pneumoniae* and *S. pyogenes*, *Staphylococcus aureus*, *Haemophilus* species and other organisms.[1,14] Patients with chronic lung diseases treated with long-term azithromycin had a 2.7-fold increased risk of macrolide-resistant bacteria, according to a recent meta-analysis.[20] This has potential adverse clinical consequences for the individual and the community.

Clinically significant drug interactions

Azithromycin has a number of clinically relevant drug interactions (see Box).[23-29] Due to its long half-life, interactions may continue for several days after it has been stopped.[10]

When is azithromycin preferable to other macrolides?

While there is no clear advantage of azithromycin over other macrolides for most respiratory infections, its pharmacokinetic properties make it useful for treatment of sexually transmitted infections (e.g. single-dose azithromycin for urethritis with *Chlamydia trachomatis*).[9] In addition, its high intracellular concentrations and high potency in vitro are proffered as reasons for use against enteric pathogens such as *Salmonella* species (which are intrinsically resistant to erythromycin due to active efflux). Azithromycin's once-daily dosing for the prevention and treatment of *M. avium* complex and its lack of interactions via cytochrome P450 may make it preferable to clarithromycin in some circumstances.

Conclusion

Azithromycin's pharmacokinetics and tolerability make it particularly useful in the treatment of sexually transmitted infections, intracellular enteric pathogens and for prophylaxis of mycobacterial disease. It is also useful for treating a range of respiratory diseases. Unfettered use of azithromycin, particularly for its immunomodulatory properties, is of concern in light of macrolide resistance. Novel non-antibiotic macrolides may be used for this role in future. ◅

Conflict of interest: none declared

Box Clinically significant interactions of azithromycin

- Azithromycin should be used with great caution if co-administered with other drugs that prolong the QT interval.[23]
- There are a number of published reports suggesting that azithromycin might potentiate the activity of warfarin, however clinical events due to excessive anticoagulation attributable to warfarin are controversial due to patient factors and study design. Some retrospective series have failed to find interactions[24,25] or found an interaction but no adverse events.[26] Given the current uncertainty about interactions, it is prudent to monitor INR carefully in patients on warfarin who require azithromycin.
- Pharmacokinetic modelling suggests reduced clearance of everolimus.[27]
- Macrolides, including azithromycin, may potentiate digoxin toxicity. This relates to P-glycoprotein. A case report describes a 31-month-old who developed symptoms of digoxin toxicity after starting azithromycin.[28]
- Azithromycin may increase colchicine concentrations, with consequent toxicity.[10,27]
- Concomitant use of statins and azithromycin may increase the risk of rhabdomyolysis.[29]
- Co-ingestion of antacids (aluminium, magnesium) may reduce the peak concentration of azithromycin.

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The full list of references is published with the online version of this article at www.australianprescriber.com/magazine/38/3/87/9.

ARTICLE

Safe disposal of prescribed medicines

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SUMMARY

The National Return and Disposal of Unwanted Medicines Program provides a free and safe method for the disposal of unwanted and expired medicines. This stops drugs being dumped in landfill and waterways.

An audit showed that over 600 tonnes of medicines are returned through the program. A substantial proportion of these medicines were still within their expiry dates.

Salbutamol, insulin and frusemide are the most commonly discarded medicines. More than $2 million of public money is wasted each year.

Hoarding and non-adherence to treatment contribute to waste. Health professionals may be able to help minimise waste by informing patients about the importance of completing prescribed courses of treatment, and discouraging them from hoarding medicines after reaching the safety net threshold on the Pharmaceutical Benefits Scheme.

Prescribe no more than the required quantity of medicines. When starting a new therapy, prescribe a minimal quantity in case the drug is unsuitable for the patient.

Advise patients to return all unwanted medicines to a pharmacy for disposal.

Introduction

Many unwanted and expired medicines in the community are disposed of via general waste or sewerage.[1] Medicines discarded in household rubbish bins end up in landfill and may damage the environment. They may also be found by unintended recipients including children and animals, increasing the risk of poisonings, misuse and abuse. Medicines discarded down sinks and toilets not only enter waterways affecting marine life, but also enter the water table via the sludge component of the sewage treatment process thereby potentially affecting human and animal life. It is therefore critical that unwanted drugs are disposed of safely.

To facilitate the safe disposal of medicines in the community, the Australian Government established the National Return and Disposal of Unwanted Medicines (NatRUM) program in 1998.[1] Through this program, anyone can dispose of medicines free of charge by returning them to community pharmacies who subscribe to the program. The NatRUM program is available to every pharmacy in Australia and is one of only a handful of such programs worldwide.

The vast majority of community pharmacies, of which there are approximately 6000 in total, participate in the NatRUM program. Medicines returned to pharmacies are placed in yellow Return of Unwanted Medicines (RUM) bins which, when full, are collected by pharmaceutical wholesalers for incineration in accordance with regulations and the Environment Protection Authority's requirements.

