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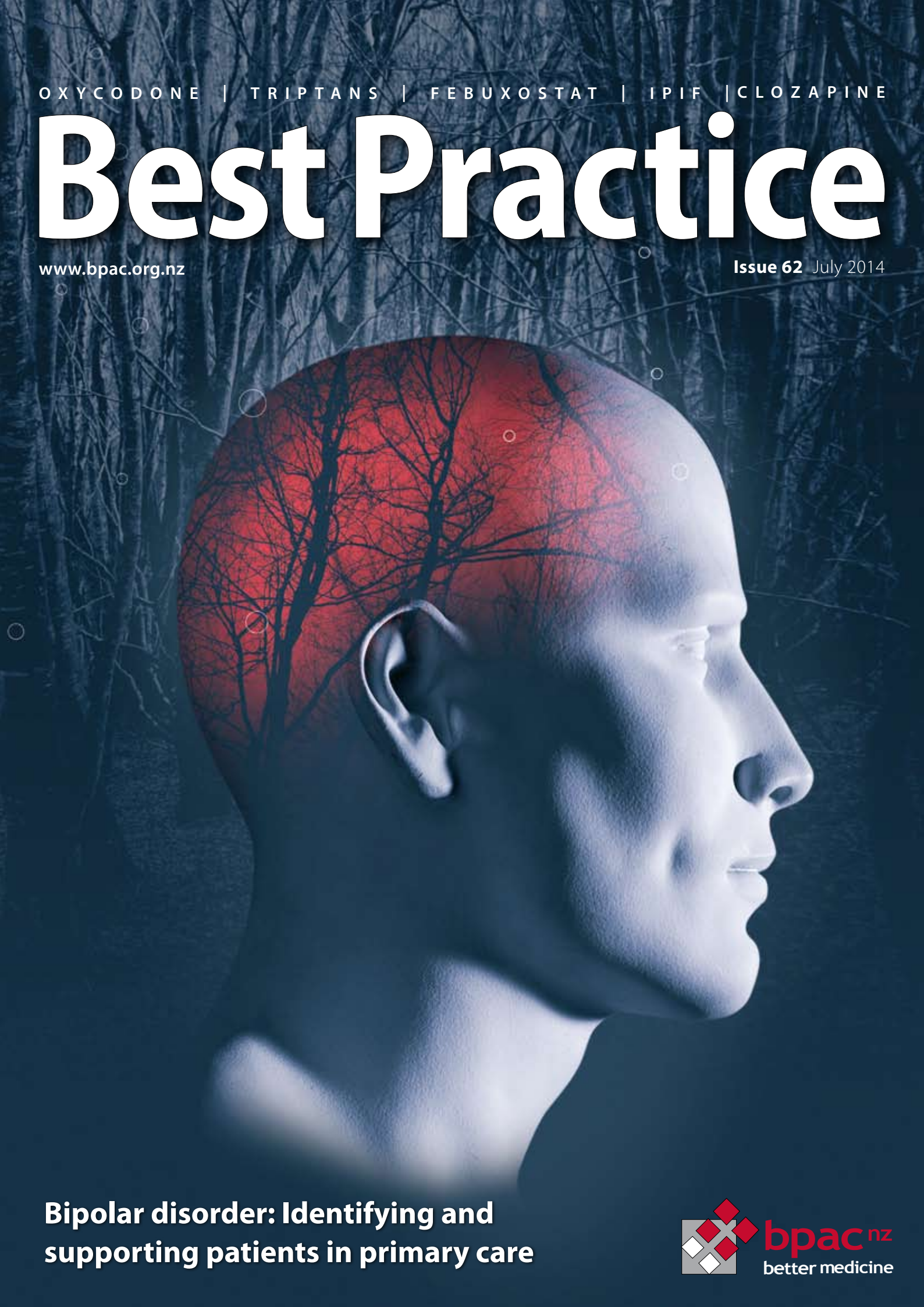

Bipolar disorder: Identifying and supporting patients in primary care

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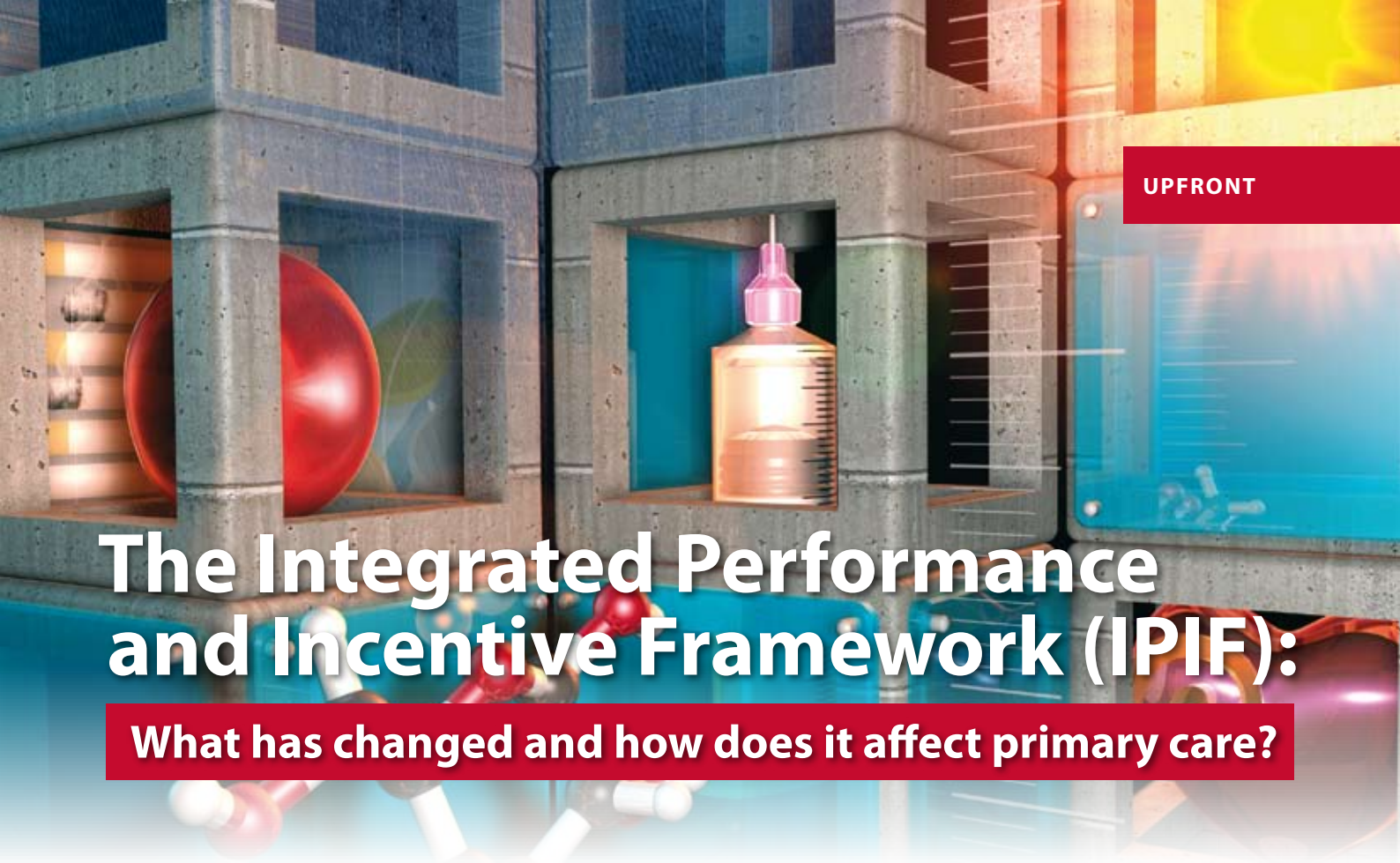


The Integrated Performance and Incentive Framework (IPIF):

What has changed and how does it affect primary care?

On June 30, 2014, the PHO Performance Programme (PPP) ceased and was replaced with an interim arrangement based on five targets previously used by the PPP. This interim arrangement will expand and evolve over the next 12 months into the Integrated Performance and Incentive Framework (IPIF). Like PPP, IPIF is a quality improvement programme. The goal of IPIF is to support the health sector in addressing equity, safety, quality and cost of services. IPIF aims to set high-level directions for improved effectiveness and productivity of health care for all New Zealanders. The development of IPIF and its implementation is an evolving process being led by clinicians, sector leaders and PHOs, that will reflect local and community priorities.

The first measures and targets for IPIF for 2014/15 were selected to provide continuity with the PPP and because reliable data exists to demonstrate performance (Table 1).

As with PPP, payments will be calculated each quarter, on the basis of the PHO's performance commencing on July 1, 2014.

IPIF recently released its second sector update and further updates will be provided at least monthly. In the first weeks of the interim programme, we asked Dr Richard Tyler, co-Chair of the IPIF Joint Project Steering Group, for his personal views on how he sees the implementation and evolution of IPIF affecting primary care.

Table 1: Measures, targets and funding for the Integrated Performance and Incentive Framework as of 1 July, 2014

Measure	Target	Proportion of funding
More heart and diabetes checks	90%	25%
Better help for smokers to quit	90%	25%
Increased immunisation rates for infants aged eight months	95%	15%
Increased immunisation rates for infants aged two years	95%	10%
Cervical screening	80%	25%

What were the key reasons for replacing the PHO Performance Programme (PPP) with the Integrated Performance and Incentive framework (IPIF)?

RT: *The idea of replacing the PPP was to find some measures which were more meaningful to good patient care and could reflect how the whole system was working. If a system is working as one there is a seamless transition from primary care to secondary care and back to primary care. A system that does this is working well for its population, and we want measures that will incentivise this.*

The New Zealand Government's budget for health spending in 2013–14 was $14.65 billion. This has increased steadily as a percentage of gross domestic product (GDP) from 6.8% in 1990 to 10.1% in 2010.* With an ageing population, improved diagnostic techniques, an ever-expanding choice of treatments, combined with a continual need to drive evidence-based improvement this cost will continue to grow. IPIF aims to create efficiency by unifying the health sector, promoting cost-effective use of resources, as well as focusing on reducing waste.

There is also a need for strategic alignment between existing and former programmes, e.g. the DHB Accountability Framework, the PHO Performance Programme, as well as various other programmes.

* Cumming J, McDonald J, Barr C, et al. New Zealand Health System Review. Health Syst Transit;4:xviii.

What are the main differences between how PPP operated and how IPIF will function in the future?

RT: *IPIF is intended to be a whole of system measure so requires the primary and secondary sectors to be working as one. Each will have important targets but the overall goal will be a synergy between the two to the benefit of the patient.*

The current challenges for the New Zealand sector are to: reduce inequalities, manage long-term conditions, reduce waiting times and improve productivity. IPIF hopes to meet these challenges by facilitating greater co-ordination than currently exists between primary and secondary care, and between other social services.

Is IPIF being modelled on international experience? What is the evidence that its implementation will improve outcomes within the health sector?

RT: *International experience is that the more care that occurs in the community the better the outcome. This is perhaps best illustrated in the care of the frail elderly who have been shown to lose condition and have poorer outcomes when hospitalised. International experience also shows much better outcomes and better patient experience when there is a seamless transition in and out of hospitals and the health system is working as one.*

A number of international studies have shown not only that investing in primary care improves patient outcomes, but that the more health care is coordinated by primary care, the better the outcome for patients. We can expect the role of the primary care clinician as "gate keeper" to health sector resources to evolve and expand as IPIF develops.

For further information on the international perspective, see: "The impact of Primary Care: A focused review". Available from: **www.hindawi.com/journals/scientifica/2012/432892/**

What are the immediate changes that clinicians in primary care may see as IPIF is implemented?

RT: *This will depend on how well local alliances are working. Over time clinicians in primary care are likely to be part of a more comprehensive team. There will also be more collaboration and interaction with hospitals and specialist services as primary care becomes better supported and is able to provide more comprehensive home care for patients and deliver more care in the community.*

The recently released sector update states that "much of the detail around IPIF has still to be developed." What changes can primary care health professionals expect to see over the coming years?

RT: *IPIF is a framework which requires the measures to be added to it. Some measures will be common across all communities and others will be specific to those communities and developed locally. Yes, there is still a lot of work to do on the specific measures.*

While many of the specific measures are yet to be announced, it would be reasonable for primary care to expect alignment and synergy with other programmes. For example, the IT Health Board's push to implement patient accessible electronic health records. This allows patient's electronic records to be shared between different areas in the health sector. In the Wairarapa DHB, this technology has been available since 2011. In the Capital and Coast DHB over 80% of patients records are accessible by electronic portal making them available to health professionals in primary care, after-hours clinics and hospital departments.

The first measures of IPIF do not refer to high need populations, i.e. people of Māori or Pacific descent, or people who live in the most deprived socioeconomic areas. How will the IPIF address issues of inequity within the health system?

RT: *I acknowledge this is lacking and this has been recognised by the steering committee as an important issue; a special work stream has been established to address this.*

Despite improvements being made since the mid-1990's, Māori and Pacific peoples continue to experience significantly lower health status than the majority of New Zealanders. With the "whole sector" approach of IPIF, it is hoped that this will result in improved partnerships between primary care and whanau ora services in Māori communities.

What tangible benefits are likely to be experienced by clinicians in primary care as a result of IPIF?

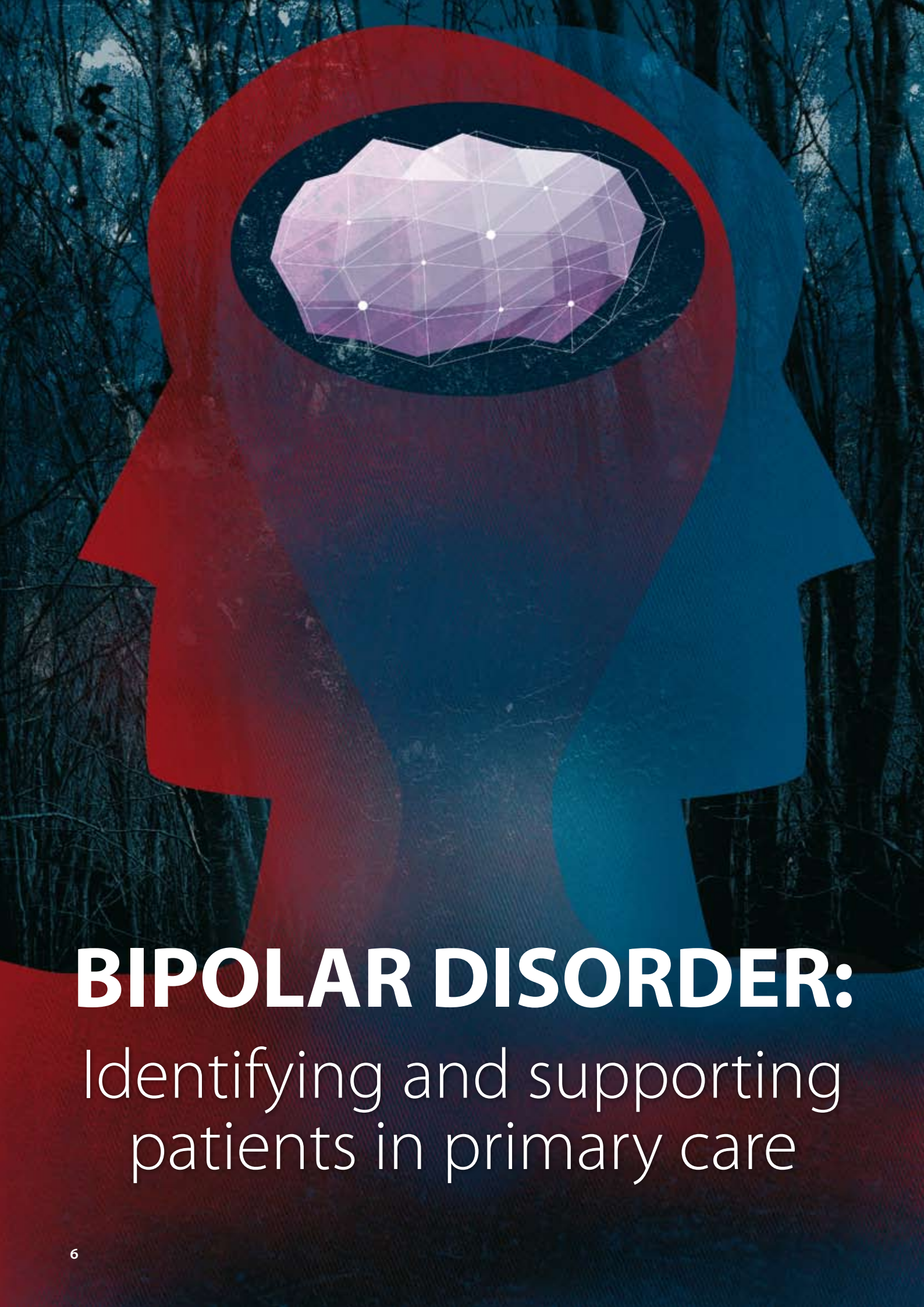
RT: *Benefits will evolve and will take time but they will likely see primary care clinicians have greater professional autonomy accompanied by better access to specialist support and investigative procedures. It is anticipated that they will be working more closely and collaboratively with hospitals, colleagues and other health professions such as Pharmacy. They will likely be part of a larger and more comprehensive primary care team. We also anticipate that primary care clinicians will have greater job satisfaction.*

In the draft IPIF framework, it is stated that it is expected that the implementation of IPIF will allow for:

- A minimum standard for service provision
- Potential support for clinical governance and professional development
- Greater individual influence over service development and priorities for professionals working within organisations that are achieving high levels of performance
- Improved access to referred services on a performance related basis

For further information on IPIF, including sector updates, see: **http://www.hiirc.org.nz/section/35484/integrated-performance-and-incentive-framework/**

Dr Richard Tyler is a General Practitioner based in Wellington. He is co-chair of the IPIF Steering Committee and is also chairman of Compass Health and the Medical Assurance Group of Companies, as well as being on the board of directors of bpac^{nz} and an Executive Committee member of General Practice New Zealand.



BIPOLAR DISORDER:

Identifying and supporting patients in primary care

Bipolar disorder can be challenging to diagnose and manage. It is often assumed to be recurrent major depression, until an episode of mania/hypomania occurs and the diagnosis of bipolar disorder is confirmed, usually by a Psychiatrist. Mood stabilising medicines, e.g. lithium and valproate, are the mainstay of pharmacological treatment. Monotherapy with antidepressants for a patient with bipolar disorder is associated with an increased risk of an episode of mania and should be avoided. A key role of general practice in the long-term management of patients with bipolar disorder is to educate the patient and their family about their condition, to encourage treatment adherence and a healthy lifestyle, to assess for treatment efficacy and monitor for adverse effects.

The burden of bipolar disorder

Bipolar disorder first appeared in the medical literature in the 1850s when alternating melancholia and mania were paired in a single condition.[1] For a number of years the diagnosis was termed "manic-depressive disorder", but this was replaced by bipolar disorder in 1980 when the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) was released.[1] Bipolar disorder is characterised by extreme mood swings – from hopeless depression to euphoric or irritable mania – with each episode usually bookended by symptom-free periods referred to as euthymia (Figure 1, over page).[2] However, many patients will have milder symptoms which can make diagnosing bipolar disorder challenging. Depression is the most common symptom and people with severe forms of bipolar disorder may be symptomatically unwell nearly 50% of the time.[3]

In New Zealand, bipolar disorder may be more prevalent among Māori (4.6%), compared to Pacific peoples (3.7%) and people of European and other ethnicities (1.8%).[4] The first noticeable mood disturbance in people with bipolar disorder often occurs during adolescence; one study found the mean age of onset was 17 years (+/- 4 years).[5]

The mood disturbances experienced by people with bipolar disorder can vary greatly. In some people, mild episodes of mania (hypomania, see opposite) are associated with increased creativity and productivity. In other patients, an episode of mania may be severe enough to require immediate hospitalisation and involuntary committal under the Mental Health Act. In between mood episodes, people with bipolar disorder may also experience cognitive impairment, e.g. problems with memory and attention, and relationship and occupational difficulties due to residual problems caused by past behaviour.[6] People with bipolar disorder are 15 times more likely to commit suicide than people in the general population and it is estimated that bipolar disorder may account for one-quarter of all completed suicides.[6] Approximately 10 – 15% of people with untreated bipolar disorder can be expected to die due to suicide.[2]

The severity of mania determines the type of bipolar disorder

General Practitioners are often the first clinician to suspect a patient has a mental illness. Although depression is the most common symptom of bipolar disorder, mania is the cardinal feature and its severity is used by Psychiatrists to categorise the patient's disorder.

A full manic episode is described as a distinct period of abnormally and persistently elevated or irritable mood, accompanied by an abnormally and persistently increased amount of goal-directed activity or energy, lasting at least one week and present most of the day, nearly every day (see: "The DSM-V criteria for episodes of mania and depression", Page 9).[6] Secondary episodes of mania caused by medicines, drugs or other disorders, e.g. attention-deficit/hyperactivity disorder or personality disorders, are not part of the bipolar spectrum.[6] During a manic episode a person may develop grandiose plans, or embark upon multiple overlapping and complex projects, often without any experience in the field, e.g. writing a novel or seeking funding for an impractical invention.[6] Full mania causes a noticeable social or occupational impairment, with poor judgement, and in some people a psychosis that causes them to be a danger to themselves and others.[6] A decreased need for sleep is an important feature of all forms of mania.[6]

Hypomania is characterised by the same features as mania but the patient's episode is less severe and does not cause the same degree of social or occupational impairment.[6] During an episode of hypomania, the patient may feel very positive, be highly productive, and function well, but people close to them will have noted the mood swing as being uncharacteristic.[7] Episodes of hypomania may last for shorter periods than episodes of mania.

Many people with bipolar disorder will experience periods of mild depression or mania not pronounced enough to be diagnosed, i.e. subsyndromal (sub-clinical), between more severe mood swings (Figure 1).[2] A study that analysed the weekly symptoms of patients with severe bipolar disorder in a mental health facility for 13 years, found that almost three-quarters (74%) of symptomatic weeks involved subsyndromal depression and hypomanic symptoms.[3] The symptomatic status of patients changed on average six times a year.[3] However, there is considerable individual variation in the duration of mood cycles and the period between mood changes can be days, weeks or even years.[2]

Types of bipolar disorder

Bipolar I disorder is diagnosed when patients have experienced at least one episode of mania (as opposed to hypomania).[6] The mean age of onset for the first mood disorder is approximately 18 years for people with bipolar I disorder, however, first onset has been seen in people aged over 65 years.[6] Many people with bipolar I disorder will be able to function fully between episodes, but 30% of people affected are reported to be severely impaired at work, which can result in reduced socioeconomic status, particularly if they experience repeat episodes.[6] The incidence of bipolar I disorder is similar among females and males.[6]

Bipolar II disorder is diagnosed in people who have had at least one episode of depression and one episode of hypomania, but have never experienced an episode of full mania. The average age of onset of bipolar II disorder is in the mid 20's; slightly later than for bipolar I disorder.[6] Fifteen percent of people with bipolar II disorder are reported to experience dysfunction between episodes.[6] Clinical data suggests that bipolar II disorder is more common in females, however, this may be because females with bipolar II disorder are more likely to seek treatment.[6]

Cyclothymic disorder is diagnosed when an adult patient has had numerous subsyndromal hypomanic episodes and numerous depressive episodes over a two year period, neither of which meet full DSM-V criteria for either mania or depression.[6] Cyclothymic disorder will progress to either bipolar I disorder or bipolar II disorder in 15 – 50% of people.[2]

"Rapid cycling" specifies that a patient has had four or more mood episodes, i.e. major depression, mania or hypomania, within one year.[6] Rapid cycling of moods in patients with bipolar disorder is associated with a reduced response to treatment and poorer outcomes.[8]

A "mixed episode" is where the patient experiences mania and depression during the same period, for a week or more.[9] For example, during a mixed episode a patient might report feeling sad or hopeless with suicidal thoughts, while feeling highly energised.[7] Outwardly they may appear agitated with disturbed sleep patterns and a major change in appetite.[7]

The cause of bipolar disorder is often multi-factorial

The cause of bipolar disorder is unknown and is likely to be multi-factorial. There is, however, a strong inheritable component to the disorder. The risk of a first degree relative of an affected person developing bipolar disorder is between 5 – 10%, but this increases to 40 – 70% for monozygotic twins.[10] There is good evidence that many genes are involved, each contributing a small portion of the risk.[10] The fact that monozygotic twins do not display identical rates of bipolar disorder suggests that environmental influences also play a role.

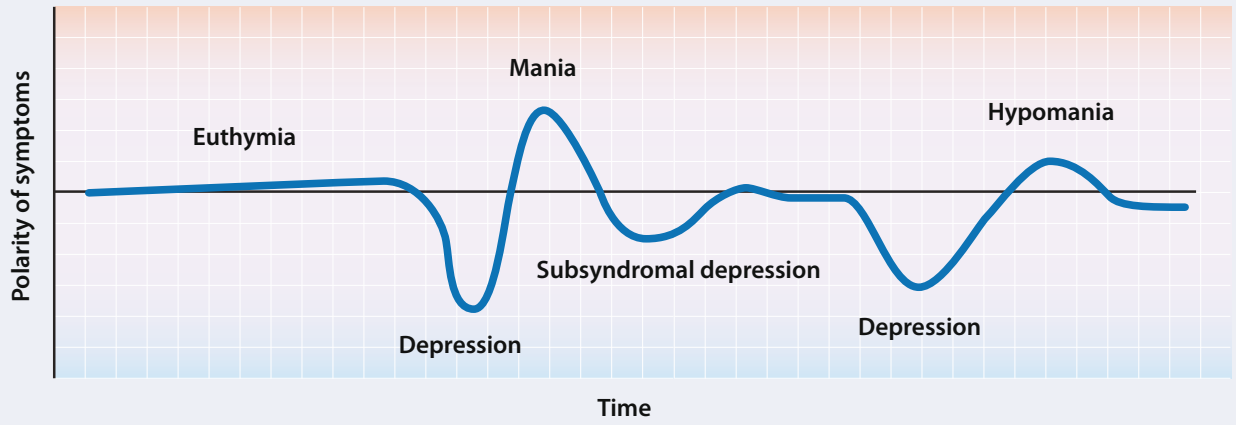


Figure 1: The typical mood fluctuations over time of a person with bipolar disorder, adapted from Muzina et al, 2007[2]

Bipolar disorder is often diagnosed as major depression

It is retrospectively reported that approximately one-third of patients with bipolar disorder will have been initially diagnosed as having major depression; this is because:[2]

1. Depression is more common
2. Depression is the most frequent symptom experienced by people with bipolar disorder and during an episode of mania people are less likely to consider themselves unwell and therefore will not present for treatment
3. The criteria for a diagnosis of major depression is the same as the diagnosis of depression in patients with bipolar disorder
4. Patients may not remember, or may be embarrassed about, manic episodes and therefore be reluctant to report them

Treatment for depression with antidepressants can have serious consequences for patients with bipolar disorder.[2] If an antidepressant is prescribed to a patient with bipolar disorder it is usually in combination with a mood stabiliser, e.g. lithium, to reduce the risk of a swing to mania (Page 13).[9] Increased mood cycling has been reported in patients with bipolar disorder taking antidepressant monotherapy.[11] A study of over 3000 patients with bipolar disorder treated with either an antidepressant alone, or an antidepressant with a mood stabiliser found that the risk of patients requiring treatment for mania was increased almost three-fold by antidepressant monotherapy.[11] The risk of mania requiring treatment was significantly decreased after three to nine months of concurrent treatment with a mood stabiliser and an antidepressant.[11]

The DSM-V criteria for episodes of mania and depression

An episode of mania must involve a sustained abnormal mood plus three of the following features present (or four features if the patient's mood is irritable rather than elevated) to meet DSM-V* criteria:[6]

- Inflated self esteem or grandiosity
- Increased talkativeness
- Decreased need for sleep, e.g. is rested after three hours sleep
- Easily distracted by unimportant or externally irrelevant stimuli
- Flight of ideas characterised by a nearly continuous flow of accelerated speech, which abruptly shifts from one topic to another
- An increase in goal-directed activity, e.g. at work, socially or sexually, or restlessness, i.e. purposeless activity such as pacing or holding multiple conversations at once
- Excessive involvement in high-risk activities, e.g. spending money recklessly, sexual indiscretion or imprudent investments

If the patient displays psychotic features or requires hospitalisation then the episode is automatically classified as manic.[6]

A major depressive episode is defined by five or more of the following symptoms, present at the same time, for at least a two-week period.[6] At least one of the symptoms must be either a depressed mood or a loss of interest or pleasure:[6]

- Depressed mood for most of the day, nearly every day
- Markedly reduced interest or pleasure in all, or almost all, of the day's activities, most of the day, nearly all day
- Insomnia or hypersomnia, nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt, nearly every day
- Significant weight loss when not dieting, or weight gain of more than 5% in a month, or a decrease or increase in appetite nearly every day
- Psychomotor agitation or retardation nearly every day
- A decreased ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death or suicide, or a suicide attempt

Episodes of major depression may last weeks or even months.

* The Diagnostic and Statistical Manual of Mental Disorder, 5th Edition

Identifying patients who may have bipolar disorder

Due to the cyclic nature of bipolar disorder it may take months, or even years, for a patient to be diagnosed. In the United Kingdom and the United States, the mean delay from the onset of symptoms to a correct diagnosis in a patient with bipolar disorder has been estimated to be ten years.[12] Mild symptoms or relatively infrequent swings to mania are likely to contribute to this delay for some patients. All patients who are suspected of having bipolar disorder should usually be referred to a Psychiatrist or an acute mental health service, depending on the severity of their symptoms and the degree of clinical suspicion. Bipolar disorder can occur in children, but is difficult to diagnose as children may switch between moods of happiness, silliness and irritability depending on the occasion and their level of development.[6]

A formal diagnosis of bipolar disorder is generally made by a Psychiatrist. An accurate and early diagnosis may decrease mortality due to suicide in patients with bipolar disorder.