Each year over 600 tonnes of medicines are collected through the program.[1] By providing a safe and easily accessible method of disposal, the NatRUM program makes a valuable contribution to the quality use of medicines (QUM) in Australia.

What is being returned?

It is helpful for health professionals to know the type of medicines being discarded as this can guide practice and minimise waste. An audit of the NatRUM program was undertaken by Monash University in 2013.[2] The contents of 686 RUM bins, representative of bins returned for incineration across Australia, were systematically audited. Over 24 000 individual items containing over 700 different active ingredients were examined. The Table lists the 20 most commonly discarded medicines.

The majority (85.4%) of discarded medicines were scheduled drugs. Prescription medicines (Schedule 4) subsidised by the Pharmaceutical Benefits Scheme (PBS) made up approximately 70% of all the medicines discarded. Approximately 44% of the drugs were still within their expiry dates.

Estimation of the quantity of medicines discarded over a 12-month period revealed that the disposal of medicines is roughly proportional to the quantities dispensed on the PBS.[3]

Medicines with the highest costs associated with wastage included tiotropium, fluticasone-salmeterol combinations and, due to the large quantities dispensed under the PBS and subsequently discarded, paracetamol. The annual total cost to taxpayers for the 31 most frequently discarded medicines dispensed under the PBS was approximately $2.05 million. These are conservative estimates as they are only for medicines that were in-date and disposed of via the NatRUM program. The true cost of discarded drugs is likely to be considerably higher.

Key messages

The amounts and types of medicines prescribed under the PBS and subsequently discarded in large quantities are a significant waste of resources, both directly through the cost of the medicines discarded and indirectly via non-adherence. Poor adherence contributes to suboptimal clinical benefit leading to medical and psychosocial complications of disease, reduced quality of life, and waste of healthcare resources. These consequences impair the ability of healthcare systems to achieve population health goals.[4]

A 2005 study (with a small sample size) found that people disposed of medicines via RUM bins for a variety of reasons including:

- concerns about safety and efficacy
- death of a family member
- change in therapy
- perceptions about the need for the medicines and unwanted effects.[5]

The reasons for returning medicines also differed depending on the therapeutic class of the medicine. For example, cardiovascular medicines were most commonly returned due to a change in treatment, whereas anti-infective drugs were mostly returned because of a perception that they were no longer needed.[5]

The high return rate of antimicrobials observed in the audit is very concerning given the widespread emergence of antimicrobial resistance combined with the dwindling development of new antimicrobial drugs.[6,7] Initiatives to improve the appropriate use of antimicrobials such as Australian National Antimicrobial Awareness Week, and the development of guidelines for antimicrobial use, are timely and critical. Health professionals must remind patients of the importance of completing prescribed courses of antibiotics.

In clinical practice it is necessary to adjust treatment according to the patient's response. This approach may require switching from one drug to another, which may lead to a quantity of the first drug being wasted. In these circumstances, the prescribing of smaller initial quantities of medicines can help minimise wastage. Some patients hoard medicines once they reach the safety net threshold on the PBS to save money on future prescriptions. However, some of this stockpile will expire, so education and awareness are critical to optimise medicine use.

It is important for health professionals to discuss the potential dangers of non-adherence, emphasise the importance of finishing prescribed courses of medicines and, if possible, prescribe smaller quantities (perhaps choosing the smallest pack size) of medicines at the start of therapy. Prescribers should avoid the automatic ordering of maximum quantities by electronic prescribing programs, as this may contribute to wastage.

Table **The 20 most commonly discarded drugs in Australia** [2]

Rank	Drug
1 (most common)	salbutamol*
2	insulin†
3	frusemide
4	prednisolone
5	glyceryl trinitrate
6	telmisartan/amlodipine
7	fluticasone/salmeterol
8	paracetamol
9	metoclopramide
10	warfarin
11	influenza vaccine‡
12	perindopril
13	metoprolol
14	paracetamol/codeine
15	atorvastatin
16	amoxycillin
17	betamethasone
18	oxycodone
19	cephalexin
20	ipratropium

* It was not possible to determine what proportion of the contents of metered dose inhalers remained unused at the time of disposal.

† Approximately 75% of all discarded insulin was in-date. The vast majority of insulin containers were full (i.e. unused).

‡ Approximately 99% of discarded influenza vaccine was past the expiry date.

Advise patients to return unwanted medicines to pharmacies participating in the program. Campaigns to create greater awareness among consumers about the NatRUM program and its potential benefits to the environment and society are also needed.