When to suspect bipolar disorder

People with bipolar disorder often have:[2]

- A family history of bipolar disorder or "manic depression"
- Problems with alcohol
- Displayed risk-taking behaviour in the past, e.g. sexual, financial or travel-related
- A history of complicated and disrupted circumstances, e.g. multiple relationships, switching jobs frequently or frequent change of address

Differentiating bipolar disorder from major depression

To reduce the likelihood of patients with bipolar disorder being diagnosed with major depression, General Practitioners should ask patients with symptoms of depression about any history of mania/hypomania. Compared to patients with major depression, patients with bipolar disorder are more likely to display racing thoughts and/or irritability when they are not depressed. Patients with bipolar disorder are also more likely to have suicidal thoughts during periods of depression.[2] Patients with depression who do not respond to antidepressants, or respond erratically, e.g. a rapid response within days of starting treatment or a brief relief with a return of symptoms, should be reassessed for bipolar disorder.[2]

Mixed mood episodes of bipolar disorder

Patients with mixed mood episodes (Page 8) can be hard to diagnose; clinicians need to be alert to mixed mood episodes because when they are combined with a lack of sleep, and/or alcohol, the risk of the patient committing suicide is greatly increased.[13]

Females with bipolar disorder are more likely to experience mixed mood episodes and to have more rapid cycling of episodes.[13] There is not known to be a causal relationship between episodes of bipolar disorder and the monthly female hormone cycle, although pregnancy may be a trigger for episodes of hypomania in females with bipolar II disorder.[6]

Referral to a psychiatric service

An acute mental health service may be the first point of contact for family when a person with bipolar disorder experiences a manic episode. General Practitioners may be involved in this referral, but in an acute situation the patient may present directly to hospital. In rural areas there is often reduced access to Mental Health Services and General Practitioners may be more closely involved in diagnosing bipolar disorder following discussion with a Psychiatrist.

The initial psychiatric assessment will be based on the patient's presenting symptoms, the frequency and amount of time symptoms are experienced and any available family history of mental illness. Once the possibility of medicine or substance-induced symptoms has been excluded, DSM-V criteria are then applied to establish a diagnosis. It is important to include information about any history of alcohol or drug use when referring patients for psychiatric assessment, as approximately 70% of patients with bipolar disorder have a substance abuse disorder.[13]

Managing patients diagnosed with bipolar disorder

Generally, the management of patients with bipolar disorder is led by a Psychiatrist, and the primary care team is involved in liaising between the psychiatric multi-disciplinary team and social services, as well as supporting the patient and their family. Family and friends are an important support network for people with mental illness and this is particularly important in rural areas if there is reduced access to Mental Health Services. General Practitioners usually provide repeat prescriptions and monitor the patient's adherence to, and the effectiveness of treatment. Many of the medicines used to treat bipolar disorder have significant adverse effects and a proactive approach to patient management, e.g. reducing cardiovascular risk, is required. More than half of patients with bipolar disorder also have an alcohol use disorder which can complicate any assessment of the patient's mood and increases the risk of the patient attempting suicide.[6]

Medicines are the mainstay of treatment, however, self-management of bipolar disorder and engagement with the patient's family is also essential. It is important to educate patients and their families about bipolar disorder, to help reduce stigma, and to address any confusion between bipolar disorder and other forms of mental illness such as schizophrenia. Ensure that the information provided is understood by the patient and their family and is presented in a culturally appropriate way. Patients who have an understanding of their condition may be better equipped to recognise when a change in mood is about to occur.

Patients can reduce the likelihood of experiencing mood swings by maintaining daily routines that include regular medicine use and healthy sleep patterns, exercise and avoidance of alcohol.[9] Maintaining a daily pattern of activity can have positive effects for patients with bipolar disorder and reduce the likelihood of new mood episodes.[15] Treatment non-adherence in patients with bipolar disorder is a major risk factor for relapse.[9] Ongoing education about bipolar disorder for the patient and their family increases the likelihood that patients will adhere to treatment.[16]

Pharmacological treatment of symptoms

Many of the medicines used to treat patients with bipolar disorder have potentially severe adverse effects and treatment choices may vary as the patient's symptoms change. The initial choice of treatment depends on whether the patient is manic or depressive, the severity of their symptoms, patient preference and the balance of benefit versus risk of adverse effects. Treatment decisions are often made by the Psychiatrist who will prescribe additional medicines if required, e.g. if the patient undergoes rapid cycling of their mood. The General Practitioner should alert the Psychiatrist to any changes in the patient's mood that might require a change in treatment.

Lithium has been used for over 60 years for the treatment of bipolar disorder and is still frequently prescribed (see: "Monitoring the safe use of lithium", Page 16).[16] Other medicines used in the management of patients with bipolar disorder include mood stabilisers, antipsychotics and antidepressants. Patients will usually require ongoing laboratory monitoring while taking these medicines (Table 1, over page), and prescribers need to consider potential medicines interactions. For example, oestrogen-containing medicines such as combined hormonal contraceptives can reduce the effectiveness of lamotrigine.

 See the New Zealand Formulary for details on medicine interactions.

Traditional Māori beliefs about mental illness

Listening, being respectful to other points of view and understanding one's own cultural values are core components of cultural competency that make reconciling different belief systems easier.

Traditional explanations for mental illnesses in other cultures can be quite different to those of Western medicine, and there is the potential for conflict between traditional Māori and Western psychiatric approaches to mental health.

For example, Mate Māori is considered to be a cause of illness or uncharacteristic behaviour resulting from an infringement of tapu or the infliction of an indirect punishment. It may take several forms, both physical and mental, and can be an explanation to Māori for emotional, behavioural or psychiatric disorders. Māori may be reluctant to discuss mate Māori with clinicians due to fear of ridicule or perceived pressure to choose between psychiatric and Māori beliefs. However, the two approaches can co-exist. Mate Māori does not exclude a mental disorder and may be used to help understand the cause of the illness.

Traditional Māori beliefs are an area of expertise of tohunga and kaumātua assisted by kaitakawaenga (Māori cultural workers). It is appropriate to seek expert cultural assistance if these concepts arise when working with Māori.

 For further information see: "Recognising and managing mental health problems in Māori", BPJ 28 (Jun, 2010).

Table 1: Guidelines for monitoring medicines used in bipolar disorder[9, 17, 18]

	Baseline investigation	Ongoing monitoring
Lithium	See: "Monitoring the safe use of lithium", Page 16.	See: "Monitoring the safe use of lithium", Page 16.
Valproate (sodium)	Identify any history of haematological or hepatic disease. Measure FBC, LFT, electrolytes and creatinine. Advise the patient to stop treatment and seek medical attention if dermatological, liver or haematological-related adverse effects develop (see next column).	Measure weight, FBC, LFTs every three months for one year and then annually. Patients should seek medical advice if they develop fever, infection, rash, abdominal pain, vomiting, yellowing of the skin, bruising or bleeding. Reproductive endocrine disorders, e.g. menstrual disorders, polycystic ovary syndrome and hyperandrogenism are more common in females taking valproate.[19] Valproate (pregnancy risk category D) should not be used during pregnancy or in females of childbearing age unless there are no safer alternatives, in which case effective contraception should be used. Valproate can reduce bone mineral density and the patient's diet should contain adequate calcium. Weight-bearing exercise can improve balance and bone strength.
Carbamazepine		Measure FBC the first month after treatment, then six-monthly. Measure LFTs, electrolytes, urea and creatinine, monthly for three months and then annually. Patients should seek medical advice if fever, rash, mouth ulcers, bruising or bleeding develops. Effective contraception is recommended when carbamazepine (pregnancy risk category D) is prescribed to females of childbearing age.
Lamotrigine		Advise patients to seek emergency medical attention if a rash develops (characteristically maculopapular and occuring within the first eight weeks of treatment).[20] Effective contraception is recommended when lamotrigine (pregnancy risk category D) is prescribed to females of childbearing age.
Atypical antipsychotics, e.g. olanzapine, quetiapine, risperidone, aripiprazole or ziprasidone	Identify any family history of cardiac issues including congenital long QT syndrome	Measure weight, weekly for first weeks of treatment to detect those at risk of rapid weight gain and then every three months. Measure blood pressure and HbA_{1c} every three months for one year, then annually. In patients with an increased risk of diabetes, test fasting glucose monthly for the first three months due to rapid rise in glucose levels, then HbA_{1c} every three months. Measure lipid profile at three months and then annually. An ECG should be requested by the prescribing clinician if the patient is at an increased risk of QT-interval prolongation, e.g. patients with bradycardia or a history of electrolyte imbalances. Atypical antipsychotics may not be appropriate for patients with a congenital long QT syndrome as use of atypical antipsychotics is associated with an increased risk of sudden cardiac death.[21] In theory this risk may be further increased by the concurrent use of lithium. Measure prolactin levels in females with unexplained amenorrhoea or males with reduced libido who are taking risperidone. CNS depression, anticholinergic effects, e.g. dry mouth and constipation, dizziness, extrapyramidal effects, e.g. dyskinesias, may also occur.

Medicine choices may be different in females with bipolar disorder who may become pregnant – lithium, valproate and carbamazepine are all associated with a risk of foetal abnormalities (Pregnancy Risk Category D) and effective contraception is recommended for all females of child-bearing age who are taking these medicines.[17] The risk to foetal development is higher if these medicines are used in the first trimester, or in combination.[17] Valproate is associated with the highest risk and should be avoided in women of child-bearing age.[17]

Treatment of episodes of mania

Patients and their families should be educated in detecting early signs of manic episodes, e.g. increased activity or a decreased need to sleep.[13] When this occurs, encouraging the patient to continue their treatment and maintain a daily routine is important; patients who are manic may not feel they need treatment. Reducing stimulants, such as coffee, is recommended and it should be reiterated that restoration of sleep is an important aspect of treatment.[9] During an acute episode of mania the patient's safety and the risk of their reputation being damaged should be assessed, along with any potential safety risk to others. It may be necessary to contact a Mental Health Service if there are safety concerns involving dependents, or where the patient exhibits a marked loss of control, poor judgement or will have difficulty managing a concurrent long-term condition, e.g. type I diabetes. During an episode of mania a person may engage in indiscriminate sexual encounters without regard for the risk of sexually transmitted infections, pregnancy or the social consequences of their actions; long-term contraception, e.g. Depo-Provera, may be appropriate for some female patients.[6]

A Psychiatrist is likely to recommend the tapering and then withdrawal of medicines that may enhance manic episodes, e.g. antidepressants.[9] Depending on the individual patient, the following medicines may be prescribed for treating mania in a patient with bipolar disorder:[9]

- Lithium is effective in treating patients during a manic episode and is useful for its antisuicidal properties. However, lithium takes six to ten days to take effect and therefore may be used initially in combination with short-term antipsychotics and benzodiazepines. For example, lorazepam may be used for several days and gradually withdrawn as the patient's condition improves.[16]
- Valproate may provide a more rapid response than lithium
- An atypical antipsychotic may be prescribed alone or in combination with either lithium or valproate
- The typical antipsychotic haloperidol is effective at controlling acute mania, but does not prevent depression and has an increased risk of extrapyramidal adverse effects

Approximately half of patients with an episode of mania can be expected to respond to monotherapy with either lithium, valproate or an atypical antipsychotic, while three-quarters of manic patients are likely to respond to a combination of either lithium or valproate with an atypical antipsychotic.[9] The same medicines that are used to treat mania may be prescribed for patients with hypomania, although the dose may be lower.[2] Electroconvulsive therapy (ECT) may be effective for patients with treatment-resistant mania or depression and may be considered if the adverse effects of pharmacological treatment are a serious concern, e.g. women who are pregnant.[23]

Treatment of episodes of depression

Early symptoms of an episode of depression may include a loss of energy, difficulty concentrating and a low mood.[13] Treatment adherence is also an issue during periods of depression as patients may feel their treatment regimen is a burden to them.[13] During a depressive episode patients are at an increased risk of suicide.[9]

A Psychiatrist may prescribe lithium, valproate or lamotrigine as a mood stabilising regimen for depression in patients with bipolar disorder.[9] This will then allow for the safe use of antidepressants, e.g. an SSRI, without an increased risk of mania developing.[9] If an antidepressant is prescribed for patients with bipolar disorder, SSRIs are preferred (in combination with another medicine) to tricyclic antidepressants as they are less dangerous if taken in overdose.[9] Atypical antipsychotics may be used to settle agitation often seen in patients with depression and mania; whether these medicines have specific antidepressant or mood stabilising actions is uncertain.

Treatment of patients with rapid cycling or mixed episodes

Patients with rapid cycling or mixed episodes may be more difficult to manage than those with either an isolated episode of mania or depression. Different combinations of medicines may be appropriate for these subtypes of bipolar disorder.

Rapid cycling can be induced by substance use and antidepressant monotherapy.[9]

Depending on the individual patient, the following medicines may be prescribed for treating rapid cycling of mood in patients with bipolar disorder:[9, 16]

- Valproate, lithium, olanzapine, lamotrigine or quetiapine as monotherapy

- Lithium with valproate and lithium with carbamazepine or lamotrigine, in combination

Depending on the individual patient, the following medicines may be prescribed for treating mixed episodes in a patient with bipolar disorder:[16]

- Olanzapine, quetiapine and valproate, usually with a mood stabiliser
- Olanzapine with fluoxetine or valproate with olanzapine in combination

Managing patients during periods of euthymia

Clinicians can anticipate changes in circumstances that make a relapse of symptoms more likely and help the patient and their family to develop stable daily routines that includes taking medicines regularly. At each consultation the clinician should consider:

- Are the patient's symptoms under control?
- Has there been any change in circumstances that may cause the patient excess stress, e.g. a change in occupation, relationship status, social isolation or finances?
- Has the overall health of the patient changed, e.g. alcohol consumption, weight, smoking status or substance use?

Discussing the patient's mood may help the patient to gain insight into their disorder and promote self-management, e.g. moderating the use of alcohol and avoiding alcohol altogether during depressive or manic episodes. If a person with bipolar disorder becomes symptomatic their family can assist by encouraging them to delay making any important decisions until their mood has stabilised.

Develop strong relationships with patients and the people supporting them

The common goal of all treatment plans should be a structured and supportive relationship between the patient and their family and the patient and the clinician. This makes communication easier and the patient is more likely to value interactions with clinicians. Regular contact is one of the best ways to achieve this and maintain the patient's adherence to treatment. During the maintenance period the primary care team in conjunction with the patient's family should:

- Monitor sleep patterns which may be an early sign of a mood change
- Monitor for subsyndromal depression
- Consider if psychological or social support, e.g. counselling, would benefit the patient. Mental Health Services are able to meet the patient regularly in their own home in some areas.