Conclusion

In Australia, the NatRUM program offers the only safe method for disposal of unwanted and expired medicines and is a fundamental component of the QUM strategy. Periodic audits of the RUM bins to collect data on medicine wastage will assist with decision making about medicines supply and use at a national level, and in the design of campaigns to facilitate quality use. Ongoing research on the reasons why consumers return or otherwise dispose of medicines is also needed to promote medicine adherence and rational prescribing of medicines, and to minimise wastage. ◁

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Erythrocyte sedimentation rate and C-reactive protein

SUMMARY

C-reactive protein is a better indicator of inflammation than the erythrocyte sedimentation rate. It is more sensitive and responds more quickly to changes in the clinical situation.

False negative and false positive results are more common when measuring the erythrocyte sedimentation rate. Renal disease, female sex and older age increase the erythrocyte sedimentation rate.

The erythrocyte sedimentation rate has value in detecting low-grade bone infection, and in monitoring some patients with systemic lupus erythematosus.

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Key words
acute phase reaction, autoimmune diseases, bone infection, C-reactive protein, erythrocyte sedimentation rate, inflammation

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Introduction

As well as the clinical evaluation of symptoms and signs indicating inflammation (pain, fever, and localised redness, swelling and tenderness), laboratory investigations are frequently used to support the diagnosis of inflammatory processes. Both acute and chronic inflammation cause cytokines, mainly interleukin-6, to be released into the bloodstream. The liver responds to this by producing acute phase reactants such as C-reactive protein (CRP). This is the most commonly used marker of an acute phase reaction and was first discovered in the serum of patients with pneumococcal pneumonia.[1]

Detecting the acute phase reaction

Although the erythrocyte sedimentation rate (ESR) is still used to assess inflammation, specific acute phase proteins are more commonly measured now. Markers of the acute phase reaction are C-reactive protein, serum amyloid A protein and procalcitonin. They increase 100-fold or more in patients with acute or chronic inflammatory processes. Many other serum proteins change during an acute phase reaction (shift up or down) but to a lesser extent.[1]

C-reactive protein

C-reactive protein has an important role in many parts of the inflammatory process. It is involved in the innate immune response by attaching to microorganisms and damaged cellular components via phosphocholine. This leads to complement activation and phagocytosis. Although C-reactive protein activation of complement increases inflammation and tissue damage, it also has some anti-inflammatory actions, thus it acts as a promoter and down-regulator of inflammation.

C-reactive protein is a useful marker of the acute phase reaction as it responds quickly to the inflammatory process, whether it is an infection, autoimmune disease or tissue necrosis.[2] C-reactive protein has a doubling time and a decay time of around six hours, and maximal concentrations are reached in less than two days. After the inflammation has resolved, concentrations fall rapidly. Once inflammation and its cause have been identified and treatment is started, there is usually no need for further C-reactive protein measurements.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate is a surrogate marker of the acute phase reaction. During an inflammatory reaction, the sedimentation rate is affected by increasing concentrations of fibrinogen, the main clotting protein, and alpha globulins. The test mainly measures the plasma viscosity by assessing the tendency for red blood cells to aggregate and 'fall' through the variably viscous plasma.

However, the sedimentation rate is often and significantly affected by many factors other than the acute phase reaction. Known influences include:

- plasma albumin concentration
- size, shape and number of red blood cells
- non-acute phase reaction proteins, in particular normal and abnormal immunoglobulins.

The non-specificity of the erythrocyte sedimentation rate means the test is more likely to be falsely positive (elevated in the absence of inflammation) than a C-reactive protein test. Also, the erythrocyte sedimentation rate's slow response to the acute phase reaction leads to false negatives early in an inflammatory process.[3] Normalisation of an

elevated erythrocyte sedimentation rate once an immunoglobulin response has occurred may take weeks to months.

Raised erythrocyte sedimentation rates are observed in patients without an acute phase reaction, for example when haematological disorders including anaemia are present. Renal failure, obesity, ageing and female sex are associated with higher erythrocyte sedimentation rates. C-reactive protein results are also higher with obesity but are not affected by renal failure.

C-reactive protein versus erythrocyte sedimentation rate

In laboratory-based studies examining consecutive patients with elevated C-reactive protein or erythrocyte sedimentation rate, C-reactive protein has been found to be a better marker of the acute phase reaction than the erythrocyte sedimentation rate.[1] It is a more sensitive test and rapidly detects changes in the acute phase reaction.

In a retrospective cohort study, discrepancies between C-reactive protein and erythrocyte sedimentation rate have been reported in 12.5% of patients.[4] Patients with raised C-reactive protein and a normal erythrocyte sedimentation rate usually have infection but some have other tissue damage (e.g. myocardial infarction or venous thromboembolism). These discrepancies may be due to timing, with the rise in C-reactive protein manifesting itself before the sedimentation rate elevates, or simply because the sedimentation rate does not change with minor inflammation.[3] Patients with a high erythrocyte sedimentation rate and normal C-reactive protein mostly have conditions without demonstrable systemic inflammation such as malignancy.

However, there are two circumstances when the sedimentation rate can be a better marker of an inflammatory process:

- some low-grade bone and joint infections (e.g. in joint prosthesis infections due to low-level pathogens such as coagulase negative staphylococci)
- autoimmune disease, in particular some people with systemic lupus erythematosus.

With systemic lupus erythematosus, a patient may have a normal C-reactive protein in the presence of significant tissue damage and inflammation. This is possibly due to high levels of type 1 interferons which inhibit the production of C-reactive protein in hepatocytes. Despite this, a C-reactive protein test is still useful as elevation will indicate concomitant bacterial infection, active serositis and chronic synovitis.

C-reactive protein is considered a better marker of disease activity in other autoimmune diseases such as polymyalgia rheumatica and giant cell arteritis, despite the erythrocyte sedimentation rate also being elevated in most of these conditions.[4] Patients with rheumatoid arthritis show considerable variation in erythrocyte sedimentation rate and C-reactive protein elevations during times of increased disease activity. A prudent approach may be to measure both initially in order to identify the best marker to use.

The erythrocyte sedimentation rate has been used as a surrogate marker for hypergammaglobulinaemia, especially myeloma protein. Where myeloma is suspected, a much better test is the protein electrophoresis and immunoglobulin measurements.

Conclusion

C-reactive protein should be used judiciously. It is not a screening test for wellness and should only be used in the diagnosis and monitoring of a patient who appears to have an inflammatory process.

Compared to the erythrocyte sedimentation rate, C-reactive protein is a more sensitive and specific marker of the acute phase reaction and is more responsive to changes in the patient's condition. There are only two circumstances where the erythrocyte sedimentation rate is superior – detecting low-grade bone and joint infections, and monitoring disease activity in systemic lupus erythematosus. ≺

Michael Harrison is chief executive officer of a private pathology laboratory that performs erythrocyte sedimentation rate and C-reactive protein tests. Although the laboratory receives Medicare funding for these tests, he does not directly benefit.

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ARTICLE

Concerns about quetiapine

SUMMARY

Quetiapine is subsidised by the Pharmaceutical Benefits Scheme to treat schizophrenia and bipolar disorder. An extended-release formulation is also approved for use, but not subsidised, for treatment-resistant depression and generalised anxiety disorder.

There is increasing off-label prescribing of quetiapine for indications such as insomnia that have little evidence to support them. This prescribing is often for at-risk patients, such as people with personality or social vulnerabilities and those at risk of metabolic complications or cardiovascular events.

More evidence is required to support prescribing decisions regarding these off-label indications. In the meantime prescribers should be supported with alternatives to prescribing for these conditions, such as psychological therapies that have a better evidence base and safety record.

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Key words
antipsychotics, off-label prescribing, quetiapine

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Introduction

Quetiapine is a short-acting antipsychotic that is available in immediate and extended-release formulations. It is registered by the Therapeutic Goods Administration (TGA) and subsidised by the Pharmaceutical Benefits Scheme (PBS) for the treatment of schizophrenia and bipolar I disorder. The extended-release preparation is also registered for treatment-resistant depression and generalised anxiety disorder, but these indications are not subsidised by the PBS. In 2014, quetiapine was the 10th most expensive drug on the PBS.

There is a high level of evidence to support the approved indications of quetiapine, but it is being increasingly used off label.[1,2] Often, clinicians are faced with difficult decisions about prescribing antipsychotics for off-label indications when dealing with distressed patients and inadequate resources for psychological treatments and other support. However, there is growing concern from within the medical community and regulatory bodies regarding the potential harm from prescribing antipsychotics off-label, particularly immediate-release quetiapine.

These concerns have been expressed in media reports of large increases in quetiapine prescribing to Australian soldiers returning from recent deployments, with a significant proportion of these personnel not accessing psychological therapies for post-traumatic stress disorder.[3] Internationally, there have been a number of high-profile court cases in the media concerning deaths related to quetiapine involving drug interactions or overdose.[4]

Off-label prescribing

Between 2000 and 2011 in Australia, there was around a twofold increase in the dispensing of antipsychotic drugs, with the greatest increase seen for quetiapine. Quetiapine's use increased from 0.01 to 2.3 defined daily doses/1000 population/day.[5] These changes cannot be accounted for by patients being switched from older to newer drugs or changes in the diagnosis of long-term mental illness over the last decade.[5,6] Much of this escalating use may relate to prescribing antipsychotic drugs for indications that are not included in the approved product information.

This off-label prescribing is commonplace in psychiatry[7] and is sometimes justifiable as some off-label indications are supported by national consensus guidelines and medicines information services. For instance, in addition to its TGA-approved indications, quetiapine may have a role in anorexia nervosa. Regulatory decisions often lag behind the generation of evidence from clinical trials.