General Practitioners should ensure they are receiving regular copies of outpatient attendance notes when the patient visits the consulting Psychiatrist.

The Ministry of Health has a list of resources available to people who are affected by bipolar disorder, go to: **https://www.health.govt.nz/your-health/conditions-and-treatments/mental-health/bipolar-disorder**

Monitor all aspects of the patient's health

Cardiovascular disease, obesity, and diabetes ("the metabolic syndrome") are common among people with bipolar disorder; long-term care of patients with bipolar disorder involves close monitoring of cardiovascular risk.[12] It is likely that the cardiovascular risk of people with bipolar disorder is increased due to higher rates of smoking and reduced physical activity during periods of depression, as well as the adverse effects of the medicines used to manage the disorder, e.g. weight gain and hyperlipidaemia. Advice about smoking cessation, alcohol reduction, diet and exercise should be included in all management plans.

Contraception and pregnancy planning should be discussed with female patients due to the risk of mood stabilising medicines causing birth defects.[18] Folic acid supplementation is recommended to reduce the risk of foetal neural tube deficits in females taking valproate and carbamazepine (although these medicines, especially valproate, are not recommended during pregnancy or in females of child-bearing age unless there are no safer alternatives). Hepatitis B vaccination may be appropriate for patients with a history of drug taking or promiscuous behaviour.

Monitor for other forms of mental illness

Patients with bipolar disorder can be expected to develop more than one psychiatric disorder during their lives. Many patients with bipolar I disorder are reported to have some form of anxiety disorder and substance misuse disorders are also common.[13] Patients with bipolar disorder and co-morbid anxiety may self-medicate with alcohol or other substances.[9] Concerns about the emergence of an additional psychiatric co-morbidity should be discussed with a Psychiatrist.

Be prepared for the lifecycle of bipolar disorder

Patients, their families and health professionals should be prepared for the cyclic nature of bipolar disorder. Some patients will need to be admitted into hospital care during episodes of acute mania with the patient returning to community-based care between episodes. When the patient transitions from tertiary to primary care the support of their family and General Practitioner is important in re-establishing routines in order to reduce the risk of a relapse.

See over page for information about the safe use of lithium.

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Monitoring the safe use of lithium

Lithium is an effective treatment for acute mania, acute depression and long-term mood stabilisation in people with bipolar disorder.[16] However, lithium is associated with a risk of serious adverse effects and patients need to be monitored closely.

Lithium has a relatively slow onset of action and will take six to ten days to produce a clinical effect in patients who are manic, and six to eight weeks for patients with bipolar depression.[16] Lithium is available in 250 mg capsules, and 250 mg and 400 mg tablets.[17] The bioavailability of the different formulations of lithium varies widely, therefore if the preparation is changed, careful monitoring is required, particularly if switching between modified and immediate-release formulations.[17]

Monitor serum lithium levels: Lithium has a narrow therapeutic index and patients need to be monitored to ensure safe and effective serum lithium levels are achieved and to prevent the development of adverse effects. Local guidelines can vary and Psychiatrists may adjust recommendations depending on the individual patient.

The patient's lithium serum concentration should be measured five to seven days after dose initiation, or dose change, with the blood sample taken 12 hours after dosing. Generally the patient's serum lithium is titrated to 0.6 – 0.8 mmol/L as this is reasonably well tolerated; a higher concentration (0.8 – 1 mmol/L) is recommended for acute episodes of mania,[17] and for patients who have experienced a relapse or have subsyndromal symptoms. Lithium levels should be monitored

Table 2: Recommended baseline and follow-up monitoring for patients taking lithium long-term[16, 17]

Test	Baseline and follow-up	Rationale
Serum lithium	Five to seven days after first dose, then weekly, until stable, then every six months	Lithium has a narrow therapeutic window
Serum creatinine	Baseline and every six months	Lithium is excreted by the kidneys, therefore there is risk of reduced renal function with long-term use
Serum electrolytes (sodium)	Baseline and then every six months	Sodium levels influence lithium levels
Thyroid function (TSH)	Baseline and then every six months. More frequently if clinically indicated	Hypothyroidism and rarely hyperthyroidism is increased with the long-term use of lithium
ECG in patients aged over 45 years or with cardiac problems, including hypertension	Baseline and then yearly (if cardiac risk)[22]	Lithium can cause sick sinus syndrome and QT prolongation and baseline ECG is useful if future complications develop, or if other medicines are added that have cardiac conduction effects
Serum calcium	Baseline and then yearly[22]	Lithium can cause hypercalcaemia secondary to elevated parathyroid concentrations

weekly after initiation and after every dose change, until a desired stable lithium level is achieved.[17] Levels should then be measured every six months and more frequently if the patient's sodium or fluid intake changes or they develop a concurrent illness.[17] Placing a patient recall in the Practice Management System (PMS) will automatically generate reminders. Patients should be educated to maintain adequate fluid intake, particularly during summer or during periods of physical exertion, or febrile illness. A serum lithium level > 1.2 mmol/L is usually considered to be toxic. A level > 2 mmol/L is a medical emergency.[17]

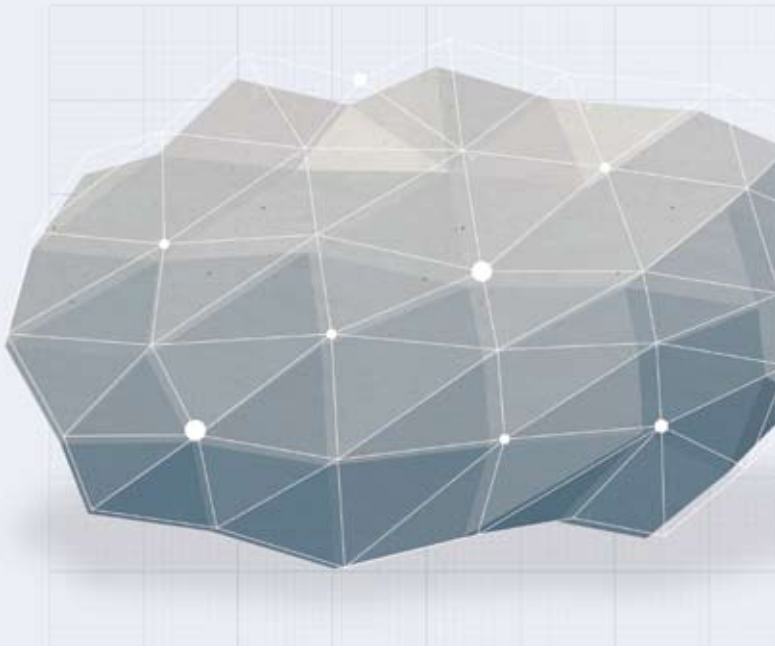
Monitor for adverse effects: Fine tremor and nausea are common dose-dependent adverse effects of lithium treatment, but often pass after one to two days. Coarse tremor, general fatigue, vomiting, diarrhoea, a metallic taste in the mouth, and a reduction in the sensitivity of the abdomen (central obtunding) indicate toxicity.[16, 17] Adverse effects mostly occur when lithium plasma levels change rapidly and should be anticipated when doses are increased.[16] Lithium overdose can cause chronic neural toxicity and may even be fatal.[16] Lithium reduces the ability of the kidneys to concentrate urine causing polyuria and increased thirst; it is reported that 10% of patients taking lithium long-term will develop reversible diabetes insipidus.[16] The dose of lithium will need to be reviewed in older patients and patients with renal impairment to avoid serum lithium reaching toxic levels.

Some patients will experience weight gain of as much as 10 kg after lithium treatment is started and this can affect treatment adherence. Hypothyroidism is reported to be six times more prevalent in patients taking lithium.[16] Patients taking lithium may develop hypercalcaemia due to elevated parathyroid concentrations.[16] If hypercalcaemia is significant then lithium treatment may need to be withdrawn.[16] Lithium should be avoided where possible during pregnancy and breast-feeding.[16]

If lithium is withdrawn abruptly there is an increased risk of manic relapse. When lithium treatment is ceased doses should be reduced over a period of at least four weeks, and preferably over a period of three months.[17]

Monitor other laboratory parameters: Local guidelines vary for the frequency of monitoring of other parameters and this is likely to be directed by a Psychiatrist. Table 2 provides a reasonable approach to monitoring patients taking lithium long-term.

Medicine interactions: Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor-II antagonists (ARBs), diuretics (particularly thiazide diuretics, e.g. bendrofluazide, hydrochlorothiazide) and non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the renal clearance of lithium and result in increased serum lithium levels.[22] Where possible the combination of any of these medicines with lithium should be avoided. If combination treatment is required the medicines should be prescribed at a stable, rather than variable dose. Patients should be aware of the potential risk of over-the-counter NSAIDs and advised to avoid these. Regular monitoring of renal function is recommended if medicines which can affect renal function are taken concurrently with lithium. Medicines that affect serotonin, e.g. SSRIs, clomipramine, tramadol and venlafaxine, can cause serotonin syndrome when taken in combination with lithium.[22] Sodium restriction can result in lithium toxicity and excess sodium, e.g. in patients taking sodium bicarbonate, can cause lithium serum levels to fall.[17]



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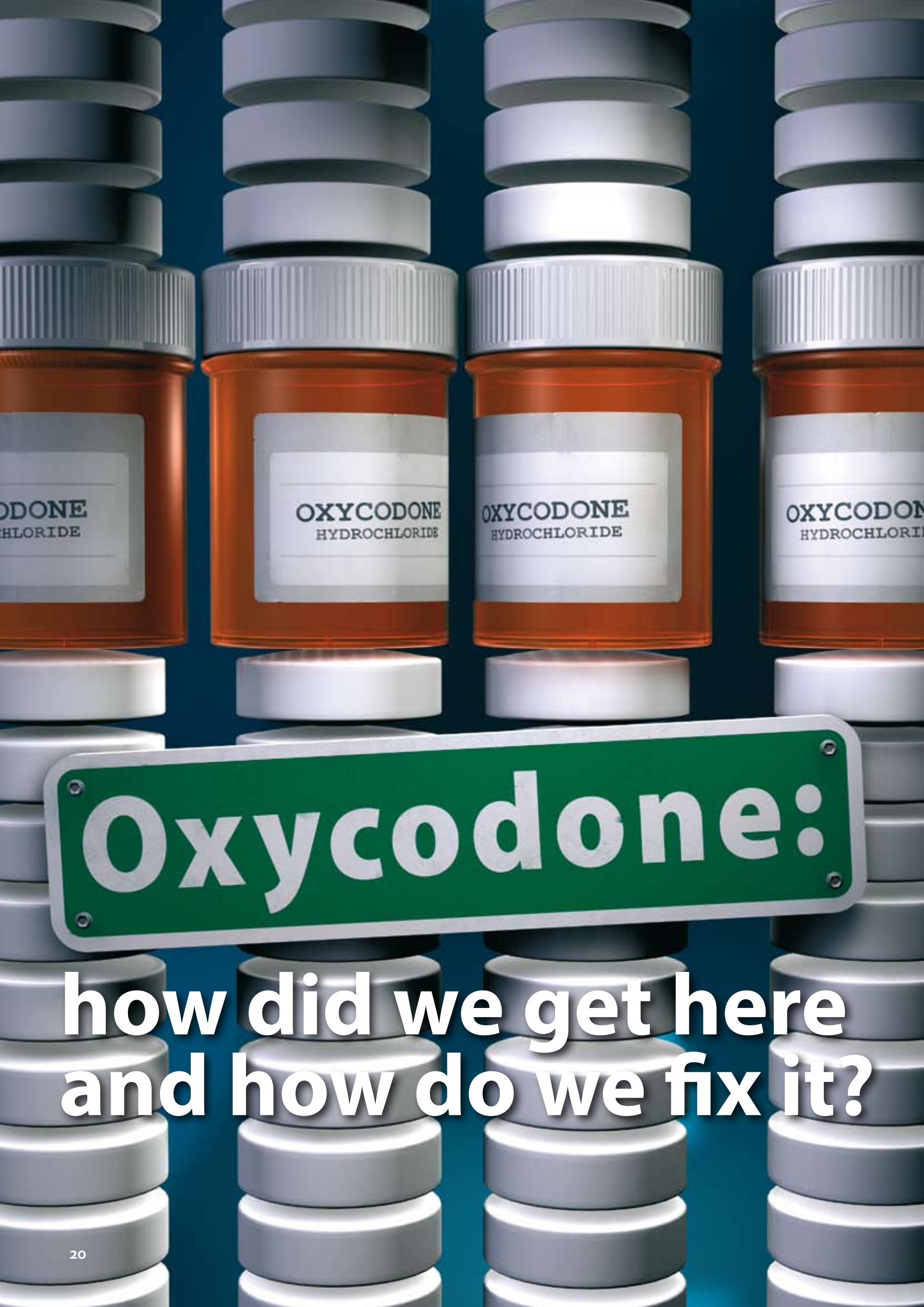

how did we get here and how do we fix it?

Following on from the interview with Dr Jeremy McMinn in the last edition of Best Practice Journal, we examine in more detail what the actual problem is with oxycodone, and how we ended up in this situation.

How did the problem with oxycodone evolve?

When oxycodone was first introduced into New Zealand in the early 2000s, it was regarded by many as a "new and improved" strong analgesic, with fewer adverse effects and perhaps none of the stigma associated with morphine. As a result, prescribing of oxycodone increased significantly over the next few years, reaching its peak in 2011/12. The number of prescriptions for morphine remained relatively stable over this same time period, suggesting that a new patient population being treated with oxycodone had been created.

Paralleling this surge in oxycodone use, reports of misuse and addiction emerged in New Zealand, following the trend observed in other countries with a longer history of oxycodone use. It has now become apparent that there is little or no advantage of oxycodone over morphine in terms of managing pain. Oxycodone is associated with the same adverse effects as morphine, and appears to be even more addictive than morphine. Therefore, there is no reason to continue to prescribe oxycodone instead of morphine (unless intolerable adverse effects have occurred with morphine), or to prescribe it when a less potent analgesic would be more appropriate.

The Wellington psychiatrist and addiction specialist Dr Jeremy McMinn commented in his interview in BPJ 61 (Jun, 2014), that in terms of the misuse of oxycodone in New Zealand, we are "looking at a disaster in the making". Clinicians are urged to assess whether oxycodone is appropriate when initiating or continuing a prescription and, if necessary, make changes to their prescribing behaviour. How is it best to manage the problem with oxycodone? According to Dr McMinn: "Don't get there in the first place".

The international experience

Oxycodone was first synthesised in Germany in 1916 and became available for use in the United States in 1939. For many years it was used overseas as a component of combination short-acting analgesics, including paracetamol and NSAIDs. The controlled-release oxycodone-only formulation, OxyContin, was approved by the Food and Drug Administration (FDA) in the United States in 1996. In New Zealand, oxycodone was approved by Medsafe in 2001 and the oral forms (controlled and immediate-release) were subsidised on the New Zealand Pharmaceutical Schedule from 2005.