A brief history of quetiapine

Quetiapine was first registered in 1997 and by 2010 it was the fifth biggest selling pharmaceutical in the USA, with annual sales of US$6.8 billion.[8] However, in 2010 the manufacturer of quetiapine agreed to pay US$520 million following government allegations of promoting off-label prescribing. This included promoting the drug to non-psychiatrists for indications such as anger management, dementia and sleeplessness. There were also allegations of remunerating doctors for articles that had been 'ghostwritten' by other people to promote off-label uses.[9]

A patent extension was granted for the extended-release formulation in 2010 until 2017 for very similar indications to the immediate-release formulation which came off patent in 2012. There are now around 17 generic forms of quetiapine available in Australia.

Who is prescribing quetiapine for what?

Concerns about the off-label use of antipsychotics prompted an evaluation by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee in 2013.[10] Off-label use was most evident for the 25 mg strength of quetiapine. The usual therapeutic dose range for the approved indications is 400–800 mg/day. The 25 mg dose has no uses that are evidence based other than for dose titration in older patients. However, the report found that 23.3% of all patients taking quetiapine were taking the 25 mg strength alone. Most (66%) initial prescriptions for quetiapine were written by GPs, suggesting that the indications were not schizophrenia or bipolar disorder. The Drug Utilisation Sub-Committee recommended liaison with TGA and drug companies to reduce the number of 25 mg tablets in a pack and to reduce the number of repeats from five to zero. Improved advice and support for prescribers was also suggested, leading to an NPS MedicineWise publication on the role of low-dose quetiapine.[11]

Limited-evidence prescribing practices

There is little evidence to support many of the off-label uses of quetiapine.[12] Indications with particularly poor evidence include anxiety, insomnia, post-traumatic stress disorder, personality disorders, behavioural and psychological symptoms of dementia, and substance misuse.[13] For example, a recent literature review of studies using quetiapine to treat insomnia in the absence of comorbid conditions found only two placebo-controlled clinical trials of 31 patients in total. The review concluded that the absence of efficacy and safety data precludes the use of quetiapine for insomnia.[14] Prescribing for indications that are not supported by evidence has safety, ethical and financial implications.

Little is known about the reasons for off-label prescribing, but a historical perspective of sedative and hypnotic prescribing trends shows a move from barbiturates in the 1920s to the 1950s[15] and then to benzodiazepines from the 1960s,[16] mainly because of safety concerns. More recently there have been increasing concerns about the harms of benzodiazepines, in particular alprazolam[17] which was rescheduled from Schedule 4 to 8 in 2014.[18] When prescribers are confronted with requests for prescriptions to treat anxiety and insomnia they are aware of the hazards of benzodiazepines, but may not have access to, or skills in, psychological therapies.[19,20] Quetiapine has sedative effects, so it is possible that quetiapine is being prescribed instead of benzodiazepines due to perceptions regarding safety and efficacy.

Harms related to quetiapine

While there is limited evidence for the efficacy of quetiapine in off-label indications, prescribing it exposes the patient to potential harm.

Overdose

According to Australian data, quetiapine is now one of the most commonly taken drugs in overdose,[21] even after adjusting for the number of prescriptions. These data are supported by a Melbourne study that found ambulance attendances related to quetiapine were substantially higher than for risperidone and olanzapine, even when adjusted for prescription rates. These cases were often associated with substance misuse.[22] A study of coronial data found that a third of deaths associated with quetiapine did not include a psychiatric diagnosis, raising concerns that off-label use or misuse contributed to the deaths.[23]

Metabolic effects and sudden death

The newer antipsychotic drugs increase weight to different degrees and this contributes to the differing relative risk of insulin resistance, dyslipidaemia and hyperglycaemia.[24] Even at low doses (<200 mg) quetiapine has been linked to significant weight gain. A retrospective study of quetiapine for insomnia found that the most commonly prescribed dose was 100 mg, and there was an average weight gain of 2.2 kg over the average treatment period of 11 months.[25] Taking quetiapine contributes to a significant risk of metabolic complications, often in patients with a number of other cardiovascular lifestyle risk factors such as smoking. Patients need to be monitored for these adverse effects.

There is an increased risk of sudden cardiac death with antipsychotics, with an aggregate adjusted risk–incidence ratio for newer antipsychotics of 1.59 for low-dose and 2.86 for high-dose therapy. Within this, quetiapine accounted for a risk–incidence ratio of 1.88 (95% confidence interval 1.30–2.71).[26]

Adverse events in older people

A study of residential aged-care facilities in Australia found that 22% of antipsychotic prescribing was off label.[27] Prescribing antipsychotics in this population has also been associated with increased risk of fatal pneumonia, stroke, hip fracture and cognitive deterioration.[28-30] Orthostatic hypotension could contribute to the risk of falls.