Since its release, the use of oxycodone has increased dramatically and many countries are now dealing with misuse and addiction issues. For example, in Ontario, Canada, the number of prescriptions for oxycodone increased by 850% between 1991 and 2007.[1] After controlled-release oxycodone was added to the Ontario state drug formulary there was a five-fold increase in oxycodone-related mortality, along with a 41% increase in overall opioid-related mortality.[1] Similar increases in the prescribing rates for oxycodone have also been observed in the USA. The national estimates for drug-related emergency department visits for oxycodone-containing medicines increased from 27.6 per 100 000 people in 2004 to 88.5 visits per 100 000 in 2009.[2] In Australia, the oxycodone supply increased 22-fold between 1997 and 2012, and oxycodone became the seventh most commonly prescribed medicine in general practice.[3] By 2007, a national sample of injecting drug users found that 51% had reported using oxycodone.[4]

The situation in New Zealand

Between 2008 and 2013, the number of dispensed prescriptions for strong opioids in New Zealand has increased significantly (Figure 1, over page). Much of this increase is attributed to a growing number of dispensed prescriptions for oxycodone. The most recent dispensing data from 2013 suggests that the number of prescriptions for oxycodone may be reaching a plateau, but the fact remains that oxycodone is a second-line option for moderate to severe pain, and should be dispensed considerably less than morphine.

The type of prescribers initiating oxycodone remained similar in 2013, compared with when first reported in 2011. **Approximately 30% of prescriptions for oxycodone are written by General Practitioners and the remaining 70% are from other clinicians**, e.g. those working in secondary care.[5] In 2013, the proportion of prescriptions initiated in secondary care and continued in general practice was 17%, the same figure as in 2011 (Figure 2).[5]

Given the current best practice recommendations that oxycodone generally be reserved for second-line treatment after morphine, it is concerning that **approximately 80% of patients prescribed oxycodone for the first time in 2013 did not have a previous prescription for morphine** in the preceding 12 months.[5] This suggests that the majority of first-time prescribing of oxycodone is occurring before a trial of morphine, or alternatively, patients are being treated in hospital with parenteral morphine or pethidine and discharged with oral oxycodone.

For further information see:

"Oxycodone use still increasing", BPJ 36 (Jun, 2011).

"Update on Oxycodone what can primary care do about the problem", BPJ 44 (May 2012).

The evidence about oxycodone

The strong marketing of oxycodone (See: "The oxycodone marketing campaign, Page 24), along with its rapid rise in popularity, means that many aspects of its pharmacology and general use may be misunderstood. There are few head-to-head trials comparing oxycodone with morphine or other opioids, yet several claims have been made about its alleged superiority, many of which are not entirely accurate. There is no debating that oxycodone is an effective analgesic, however, there is no compelling clinical reason to choose it over morphine, and the associated risks and problems with its use, clearly place oxycodone as a second-line option.

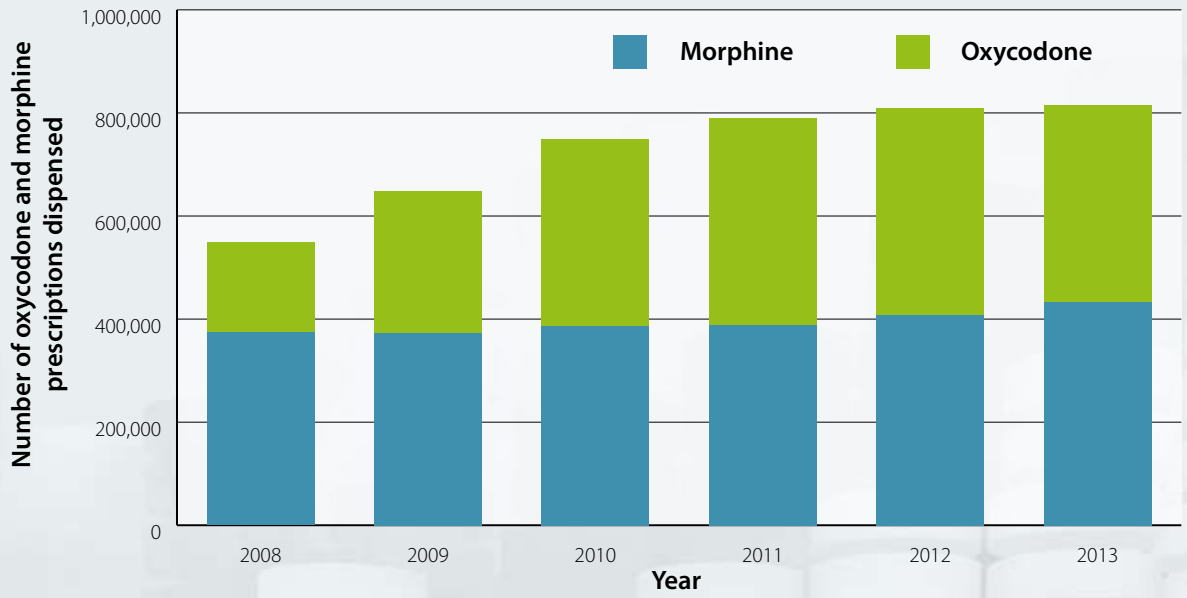

Figure 1: Number of oxycodone and morphine prescriptions dispensed (excluding injected preparations).[5]

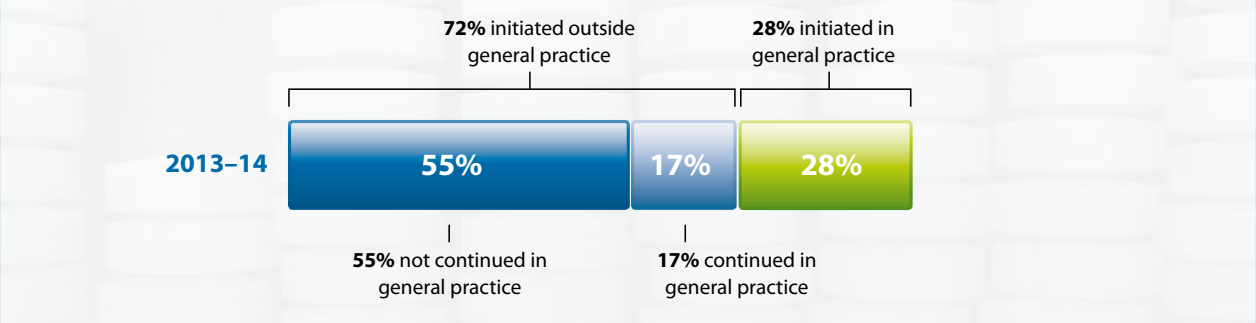

Figure 2: Source of oxycodone prescriptions for patients initiated in 2013/14 (Apr 2013 – Mar 2014)

Potency: oxycodone is a strong opioid

Despite its name, oxycodone is not a "natural version of codeine" or a "gentle analgesic" – it is approximately twice as potent as morphine, i.e. 10 mg of oxycodone is equivalent to 15–20 mg of morphine.[6, 7] A clinical trial reported that oral controlled-release oxycodone was twice as potent as oral controlled-release morphine in patients who received single doses for post-operative pain following hysterectomy.[8] For total and peak analgesic effects, the doses of 20 mg and 40 mg oxycodone were comparable to morphine doses of 45 mg and 90 mg, respectively.[8]

Oxycodone is approximately 7.5 – 20 times more potent than codeine, i.e. 10 mg of oxycodone is equivalent to 75-200 mg of codeine.[6]

The stigma associated with morphine is a reason that some patients are reluctant to use it, however, the same patients are comfortable using oxycodone. When discussing appropriate analgesic treatments with patients, clinicians need to ensure that patients understand that oxycodone is used for the same purpose as morphine and is actually more potent.

Addictive potential: oxycodone rates higher than morphine

All opioid analgesics (including weak opioids) are potentially addictive, but the marketing campaign for oxycodone promoted the belief that it had a lower addictive potential than other strong opioids. However, the literature suggests that oxycodone actually has a higher addictive potential than morphine.

A systematic review of nine randomised trials compared the likeability and likelihood of misuse of oral oxycodone, morphine and other selected opioids in recreational drug users and people with a history of opioid misuse. It was found that oxycodone was more favoured and more likely to be misused than either morphine or hydrocodone (not available in New Zealand).[9] Oxycodone demonstrated high subjective attractiveness ratings with a few negative ratings across the majority of studies included in the review. Oxycodone was also associated with consistently higher "take again" ratings than morphine.[9]

The addictive potential of strong opioids needs to be discussed with and understood by patients before they are prescribed. A psychological assessment of the likelihood of addiction forms part of the risk-benefit analysis for the decision to prescribe an opioid.

Renal impairment: use oxycodone with caution

Many clinicians have prescribed oxycodone in preference to morphine due to the belief that oxycodone is safer in patients with renal impairment. However, oxycodone should be used with caution in patients with renal failure and prolonged use avoided in patients with an eGFR < 10 mL/min/1.73 m^2 (due to the risk of accumulation of metabolites).[10] Case reports of oxycodone toxicity in patients with renal impairment have been reported, along with increased sedation.[11]

In many cases, morphine can still be safely used in patients with renal impairment, if it is dosed carefully; use the lowest effective dose and consider the cumulative effect. Patients will have an individual response to morphine in terms of its effect on their renal function.

Fentanyl is regarded as the safest strong opioid for patients with renal impairment (although does have other adverse effects).[10] Methadone is also an appropriate option for patients with renal impairment, but can be complex to dose and should only be prescribed if the clinician is familiar with its use.[10] Codeine, pethidine and tramadol should be avoided in people with renal impairment.

The two main metabolites of oxycodone are oxymorphone (a very potent analgesic) and noroxycodone (a weak analgesic), which are both renally excreted.[6] It is reported that up to 19% of oxycodone is eliminated unchanged in the urine.[12] There is limited data on renal clearance of oxycodone. A small study in people with mild-to-moderate renal dysfunction showed that the peak plasma oxycodone and noroxycodone concentrations were approximately 50% and 20% higher, respectively, than in people without renal failure.[13] The AUC (area under the curve – a measure of total exposure to a drug) values for oxycodone, noroxycodone and oxymorphone were approximately 60%, 50% and 40% higher in people with renal dysfunction than in people with normal renal function, respectively.[13]


For further information see:

"Fentanyl patches to be available without Special Authority in 2011", BPJ 33 (Dec, 2010).

"Methadone – safe and effective use for chronic pain" BPJ 18 (Dec, 2008).

The oxycodone marketing campaign

It has been suggested that the high use of oxycodone is partly related to the marketing campaign for OxyContin. When Perdue Pharma introduced OxyContin to the United States in 1996 it embarked on an expensive marketing and promotion campaign.[14] During the first six years on the market the company invested 6 – 12 times more on marketing and promotion (including $US 200 million in 2001 alone) than it spent on promoting MS Contin (morphine) or that Janssen Pharmaceuticals spent on Duragesic (transdermal fentanyl).[14] Sales increased from $US 48 million in 1996 to $US 1.1 billion in 2000.[14]

A consistent feature of the promotion and marketing campaign for OxyContin was the minimisation of the risk of addiction, which Perdue claimed was very small, in patients with chronic non-malignant pain.[14] This misrepresentation proved costly for Perdue who subsequently pleaded guilty to criminal charges of misbranding as a consequence of their incorrect claim that oxycodone was less addictive and less subject to misuse and diversion than other opioids. The company was ordered to pay $US 634 million in fines.[15] Perdue trained its sales representatives to carry the message that the risk of addiction was less than 1%.[16] However by 2004, OxyContin had become the most misused prescription opioid in the US.[17]

Adverse effect profile: similar overall to morphine

Overall, oxycodone and morphine have similar adverse event profiles that are consistent with other opioid analgesics. The most common adverse events reported with use of oxycodone (with approximate rates) are constipation (25–30%), nausea (25%), drowsiness (15%), vomiting (10–15%) and pruritis (10–15%).[6] It has been reported that constipation occurs more frequently in people taking oxycodone compared to those taking morphine.[6] The incidence of the other adverse effects are generally similar, however, a few studies have reported that the rates of nausea and vomiting, hallucinations and pruritis may be lower in people taking oxycodone compared to those taking morphine.[6]

Oxycodone, unlike morphine, is mainly metabolised by the CYP3A and CYP2D6 enzymes in the liver.[7] The involvement of CYP3A in the metabolism of oxycodone makes it more prone to interactions with drugs that inhibit or induce this enzyme.[7] Inhibitors of CYP3A, e.g. ritonavir, clarithromycin, itraconazole, miconazole and grapefruit juice potentiate the effect of oxycodone, resulting in an increased risk of adverse effects.[7] Inducers of CYP3A, e.g. St John's wort and rifampicin, reduce exposure to oxycodone.[7] This may result in people taking higher doses of oxycodone, which becomes problematic if the enzyme-inducing medicine is stopped.

CYP2D6 is a highly polymorphic enzyme; gene mutations and deletions cause the enzyme to be non-functional or over-expressed. This results in people having phenotypes for poor, intermediate, extensive or ultra-rapid metabolisers of drugs which are dependent on this enzyme. Most evidence has found that the CYP2D6 genotype does not have a significant influence on the analgesic effect of oxycodone or risk of adverse effects, but this is an ongoing area of research.[7]

What lessons can be learnt?

The New Zealand statistics show that although the growth in oxycodone prescriptions may have slowed in recent years, prescribing rates are still very high. The data from Canada, the USA and Australia regarding illicit use, hospitalisations and deaths as a result of oxycodone should be of great concern to New Zealand as these countries have a longer experience with oxycodone use. The overriding message is that continued high prescribing rates will eventually result in more illicit use of oxycodone, more people addicted to oxycodone, and associated downstream effects, which New Zealand is already starting to see (this will be examined in further detail in the next article in this series).

Oxycodone prescribing in secondary care

Dispensing data shows that in New Zealand, the majority of prescriptions for oxycodone are not being written by General Practitioners.[5] This suggests that a considerable proportion of oxycodone is being prescribed to patients on discharge from hospital, e.g. for post-surgical pain management. Some General Practitioners feel compelled to continue this prescribing, therefore adding to the problem. Studies have suggested that hospital and specialist prescribing is an important influence on General Practitioner's prescribing behaviours.[18, 19]

The key messages for secondary care are:

1. Avoid prescribing oxycodone instead of morphine in a hospital setting, unless the patient cannot tolerate morphine
2. Consider whether it is appropriate to be sending a patient home with a strong opioid
3. Do not give patients the expectation that a General Practitioner will continue a prescription for a strong opioid once they are discharged. Emphasise that all opioids have the potential to be addictive and in most circumstances, they are for short-term use only.

In response to this issue, South Australia's Health Department (SA Health) has developed guidelines for prescribing opioids on hospital discharge.[20] Immediate-release opioids may be appropriate on discharge if they have been newly commenced for acute or breakthrough pain in hospital, and are still required. Slow-release opioids should only be prescribed on discharge if the patient was already taking long-term opioids prior to their hospital admission, and their dose requirements have changed. Patients commenced on long-term opioids in hospital for chronic pain, e.g. cancer pain, should receive appropriate follow-up on discharge from their hospital specialist or General Practitioner.[20]

The SA Health guidelines suggest that the following points are considered when determining whether to prescribe an opioid on discharge:[20]

- Review the patients opioid requirements over the 24 hours prior to discharge
- Patients with acute non-malignant pain whose opioid requirements have not reduced during their admission may not yet be ready for discharge
- The discharge prescription dose should not exceed the patient's dose administered in hospital
- The dose should be calculated based on the preceding 24 hours in hospital, not the patient's initial analgesic requirements
- Prescribe a quantity appropriate to the patient's anticipated requirements (usually no more than enough for three days or 20 pills)[21]

An additional point to consider (not included in the guidelines) is whether a strong opioid is still required or whether it may be more appropriate to prescribe a weaker opioid on discharge, such as codeine.

The patient should be given clear instructions on the use of analgesics they are prescribed, the adverse effects they may expect and a pain management plan. It is recommended that if a patient is discharged with a prescription for an opioid, this is communicated to the patient's General Practitioner, including information on opioid dose frequency, suggested duration of treatment and plan for dose reduction.[20]

The patient should be reviewed by their General Practitioner within three to five days.[21] The aim should be to step down to other forms of analgesia, such as a weaker opioid (e.g. codeine), an NSAID or paracetamol when possible.[21] The decision to continue strong opioids should only be made after an assessment of the cause of pain and why it is not resolving and a discussion about the risks and benefits to the patient of continuing treatment.[21]

Best practice points for the use of opioids for acute pain:[21]

- Maximise appropriate non-opioid treatments
- Use a shared decision making approach and ensure the patient is educated about the risks and benefits of opioid treatment
- Avoid prescribing more than three days' supply or more than 20 pills of low-dose, short-acting opioids unless circumstances clearly warrant additional opioid treatment
- Prescribe opioids with caution in elderly patients: take into account renal function and consider prescribing lower doses
- Follow up with the patient within three to five days to assess the response to treatment and any adverse events
- Make sure the patient is aware that opioids can affect their work duties and driving
- Ensure the patient is aware about storing opioids in a secure place away from children, and safe disposal

Key points for reducing the use of oxycodone:

- Morphine is the first-line treatment when a strong opioid is indicated for moderate to severe pain; this applies in any setting
- Oxycodone is not an appropriate analgesic for mild to moderate pain
- If patients are discharged from hospital with a strong opioid, the prescription should cover a short time period only and the patient should have a treatment plan for tapering use of analgesics
- Primary care clinicians do not need to repeat a prescription for patients discharged from hospital on a strong opioid
- The decision to prescribe oxycodone, or any strong opioid, should take into account the predicted net benefits from treatment, weighed up with the risks of adverse effects, misuse and addiction

Suggested further reading:

Upfront: "A disaster in the making": it's time to take action against misuse of oxycodone, BPJ 61 (Jun, 2014), available from: **www.bpac.org.nz**

The Institute for Clinical Systems Improvement Acute Pain Assessment and Opioid Prescribing Protocol guidelines, available from: **www.icsi.org/_asset/dyp5wm/Opioids.pdf**

Appendix B – "Scripting Support for Saying No to a Patient and an Opioid Prescription" may be particularly useful for primary care clinicians.

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The role of **triptans in the treatment of migraine** in adults

Paracetamol or a non-steroidal anti-inflammatory drug (NSAID) can be used first-line for pain relief in acute migraine. A triptan can then be trialled if this was not successful. Combination treatment with a triptan and paracetamol or NSAID may be required for some patients. Most triptans are similarly effective, so choice is usually based on formulation, e.g. a non-oral preparation may be more suitable for patients with nausea or vomiting. To avoid medication overuse headache, triptan use should not exceed ten or more days per month.

Migraine is a condition characterised by attacks of moderate to severe, throbbing headache, which is usually unilateral. This is often associated with other symptoms, including nausea, vomiting, photophobia or phonophobia. Approximately one-third of patients with migraines also experience a preceding aura. Worldwide, approximately one in every seven people are affected by migraines, which are often associated with significant personal and socioeconomic impact.[1] In the Global Burden of Disease Survey 2010, migraine was ranked as the third most prevalent disorder and the seventh-highest specific cause of disability.[2]

For information on diagnosing migraine, see:

National Institute for Health and Care Excellence (NICE) Guideline: Headaches. Diagnosis and management of headaches in young people and adults, 2012. Available from: **www.nice.org.uk**

British Association for the Study of Headache (BASH) Guidelines for the diagnosis and management of migraine, tension-type headache, cluster headache, medication-overuse headache, 2010. Available from: **www.bash.org.uk**

"Headache in primary care", BPJ 7 (Aug, 2007), available from: **www.bpac.org.nz**

A stepwise approach to managing migraine: triptans are appropriate at step two

There are a number of treatment guidelines for acute migraine, all of which differ slightly in their recommended approach (see the NICE and BASH guidelines).[3, 4] Most algorithms, however, recommend stepwise treatment, with triptans usually tried after paracetamol and NSAIDs.

A reasonable approach is:

Step 1: Over-the-counter analgesics (paracetamol, NSAIDs)

Step 2: Triptan

Step 3: Combination treatment with a triptan and an NSAID

+/- anti-emetic (prochlorperazine, metoclopramide) at any step

Recommended doses for these medicines can be found in Tables 2 and 3.

NICE guidelines recommend considering an anti-emetic in addition to other acute treatment for migraine, even in the absence of nausea and vomiting.[4]

Non-oral preparations can be offered to patients who have tried oral preparations and found them ineffective or intolerable, e.g. buccal prochlorperazine, diclofenac suppositories, subcutaneous sumatriptan or intranasal zolmitriptan.[4]

Ergotamine and opioids are generally not recommended for the treatment of patients with acute migraine (Page 35).[4]

N.B. Triptans are not used to treat patients with rarer types of migraine, such as hemiplegic, basilar or ophthalmoplegic migraine.[5] This is because theoretical concerns about the safety of using a medicine with vasoconstrictor effects in patients with focal migraine mean that these patient groups were not included in clinical trials.

Triptans available in New Zealand

Currently there are four triptans available in New Zealand: sumatriptan, rizatriptan, naratriptan and zolmitriptan. These have slightly differing pharmacokinetic and pharmacodynamic profiles (Table 1). Almotriptan, eletriptan and frovatriptan are other triptans available internationally, however, they are not currently available in New Zealand.[6]

Choice of triptan can be guided by a patient's symptoms

As all triptans have similar effectiveness (see: "How effective are triptans at relieving migraine", Page 32), it is appropriate to choose a triptan based on patient preference. Patients often prefer oral treatment, and oral sumatriptan is an acceptable first choice.[14]

Table 1: Triptans – formulations and number needed to treat (NNT)[7, 8]

Triptan	Formulations available	Onset of action	NNT for two hours pain free response vs placebo	Drug interactions
Sumatriptan	Subcutaneous injection 6 mg; tablet 50 mg, 100 mg	Subcutaneous 15 minutes; oral 30 minutes	2.3 (subcutaneous) 6.1 (50 mg tablet) 4.7 (100 mg tablet)	MAOIs (avoid use within 14 days); ergotamine, other triptans (within 24 hours)
Rizatriptan	Orally disintegrating tablet 10 mg; wafer 10 mg (NS)	0.5 – 1 hour	3.1	MAOIs (avoid use within 14 days); propranolol (increased bioavailability of rizatriptan – do not use concurrently because there is no lower strength rizatriptan tablet available in New Zealand); ergotamine, other triptans (within 24 hours)
Zolmitriptan	Nasal spray 5 mg (NS)	10 – 15 minutes	4.3	MAOIs (avoid use within 14 days); CYP1A2 inhibitor medicines (e.g. ciprofloxacin); ergotamine, other triptans (within 24 hours)
Naratriptan	Tablet 2.5 mg (NS)	1 – 3 hours	8.2	Ergotamine, other triptans (within 24 hours)

Key: NNT= number needed to treat; NS=Not subsidised; CI=confidence interval; MAOI=monoamine oxidase inhibitor

Subsidy: For current subsidy information consult the New Zealand Formulary or the Pharmaceutical Schedule. At present the tablet and subcutaneous injections of sumatriptan are subsidised, as is the orally disintegrating rizatriptan tablet. The other triptans are not currently subsidised. Zolmitriptan nasal spray and sumatriptan 50 mg tablets are available without prescription as pharmacist-only medicines.

Vomiting and nausea may restrict oral treatment for some patients and in these cases, an alternative form of treatment such as subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (5 mg) are appropriate choices.[4, 16] Subcutaneous sumatriptan may be the best choice for patients who have rapidly developing migraines or for patients with nausea or vomiting that develop early in the migraine.[14]

"Melt" preparations dissolve on the tongue and are only absorbed after swallowing.[16] They may be useful for people who find drinking water intolerable during a migraine or who are unable to swallow tablets, but are not usually suitable if vomiting is problematic.[3]

There is evidence that patients who do not respond to one triptan may respond to another.[15] Therefore, it is reasonable to try an alternative triptan for a subsequent attack if one proves to be ineffective.[16] In particular, patients who do not respond to oral triptans should be encouraged to try subcutaneous sumatriptan.[14]

Prescribing triptans and monitoring use

A triptan should be taken early during a migraine attack but not during the aura phase

Triptans are most effective if taken early in a migraine attack while the pain is still mild.[7] Triptans should not be taken during the aura phase of a migraine because:

1. Trials in which triptans were administered in the aura phase showed no significant benefit of triptan use over placebo.[7]
2. There are concerns around distinguishing migraine aura from early stroke symptoms, particularly in patients with complex aura presentations.[7]

Do not repeat the dose of triptan if not responding to first dose

Individual advice varies for the different triptans but in general patients should not repeat the dose of a triptan if there is no relief of migraine after the first dose. The dose can be repeated

Table 2: Triptan dose and instructions[5]

N.B. If there is no response to the first dose, patients should not take a second dose for the same attack

Triptan	Dose	Instructions
Sumatriptan	Oral: 50 mg (some patients may require 100 mg)	Dose may be repeated after at least two hours if migraine recurs; maximum 300 mg in 24 hours
	Subcutaneous: 6 mg	Dose may be repeated once after at least one hour if migraine recurs; maximum 12 mg in 24 hours
Rizatriptan	Oral: 10 mg	Dose may be repeated after at least two hours if migraine recurs; maximum 30 mg in 24 hours. If prescribing the wafer formulation, advise patient that it should be placed on the tongue and allowed to dissolve.
Zolmitriptan	Intranasal: 5 mg into one nostril	Dose may be repeated after at least two hours if migraine recurs; maximum 10 mg in 24 hours. N.B. this advice is from the UK datasheet for zolmitriptan nasal spray; the New Zealand datasheet does not include information about repeat dosing.
Naratriptan	Oral: 2.5 mg	Dose may be repeated after at least four hours if migraine recurs; maximum 5 mg in 24 hours.

How effective are triptans at relieving migraine?

The evidence shows that triptans are effective in reducing the pain associated with acute migraine. There is little difference in efficacy between different types of triptans.

Recent systematic reviews of the effectiveness of sumatriptan concluded that sumatriptan (oral and subcutaneous) was superior to placebo for all efficacy outcomes.[9, 10] For oral sumatriptan 50 mg versus placebo, the number needed to treat (NNT) was 6.1 for pain-free response at two hours. For oral sumatriptan 100 mg, the NNT was 4.7 and for subcutaneous sumatriptan 6 mg, the NNT was 2.3 for the same outcome.[9, 10]

Other reviews have found that all triptans are superior to placebo, with small differences in efficacy between the various triptans.[11, 12] A study in 2002 found that rizatriptan, zolmitriptan, almotriptan, eletriptan and frovatriptan were therapeutically similar to 100 mg oral sumatriptan, but naratriptan was marginally less effective.[12] A more recent review in 2013 found that eletriptan (not available in New Zealand) appeared to be the most effective triptan at relieving pain at two and 24 hours.[11] Rizatriptan appeared to be the second most favourable treatment and was effective at two hours but did not have the same efficacy at 24 hours. Oral sumatriptan 100 mg was the third most effective treatment at two hours and appeared to maintain efficacy at 24 hours.[11]

The mechanism of action of triptans

Triptans are selective 5-hydroxytryptamine (5-HT) receptor agonists with high affinity for 5-HT1B and 5-HT1D receptors.[13] Stimulation of the 5-HT1B receptors on smooth muscle cells of blood vessels causes cranial vasoconstriction. This was originally thought to be the main mechanism of action of triptans in relieving migraine.[13] 5-HT1D receptors lie on the perivascular trigeminal nerve terminals and in the dorsal horn. It is thought that stimulation of these receptors blocks the release of vasoactive peptides from trigeminal neurons and of neurotransmitters in the dorsal horn, which convey nociceptive information to the thalamus.[13]

after two to four hours if there was initial relief from the migraine and it has then reoccurred (Table 2).

Avoid using triptans for ≥ ten days per month

Medication overuse headache can result from excessive use of analgesics used to treat headache, including the use of triptans for migraine. To avoid this, triptans should not be used for more than (or equal to) ten days per month on a regular basis.[3] It is also recommended that paracetamol and NSAIDs should not be taken for headache on more than 15 days per month.[3] Most guidelines advise that codeine and other opioids should not be used to treat migraine or other primary headache disorders, because of high rates of medication overuse headache with these preparations.

Medication overuse headache may manifest as a tension-type daily headache or migraine-like attacks. Headaches often improve within two months following the withdrawal of the overused medicine, although symptoms typically initially worsen before this improvement is seen.[2, 7]

Withdrawing triptans

There are a number of different strategies to manage withdrawal of triptans in people who have overused this medicine. Most involve the abrupt withdrawal of the triptan and the use of other medicines to cover symptoms after the triptan is withdrawn, e.g. headache, nausea and vomiting.

The following medicines may be used for withdrawal symptoms:[17]

- Naproxen 250 mg, three times daily or 500 mg, twice daily, or as required. Treatment may be continued for three to four weeks (some experts recommend only two to three weeks).
- Prednisone 60 – 100 mg tapered over five to six days; there is less evidence that this is effective for medication overuse headache
- Metoclopramide or domperidone can be used as required for nausea and vomiting

The patient should be reviewed after two to three weeks to ensure withdrawal has been achieved. Prophylactic medicines for migraine may be required, e.g. beta-blockers. Triptans may need to be reintroduced for acute migraine, but the patient should be advised to avoid using them for more than two days per week.[17]

A study of 98 patients with medication overuse headache found that following triptan withdrawal, the mean duration of

headache was 4.1 days, and overall improvement in associated symptoms, e.g. nausea, vomiting, sleep disturbance, occurred within 7 – 10 days.[18]

Referral to a Neurologist is sometimes useful for patients who are unable to successfully withdraw from overused medicine.

For further information, see: "Medication overuse headache: when the cure becomes the cause", BPJ 16 (Sept, 2008).