In 2005 the Food and Drug Administration (FDA) issued a black box warning in the USA because of an increase in sudden cardiac deaths related to antipsychotic drugs in older patients. Despite this warning quetiapine use continued to rise.[31]

Drug dependence

Within a population of patients being treated for addiction, 17% reported the past misuse of antipsychotics along with other drugs.[32] Quetiapine appears to be the most prevalent, with reports of increasing use of both prescribed and diverted quetiapine by intravenous drug users.[33] Quetiapine appears to be the most documented antipsychotic bought and sold illicitly on the street. There are also numerous case reports of abuse and dependence.[34,35]

Future directions

There is a pressing need to identify the reasons for the escalating use of quetiapine. Conditions such as insomnia and anxiety have been identified as common indications that lack robust evidence. Gathering evidence is imperative to support or refute the ongoing use of quetiapine for these indications. In the meantime, it is important to support doctors with alternatives to prescribing – for instance with resources to improve assessment and management of these conditions and manage them with psychological therapies that have a greater evidence base.

Conclusion

Quetiapine has proven safety and efficacy when used for its approved indications. However, there are concerning increases in the rates of off-label prescribing for indications with limited evidence. Adverse outcomes are most likely to occur in already vulnerable populations such as older people, those with mental health problems and substance misusers. Prescribers should therefore be cautious when considering a prescription for quetiapine for an off-label indication. ⋖

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ARTICLE

Acute use of oxygen therapy

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chronic obstructive pulmonary disease, hypercapnia, hypoxaemia, oxygen inhalation therapy

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SUMMARY

A major change is needed in the entrenched culture of routinely administering high-concentration oxygen to acutely ill patients regardless of need.

Oxygen is a drug that should be prescribed for specific indications. There should be a documented target range for oxygen saturation, and regular monitoring of the patient's response.

There are risks from unrelieved hypoxaemia due to insufficient oxygen therapy, and from provoked hyperoxaemia due to excessive oxygen therapy. Oxygen therapy should therefore be titrated so that the saturation is within a range that avoids these risks.

If oxygen requirements are increasing, the clinician should review the patient and consider transfer to a higher level of care. If oxygen requirements are decreasing, consider reducing or discontinuing oxygen therapy.

Introduction

Management of the acutely hypoxaemic patient requires evaluation and treatment of the underlying cause of the hypoxaemia. Oxygen therapy relieves hypoxaemia, but not the underlying cause.

Oxygen is a drug and it should be prescribed for specific indications. This prescription should include the target range for oxygen saturation. The response to oxygen administration requires regular monitoring.[1-3]

Identifying the need for oxygen

In the first assessment of an unwell patient, oxygen saturations can be determined by pulse oximetry. However, clinicians need to be aware that the accuracy of pulse oximetry is variable in clinical practice.[4] Arterial blood gases should be measured in patients who are critically unwell, when an oximetry reading cannot be obtained or when hypercapnia is suspected. In view of the widespread use of venous blood gas measurements, clinicians need to be aware that this method cannot accurately determine arterial carbon dioxide.[5]

Oxygen therapy is indicated in patients with oxygen saturations below the target saturation range. It is not indicated for the treatment of breathlessness in patients with adequate oxygen saturations, apart from certain patients with carbon monoxide poisoning and with pneumothorax.[3,6]

Prescribing the appropriate dose

Just like any other drug, oxygen should be prescribed at the appropriate dose, to achieve a desired outcome. For oxygen this is the designated saturation range. This approach is important because unrelieved hypoxaemia due to insufficient oxygen therapy, and provoked hyperoxaemia due to excessive oxygen therapy, are both associated with adverse clinical outcomes.[7-10]

Target oxygen saturation ranges

The recommended target saturation range should be included as part of the patient's oxygen prescription on the drug chart.

COPD and conditions associated with chronic respiratory failure

In the treatment of exacerbations of chronic obstructive pulmonary disease (COPD), oxygen should be titrated to achieve a target oxygen saturation range of 88–92%. This results in a greater than twofold reduction in mortality, compared with the routine administration of high-concentration oxygen therapy (see Box).[9]

Uncontrolled oxygen therapy for patients with COPD can cause hypercapnia. Due to concerns that the risks of high-concentration oxygen therapy may also apply in other conditions that place patients at risk of hypercapnic respiratory failure (cystic fibrosis, neuromuscular disorders, chest wall disorders, morbid obesity), the saturation target of 88–92% has also been recommended for these patients.[3]

Other acute medical conditions

Due to limited evidence from randomised controlled trials to guide clinical practice, it has been difficult to set a target saturation range for other acute medical conditions, such as asthma, pneumonia and acute coronary syndrome.[8,11-13] A pragmatic guide is to only

Box **Evidence for a target oxygen saturation of 88–92% in acute exacerbations of chronic obstructive pulmonary disease**[9]

In a randomised controlled trial, ambulances were allocated to treat patients having an acute exacerbation of chronic obstructive pulmonary disease with either:

- titrated oxygen therapy – oxygen delivered by nasal cannulae as required to achieve target pulse oximetry saturations of 88–92% and bronchodilators delivered by an air-driven nebuliser

or

- high-concentration oxygen therapy – 8 L/min via a non-rebreather mask, regardless of oxygen saturation, and bronchodilators given by an oxygen-driven nebuliser.