Safety and precautions with triptans

Cardiovascular safety

All triptans are associated with "triptan sensations", which are symptoms of burning, tingling, or tightness in the face, neck, limbs or chest. Chest pressure may be alarming for the patient, however, in most cases it is not associated with ECG changes or other evidence of decreased myocardial perfusion.[14] To improve tolerability, the triptan dose may be lowered in patients who are very sensitive to the adverse effects.[14]

There have been reports of serious cardiovascular events, including death, associated with triptan use. Most of these cases were linked to patients having prior cardiovascular risk factors. Patients with multiple cardiac risk factors may require cardiac evaluation before triptans are initiated.[15]

Triptans are contraindicated in people with uncontrolled or severe hypertension, ischaemic heart disease, or previous myocardial infarction, stroke or coronary vasospasm (including Prinzmetal's angina) due to their vasoconstrictive effect.[5]

Safety in pregnancy and breastfeeding

Migraines are approximately three times more common among females than males, with an average age of onset of 18 years. The peak prevalence of migraine in females occurs between ages 25 and 55 years, making the safety of triptans in pregnancy and breastfeeding a potentially significant issue.[19]

Sumatriptan can be considered for the acute treatment of migraine in pregnant women if clinically indicated (see: "Management of acute migraine in pregnancy"). It is the triptan with the most evidence of use during pregnancy because it has been available for longer than other triptans. A large number of studies have confirmed that sumatriptan exposure during any stage of pregnancy has not been associated with an increased risk of major malformations.[20] Other triptans require more study. There is also no compelling evidence of other adverse

Management of acute migraine in pregnancy

There is no clear evidence that migraines are a significant risk factor for adverse outcomes during pregnancy, however, recent population-based studies have found a possible link suggesting that pregnant women with migraines may be more at risk of pregnancy-induced hypertension and pre-eclampsia.[2] Many women with a history of migraine report that the incidence of their migraines decreases during pregnancy, especially in the second and third trimesters. This is thought to be due to sustained oestrogen levels.[2] However, in women who do get migraines during pregnancy it is important that they are offered appropriate and adequate treatment to avoid adverse effects on maternal wellbeing, e.g. sleep deprivation, poor nutrition (due to vomiting and nausea) and increased stress.[20]

Paracetamol is recommended first-line for the acute treatment of migraine in pregnant women. Sumatriptan can be considered as a second-line option, depending on the need for treatment balanced against the risk. NSAIDs (ibuprofen is preferred) may be considered in the second trimester, but should be avoided in the first and third trimesters, and are generally only used in pregnant women if their benefit outweighs the risk.[5]

Table 3: Other pharmacological options for the treatment of migraine in adults[5, 29]

Drug class	Drug name	Dose and instructions
Analgesics	Paracetamol	1 g every 4–6 hours, no more than 4 doses in 24 hours
	Aspirin	600 – 900 mg every 4–6 hours, no more than 4 doses in 24 hours
	Ibuprofen	200 – 400 mg every 4–6 hours, no more than 2.4 g in 24 hours
	Naproxen	750 mg at onset, followed if necessary by a further 250 – 500 mg at least 1 hour after initial dose, no more than 1250 mg in first 24 hours; if ongoing migraine relief required, 250 mg every 6 – 8 hours as necessary, no more than 4 doses in 24 hours (or a maximum of 1 g daily) Naproxen sodium*: 825 mg at onset, followed if necessary by a further 275 – 550 mg at least 30 minutes after the initial dose. Maximum 1375 mg (5 tablets) in 24 hours * not subsidised, can be purchased over-the-counter (Naprogesic, Sonaflam)
	Diclofenac	Diclofenac sodium (oral): immediate release 50 – 75 mg at onset, repeated after 2 hours if necessary and then after 4 – 6 hours, no more than 200 mg in first 24 hours; if ongoing migraine relief required, modified release 75 mg once or twice daily as necessary, no more than 150 mg in 24 hours Diclofenac sodium (rectal): 100 mg at onset, repeated up after 2 hours if necessary by 100 mg rectally, up to 200 mg on the first day if required; if ongoing migraine relief required, 50 mg as necessary up to 3 times daily, no more than 150 mg in 24 hours Diclofenac potassium (oral)*: 50 mg at onset, repeated after 2 hours if necessary and then after 4 – 6 hours, maximum 150 mg in 24 hours * not subsidised, can be purchased over-the-counter (Voltaren Rapid)
Anti-emetics	Domperidone	10 mg, up to 3 doses in 24 hours
	Metoclopramide	10 mg, up to 3 doses in 24 hours. Do not prescribe for longer than 5 days (risk of neurological adverse events – see NZF for further details)
	Prochlorperazine	Oral tablets: 20 mg at outset, repeated if necessary by 10 mg 2 hours later; if ongoing anti-emetic required, 5–10 mg as necessary up to 3 times daily. Buccal tablets: 3 – 6 mg, up to 2 doses in 24 hours
Combination drugs	Paracetamol and metoclopramide (Paramax)* * Paramax to be delisted on 1 November 2014 due to supplier discontinuation.	Paracetamol (500 mg) + metoclopramide (5 mg): two tablets should be taken at the onset of the attack, repeated four-hourly as required; no more than 6 doses in 24 hours

pregnancy outcomes from exposure to sumatriptan during pregnancy,[21] although some evidence suggests that triptan use later in pregnancy is associated with a slightly increased risk of complications, especially pre-term birth, atonic uterus and haemorrhage during labour (due to 5-HT effects on uterine blood vessels and platelet aggregation).[22, 23]

Data regarding the use of triptans during breastfeeding is limited, but sumatriptan is considered compatible with breastfeeding.[5, 20] In one study of five women who received subcutaneous sumatriptan, infants received approximately 3.5% of the weight-adjusted maternal dose through breast milk.[24] Given the low oral bioavailability of sumatriptan, the dose that infants would receive following a mother taking intermittent doses of oral sumatriptan is expected to be even lower.

Medicine interactions

There are several medicine interactions to be aware of when prescribing triptans. Triptans are contraindicated in people either currently taking monoamine oxidase inhibitors (MAOIs) or within two weeks of stopping a MAOI. Clinical evidence suggests that moclobemide approximately doubles the bioavailability of sumatriptan and other MAOIs (phenelzine and tranylcypromine) would be expected to interact in a similar way.[5, 25]

There is also a potential risk of serotonin syndrome with the concurrent use of triptans in patients taking serotonin reuptake inhibitors (SSRIs), however, this interaction appears to be rare. The American Headache Society advised that the limited evidence provided by case reports does not support limiting the use of triptans with SSRIs or serotonin-noradrenaline reuptake inhibitors.[26] If these medicines are used together, monitor patients for signs of serotonin syndrome, e.g. weakness, hyperreflexia and poor co-ordination.[5] There is also a possible risk of serotonin syndrome with the combination of St John's wort and triptans (one case report in the literature).[25]

There is a theoretical risk of additive vasoconstriction, and possible significant coronary vasoconstriction, with the combined use of triptans and ergot derivatives (e.g. ergotamine) and the combination is generally contraindicated.[25] It is advised to avoid using ergotamine for six hours after using sumatriptan, and to avoid using sumatriptan for 24 hours after using ergotamine.[5]

Propranolol increases the plasma concentration of rizatriptan. International advice is to use a 5 mg dose of rizatriptan and limit the number of doses to two in 24 hours.[25] However, New Zealand does not currently have a 5 mg formulation and the 10 mg formulations available are unable to be halved. Therefore in New Zealand, it may be best to avoid using this combination.

Other treatment options for the relief of acute migraine

Triptans are one of a number of therapeutic options available for the management of migraine. Other treatments that are used to manage migraine include paracetamol, NSAIDs and anti-emetics (see Table 3 for recommended doses). Ergotamine and opioids are not generally recommended.

There is limited evidence that directly compares triptans with other classes of medicines used for treating migraine. Two reviews found that triptans are superior to ergotamine compounds for treating migraine, however, both reviews found no significant difference in the effectiveness of triptans compared with other pharmacological approaches to treating migraine.[13, 27]

A Cochrane review evaluated the combination of naproxen and sumatriptan to treat migraine. It was concluded that naproxen plus sumatriptan was significantly better that naproxen alone. However, there was only a small benefit when using the combination compared with using sumatriptan alone.[28]

Ergotamine (combined with caffeine in Cafergot) is an older treatment for migraine that is still occasionally used. Current advice suggests that it is not appropriate to use ergots for migraine as there is evidence that they are not as effective as triptans and they are associated with an increased risk of adverse effects.[4, 16]

Opioids are also not recommended as they may exacerbate nausea, increase the risk of medication overuse headache, and have the risk of potential addiction.[13]

ACKNOWLEDGEMENT: Thank you to **Dr John Mottershead**, Consultant Neurologist and Clinical Senior Lecturer, Dunedin School of Medicine, University of Otago, Dunedin and **Dr Lynette Murdoch**, General Practitioner and Senior Teaching Fellow, University of Otago, Christchurch for expert review of this article.

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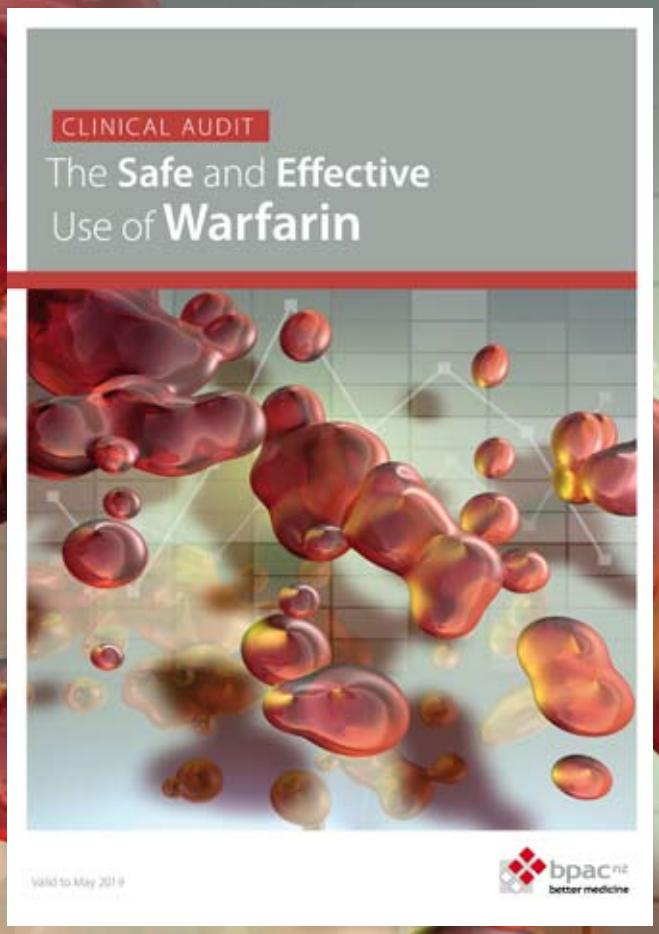

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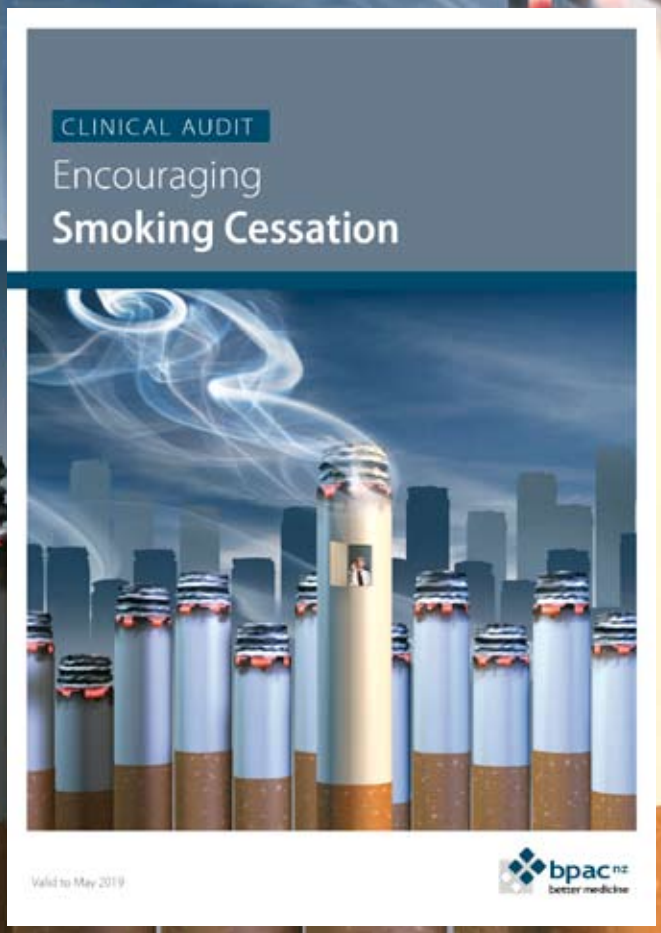

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SAFER PRESCRIBING

Safer prescribing of high-risk medicines: tricks, tips and tales of caution

Pharmacological treatment is an integral part of the practice of medicine, and is one of the most significant factors in improving patient health. However, some medicines, when used outside of therapeutic indications or doses, or even when used appropriately, can become a "poison" rather than a "cure".

Medicine-related adverse events can occur due to many reasons, including routine use of the medicine, an error in prescribing, acute illness and medicine interactions. Certain patients are more likely to be at risk of medicine adverse effects, e.g. elderly people, young children, people with multiple co-morbidities, people taking multiple medicines and people who are immunocompromised. Certain medicines are also more commonly associated with adverse events, including those that are prescribed most often (e.g. paracetamol, NSAIDs, ACE inhibitors, statins) and those with a narrow therapeutic index (e.g. warfarin, lithium and digoxin).

In addition to medicines themselves which are associated with a higher risk of adverse effects, there are also situations in which the way medicines are prescribed can pose an increased risk. For example, prescribing medicines on discharge from hospital can result in adverse events if patients are uncertain about medicine doses or instructions, or new medicines are prescribed which are similar to, or interact with, medicines in the patient's usual regimen. Stat dispensing (i.e. patients are given the full 90 day supply of their medicine) also has the potential to increase the risk of adverse events or pose a safety risk, e.g. taking a medicine when it is no longer necessary, fewer visits to pharmacies and therefore less opportunity to discuss adverse effects and the potential risk of accidental poisoning or intentional overdose (although these risks can apply to any volume of some particular medicines).

One strategy for minimising the risk of harm of medicines is to have up to date knowledge, including recommended dosing, monitoring requirements and potential adverse effects to observe for. The following article on clozapine marks the beginning of a new series in Best Practice Journal, focused on medicines which have significant risks that can occur alongside their beneficial effects. The use of these medicines needs special care to reduce the likelihood of serious adverse outcomes; vigilance by both prescribers and patients is needed.