Key findings were:

- mortality was over two times higher in patients who received routine high-concentration oxygen compared with those who received titrated oxygen therapy
- the number needed to harm (death) with the routine use of high-concentration oxygen was 14 (one additional person died for every 14 treated).

give oxygen if saturations are under 92%, with a target saturation range of 92–96%.

Selecting the appropriate delivery method

Oxygen can be delivered through a number of devices (Table). For most patients, standard nasal cannulae are the preferred method of delivery. The flow rate is varied to achieve the target oxygen saturation.

Nebulisers

In patients with COPD, titration of oxygen therapy should continue during bronchodilator administration, if required, to achieve the 88–92% target oxygen saturation range. This can be done by giving titrated oxygen through nasal cannulae and giving the bronchodilator through an air-driven nebuliser. There is evidence from a randomised controlled trial for this approach (see Box).[9]

An alternative to nebulisation that allows for the ongoing titration of oxygen therapy is to give the bronchodilator from a metered dose inhaler via a spacer. If an oxygen-driven nebuliser must be used, the duration of each nebulisation should be limited.[3]

Patients who improve

If the patient's clinical condition improves to the extent that their oxygen saturation exceeds the target oxygen saturation range, this is an indication to reduce the concentration of inspired oxygen. Monitoring of oxygen saturations should be continued to detect subsequent deterioration of the underlying condition and the requirement to increase or resume oxygen therapy.

Patients who deteriorate

If oxygen saturations fall or increasing oxygen concentrations are required to maintain oxygen saturation within the target range, review the

Table **Oxygen-delivery devices**

Device	Oxygen delivery	Advantages
Standard nasal cannulae	24–35% FiO_2 at a flow of 1–4 L/min	Comfort, cost, easy titration
Simple face mask	40–60% FiO_2 at a flow of ≥5 L/min*	Delivery of higher FiO_2 levels than nasal cannulae
Non-rebreather reservoir mask	>60% FiO_2 at a flow of 15 L/min	Delivery of higher FiO_2 than simple mask
Venturi masks	FiO_2 set at 24–60%	To deliver controlled FiO_2, particularly at 24–28% in patients with COPD and others at risk of hypercapnic respiratory failure
High-flow nasal cannulae	FiO_2 set at 21–80%	Comfort, humidification and easy titration across a wide FiO_2 range

FiO_2 fraction of inspired oxygen COPD chronic obstructive pulmonary disease
* To avoid rebreathing of carbon dioxide exhaled into the mask

patient and consider measurement of their arterial blood gases.

In hospital a need for a fraction of inspired oxygen (FiO_2) greater than 40% should trigger a review by a senior clinician. If the patient requires an FiO_2 greater than 50%, consultation with intensive care is recommended. Increased monitoring and non-invasive or invasive ventilation should be considered.

If oxygen-induced hypercapnia develops, oxygen therapy should not be abruptly stopped. This may lead to rebound hypoxaemia (with a fall in oxygen saturation to below the level seen before oxygen was given).[14,15] Oxygen should be gradually down-titrated and non-invasive ventilation considered.

Prophylactic oxygen therapy

There are risks in the practice of administering prophylactic oxygen to a breathless patient who is not currently hypoxaemic, in the belief that it may prevent hypoxaemia if the underlying condition deteriorates. This practice has the potential to cause delay in recognising clinical deterioration and reduce the time available to start additional treatment.[16]

Conclusion

A major shift is occurring in the use of oxygen therapy. This shift is based on the recognition that the routine administration of high-concentration oxygen to acutely unwell patients has the potential to cause harm. Oxygen therapy should be titrated to ensure patients have an oxygen saturation within a target range. This reduces the risks of both hypoxaemia and hyperoxaemia. ◅

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New drugs

Vortioxetine

Approved indication: major depression
Brintellix (Lundbeck)
5 mg, 10 mg, 15 mg and 20 mg film-coated tablets
Australian Medicines Handbook section 18.1.5

Most antidepressants are presumed to work by increasing the synaptic availability of serotonin or noradrenaline. Based on non-clinical studies, the manufacturers of vortioxetine say it has a multimodal mechanism of action. They claim that it selectively inhibits reuptake of serotonin (5-HT) via the serotonin transporter and acts as an agonist or antagonist at various serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_{1D} and 5-HT_7).

Numerous short-term clinical trials (6–8 weeks) have compared the efficacy of vortioxetine to placebo with variable results (Table).[1-6] Not all of the studies have been published in full. One randomised trial found that daily vortioxetine at doses of 15 mg or 20 mg was significantly more effective than placebo at lowering scores on a depression rating scale.[1] In other trials, doses of 1 mg, 5 mg and 10 mg also lowered depression scores more than placebo.[2,3] In a trial enrolling people aged 65 years and over, vortioxetine 5 mg was better than placebo.[4] However, in two other trials of younger people (mean age 42–43 years) the 5 mg dose was no better than placebo.[5,6]

In a longer term relapse trial, 396 patients who responded to 12 weeks of vortioxetine 5 mg or 10 mg were randomised to continue treatment or receive placebo. After a total of 24 weeks, fewer patients in the vortioxetine arm than in the placebo arm had relapsed (13% vs 26%, p=0.0013).[7]

Nausea was the most common adverse event with vortioxetine. Its incidence was dose-related, occurring in 32% of patients who received the 15 mg or 20 mg dose. Other common events included diarrhoea, dizziness, constipation and vomiting.

In an analysis of seven placebo-controlled trials, sexual dysfunction was reported by up to a third of men and women taking the 15 mg or 20 mg dose.

Table **Short-term placebo-controlled trials of vortioxetine for major depression**

Trial	Number of patients (mean age)	Daily treatment (active reference comparator)	Outcome: mean change from baseline on depression rating scale at 6–8 weeks compared to placebo
Boulenger 2014[1]	607 (47 years)	vortioxetine 15 or 20 mg placebo (duloxetine 60 mg)‡	15 and 20 mg doses statistically better on MADRS than placebo (p<0.0001)
Henigsberg 2012[2]	560 (46 years)	vortioxetine 1, 5 or 10 mg placebo	All doses statistically better on HAM-D 24 (p<0.001)
Alvarez 2012[3]	429 (43 years)	vortioxetine 5 or 10 mg placebo (venlafaxine 225 mg)‡	5 and 10 mg statistically better on MADRS than placebo (p<0.0001)
Katona 2012[4]	453 (71 years)	vortioxetine 5 mg placebo (duloxetine 60 mg)‡	5 mg statistically better than placebo on HAM-D 24 (p=0.0011)
Jain 2013[5]	600 (42 years)	vortioxetine 5 mg placebo	Not significantly better than placebo on HAM-D 24
Mahableshwarkar 2013[6]	611 (43 years)	vortioxetine 2.5 or 5 mg placebo (duloxetine 60 mg)‡	Not significantly better than placebo on HAM-D 24

MADRS Montgomery–Asberg Depression Rating Scale HAM-D 24 24-item Hamilton Depression Rating Scale
‡ Venlafaxine or duloxetine was included as an active reference comparator which was compared to placebo but not to vortioxetine.

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.

NEW DRUGS

Sexual problems were also reported in up to 20% of people taking the placebo. As these events are often under-reported, doctors should ask the patients about these possible effects.

Following multiple oral doses, maximum plasma concentrations are reached after 7–8 hours. Bioavailability is 75% and vortioxetine's mean terminal half-life is about 66 hours. Vortioxetine is mainly metabolised by cytochrome P450 (CYP) 2D6 and metabolites are eliminated in the faeces (59%) and urine (26%).

The recommended starting dose of vortioxetine is 10 mg per day. However, because exposure is increased in people over 65 years old, the recommended starting dose is 5 mg per day in this age group.

Dose reduction should be considered if co-administration of strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine) is necessary. Conversely, the vortioxetine dose may need to be increased if strong CYP2D6 inducers (e.g. rifampicin, carbamazepine) are used.

Because of the risk of serotonin syndrome, concomitant use of monoamine oxidase inhibitors is contraindicated during vortioxetine treatment and for 14 days after it is stopped. Consult the product information if switching a patient between a monoamine oxidase inhibitor and vortioxetine, as washout periods are needed. Serotonin toxicity can also occur with other serotonergic medicines such as sumatriptan, tramadol and St John's wort. Prescribers should be vigilant for symptoms if these drugs are taken concurrently. As with other antidepressants, vortioxetine may increase the risk of suicide or mania in some patients.

Vortioxetine is a pregnancy category B3 drug. Although there is no human data, animal studies found that vortioxetine reduced fetal weight and delayed ossification. In rats, survival of pups was lower in mothers receiving vortioxetine.

Vortioxetine offers another option for people with major depression. However, the nausea and sexual adverse effects are common and may put some patients off. In general, vortioxetine reduced symptoms of depression and prevented relapse.

However, it was not clear from the trials how vortioxetine's purported multimodal mechanism of action contributes to its antidepressant effect. The efficacy and tolerability of vortioxetine in comparison with other antidepressants is not currently known.

T manufacturer provided the product information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

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