Adverse drug reaction reporting is one of the most important sources of data for assessing the safety and quality of a medicine. If your patient has experienced an adverse effect related to a medicine, regardless of whether you feel it is serious or significant, this should be reported to the Centre for Adverse Reactions Monitoring (CARM). You can submit a report directly using the "Adverse Drug Reactions Reporting" module on your bestpractice decision support dashboard. Once opened, the tool automatically pre-populates the patient's relevant details.

Clozapine and its adverse effects: neutropenia, agranulocytosis and constipation

Clozapine is an atypical antipsychotic used in the treatment of patients with schizophrenia. It is the only antipsychotic shown to be effective for treatment-resistant schizophrenia, and at least one-third of patients show a moderate improvement after a 6 to 12 month trial of this medicine.[1] Despite there being clear benefits associated with clozapine, its use is very restricted because of significant safety concerns. Clozapine can only be initiated by a Psychiatrist for patients with schizophrenia after at least two other antipsychotics have been trialled. General Practitioners and Pharmacists have an important role in helping to recognise and manage adverse effects and medicine interactions with clozapine.

Clozapine has significant adverse effects

Clozapine is associated with several significant adverse effects, including agranulocytosis, neutropenia, constipation (which can be severe), myocarditis and adverse metabolic effects. These adverse effects are not necessarily dose-related and may occur at any time during treatment. For this reason, patients taking clozapine require close monitoring for the development of any adverse effects, and should be regularly questioned about the onset of any symptoms.

Clozapine can cause potentially fatal neutropenia and agranulocytosis

Clozapine has been reported to cause neutropenia in 2 – 3% of people taking this medicine and agranulocytosis in 1%.[1] These are rare adverse effects but can be fatal. Patients taking clozapine are monitored with regular leukocyte and differential blood counts, weekly during the first 18 weeks of treatment, followed by blood tests every four weeks for the duration of their treatment.[2] These blood tests are required as part of the safety protocol for clozapine treatment. This protocol requires that patients are registered on the manufacturer's blood monitoring database and that they comply with regular blood tests in order for ongoing supply of clozapine to be made by the dispensing Pharmacist.

What can General Practitioners do?

- Patients who present with evidence of infection, such as flu-like symptoms, sore throat or fever must have a white blood cell and differential blood count requested immediately to rule out neutropenia or agranulocytosis. It should be indicated on the laboratory form that the patient is taking clozapine and that results are required on the same day. Depending on the result, urgent haematology referral or emergency hospital admission may be required.
- Where possible, avoid prescribing other medicines concurrently which may cause additive bone marrow suppression, e.g. co-trimoxazole, trimethoprim, nitrofurantoin, carbamazepine and antineoplastics.

Constipation can be severe and fatal

Constipation is a frequent adverse effect of clozapine; up to 60% of patients may become constipated while taking it.[3] A common scenario is for patients to present with symptoms of constipation, after a prolonged period (i.e. greater than one week) without having a bowel motion. The mechanism by which clozapine slows the gut is unclear but has been postulated to be due to the anticholinergic and anti-serotonergic properties of clozapine.[4] This hypomotility can result in intestinal obstruction, bowel ischaemia, necrosis, perforation, toxic megacolon and related aspiration pneumonia.[5]

Risk factors for gastrointestinal hypomotility include recent initiation of clozapine treatment, higher clozapine doses, concomitant use of other anticholinergics (e.g. benztropine and tricyclic antidepressants) and concurrent illness – some case reports suggest that illness and fever can increase serum clozapine levels and lead to an increased risk of adverse effects.

Between 2007 and 2011, the Centre for Adverse Reactions Monitoring (CARM) received 14 reports of clozapine-related gastric hypomotility; of those, two cases were fatal and another two cases were life-threatening.[5]

What can General Practitioners do?

- Treat pre-existing constipation, advise patients about the high risk of constipation when taking clozapine and provide advice about diet, exercise and fluid intake
- Ask patients regularly about bowel function; the first four months of treatment appears to be the highest risk period for developing constipation[3]
- Have a low threshold for prescribing laxatives for constipation; a stimulant and softening laxative such as senna with docusate or a macrogol laxative* are appropriate options.[3] Regularly review treatment. An alternative option is to prescribe preventative laxative maintenance treatment, e.g. a macrogol laxative*, in all patients treated with clozapine.[6]
- Where possible, avoid prescribing other constipating medicines (e.g. opioids), particularly those with anticholinergic properties (e.g. tricyclic antidepressants), for patients taking clozapine

* Macrogol laxatives are currently only subsidised with Special Authority approval; see New Zealand Formulary for details.

Myocarditis and later onset cardiomyopathy have been reported

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy. Fatalities have been reported in New Zealand.[7] Although these adverse effects can occur at any time, there is an increased risk of myocarditis in the first one to two months of treatment with clozapine, while cases of cardiomyopathy have generally occurred later, approximately nine months after treatment initiation.[8]

What can General Practitioners do?

- Consider the possibility of myocarditis in patients taking clozapine who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations or other signs and symptoms of heart failure, particularly during the first two months of treatment[8]
- If myocarditis is suspected, it may be useful to arrange an immediate ECG, CRP, CK, full blood count (check eosinophils in particular) and troponin tests to assess the urgency of a cardiology assessment and to indicate if hospital admission is required[8]
- If myocarditis or cardiomyopathy is suspected, this should be reported to the patient's Psychiatrist immediately; it is likely that clozapine treatment will be ceased

Clozapine can be associated with weight gain, hyperglycaemia and dyslipidaemia

Metabolic disturbances, including weight gain, dyslipidaemia, hyperglycaemia and diabetes mellitus are associated with the use of all typical and atypical antipsychotics, to varying degrees, depending on the individual medicine.[2] Patients taking clozapine have an increased risk of all of these adverse effects, particularly type 2 diabetes mellitus.[9]

What can General Practitioners do?

- Give practical advice about diet and exercise and help patients to find activities that they are motivated to participate in
- Monitor lipid levels, HbA_{1c} (fasting blood glucose may be more useful in the first three months of treatment due to rapid increases in glucose levels), blood pressure, weight, waist circumference and body mass index

Important medicine interactions

Clozapine levels are affected by cigarette smoking

People who smoke metabolise clozapine faster than those who do not smoke. This is due to the aromatic hydrocarbons in cigarette smoke (it is not due to nicotine). Therefore if a person taking clozapine stops smoking their clozapine levels can become elevated, leading to adverse effects, such as seizures.[7] Some evidence suggests that a 50% increase in clozapine levels may occur within two to four weeks of smoking cessation. Alternatively, if a patient begins smoking during treatment, clozapine levels may decrease and therapeutic effect may be compromised requiring an increase in the clozapine dose.[10]

What can General Practitioners do?

- Ensure the patient is aware that clozapine levels are affected by smoking and to report if their smoking status changes
- Smoking cessation should be planned with the clinical

team so that this effect can be monitored and managed; clozapine plasma levels may need to be monitored and the dose reduced[7]

- If clozapine plasma levels are monitored appropriately, nicotine replacement treatment is safe for patients taking clozapine who wish to give up smoking

Clozapine is subject to CYP interactions

Clozapine is metabolised by the CYP450 isoenzymes, therefore clozapine levels may be affected by the concomitant use of medicines that inhibit or induce these enzymes. Inducers will decrease clozapine levels, e.g. carbamazepine, phenytoin, rifampicin and omeprazole. Inhibitors may significantly increase clozapine levels, e.g. erythromycin and SSRIs (paroxetine and fluoxetine).

What can General Practitioners do?

- Avoid, wherever possible, prescribing medicines that interact with clozapine to patients taking clozapine. If there is no alternative and interacting medicines are co-prescribed with clozapine, more frequent monitoring of clozapine levels and for adverse effects will be necessary.

ACKNOWLEDGMENT: Thank you to **Andrew McKean**, Senior Pharmacist, Hillmorton Hospital, Christchurch for expert review of this article.

Pharmacists – be alert for adverse effects

Pharmacists also have an important role in ensuring the safe use of clozapine.

When interacting with a patient who is taking clozapine, Pharmacists can:

- Ask regularly about bowel function
- Consider the possibility of neutropenia or agranulocytosis (and the need for referral for a white blood cell and differential blood count) in patients who present with evidence of infection such as flu-like symptoms, sore throat or fever
- Consider the possibility of myocarditis in patients who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations or other signs and symptoms of heart failure – particularly during the first two months of treatment

Pharmacists are also in the position of counselling patients on the safe and effective use of clozapine, including the importance of:

- Compliance with their treatment regimen
- Reporting the first sign of a cold, influenza, sore throat or other infection immediately
- Having the next blood test on the day it is due
- Safe storage of clozapine

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Evidence that alternate dosing of paracetamol and ibuprofen in children with fever may reduce temperature: other benefits uncertain

A recently published systematic review provides evidence that the use of alternating, or combined, antipyretics (paracetamol and ibuprofen) may reduce body temperature in children with febrile illness. However, there was inconclusive evidence as to whether either practice would improve overall discomfort of the child. The aim should be to treat the underlying cause of the fever. Practice recommendations for the use of antipyretic medicines in children with febrile illness therefore remain unchanged.

Febrile illness is reported to be the number one reason that parents take their children to a General Practitioner; 20 – 40% of parents report a child having a fever each year.[1] Paracetamol and ibuprofen are both indicated for the treatment of pain, and fever with discomfort in children.[2] Current guidelines are clear in that each of these medicines should only be used as an antipyretic in children for the purposes of reducing distress and discomfort, rather than temperature reduction alone, and that the two medicines should not be combined, i.e. not given simultaneously.[1] However, guidelines are less clear about the role of alternate dosing of antipyretics in the treatment of fever with discomfort. Alternate dosing involves starting with one antipyretic medicine and administering the second if the child's discomfort is not sufficiently reduced within one to four hours of treatment.[3] NICE guidelines state that alternating doses of paracetamol and ibuprofen may be considered, but only if a child's distress persists or recurs before the next dose of medicine is due.[1]

A 2013 Cochrane review of six studies, involving 915 children, is the first systematic review reporting evidence of effectiveness of alternating, or combined, paracetamol and ibuprofen for temperature reduction, compared with antipyretic monotherapy.[3] The children included in the studies were between the ages of six months and 14 years, with the majority of children being at the younger end of this scale.[3] Fever was defined as a temperature greater than 37.8°C and was presumed to be of infectious origin in all children.[3] Three studies compared alternating paracetamol and ibuprofen treatment to ibuprofen alone, and two studies compared alternating treatment to paracetamol alone.[3] Three studies assessed combined treatment versus ibuprofen alone, and two studies focused on combined treatment versus paracetamol alone.[3] No significant adverse effects were reported in any of the included studies. The review was limited by the small number of participants in some studies, variations in dosing regimens and the frequency and type of assessment that was conducted on the children.

The review concluded that there was low quality evidence suggesting that alternating treatment was more effective at lowering body temperature for the first three hours after the second dose, compared to either paracetamol or ibuprofen alone.[3] However, it was uncertain if alternating treatment was more effective at improving comfort in febrile children compared to antipyretic monotherapy.[3]

The Cochrane review also found moderate evidence that giving both paracetamol and ibuprofen together is likely to be more effective at lowering body temperature in children with febrile illness for the first four hours after treatment.[3] However, the one trial that assessed child comfort did not detect a benefit of combined treatment over treatment with either medicine alone.[3]

Treatment of the underlying cause is central to the management of febrile children. A symptom-based approach to treatment has the potential to mask signs of serious illness, e.g. meningococcal disease. Furthermore, the increased temperature of fever can suppress bacterial growth and slow viral replication. Paracetamol and ibuprofen should therefore not be prescribed for the sole purpose of reducing body temperature in febrile children.[1] The role of antipyretics in the treatment of febrile children is to improve comfort, in order to ensure the child maintains adequate intake of fluids and food, thus reducing the risk of fever-associated complications.

Many General Practitioners are already safely advising parents with distressed children to use alternate dosing, if antipyretic monotherapy initially fails to improve child comfort. The regimen that was used by the largest study in the review was to alternate doses of paracetamol and ibuprofen every four hours.[4] This is a reasonable approach to take in select children, depending on any contraindications to treatment. Ibuprofen

is contraindicated in children with hypersensitivity to aspirin or any other non-steroidal anti-inflammatory drug (NSAID), in children with heart failure, and in children with a history of gastrointestinal bleeding or ulceration.[2] It should also be remembered that the use of NSAIDs in children at recommended doses is associated with an increased risk of acute kidney injury (AKI).[5]Acute illness and volume depletion further increase the risk of AKI in children therefore ibuprofen should be used cautiously in children with fever. Paracetamol is generally considered to be a safer treatment option in children, although it does have the potential to cause hepatotoxicity, e.g. if overdosed or used in a child with dehydration or existing hepatic impairment.

None of the studies included in the Cochrane review reported any significant adverse effects from combined or alternate dosing of paracetamol and ibuprofen, however, adverse effects were not a primary focus of these studies. Due to their mechanisms of action, using paracetamol and ibuprofen together theoretically increases the risk of renal and hepatic toxicity. Until further safety data emerges, alternate dosing of antipyretics should only be done cautiously in select children. To minimise dosing errors, parents should be encouraged to write down the medicine, the dose, when it was given as well as the earliest time the next dose can be given; assuming the child continues to experience fever-related discomfort. This is especially important if there is more than one child in the household being treated.

Until more data is available on the safety and benefits of combined (simultaneous) dosing of paracetamol and ibuprofen the recommendation to avoid this practice in children remains.

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DECISION SUPPORT FOR HEALTH PROFESSIONALS

Are prescribing restrictions for oxycodone appropriate?

Dear Editor,

Thank you for the excellent article on oxycodone prescribing by Jeremy McMinn. My only quibble is the title – sadly it is not "a disaster in the making", the disaster is here already. My simple question is why in the world can PHARMAC not make this a Special Authority Drug as soon as possible with strict prescribing criteria. I have NEVER had reason to initiate this drug and am regularly appalled by its careless prescription – often by very junior hospital doctors. Obviously existing dependent patients would need to be catered for but there is no reason in the world why this shouldn't have very tight PHARMAC restrictions placed on it.

Dr Paul Corwin
General Practitioner
Greymouth

We asked Medical Director of PHARMAC, Dr John Wyeth to respond to this letter. His response is as follows:

We appreciate the opportunity to respond to the concerns that have been outlined above on prescribing of oxycodone. We have been aware of the increased use of oxycodone over the last few years and have provided a range of support tools and information to prescribers in order to support appropriate pain management.

PHARMAC's major function is to manage the pharmaceutical budget. The use of the Special Authority mechanism is primarily as a tool to manage pharmaceutical expenditure by targeting access to subgroups of the population who will benefit the most from a medicine, and not to manage appropriate prescribing.

PHARMAC is cognisant of the administrative burden that is required for initiating Special Authorities and we have been spending some time looking at ways that we can reduce this burden over time, by removing those Special Authorities where we consider they have little to no effect on pharmaceutical expenditure. Having no Special Authority should not indicate to prescribers that the medicine is more effective, safe, or appropriate than any other medicines funded on the Pharmaceutical Schedule – a Special Authority is primarily there to manage expenditure by targeting access to subgroups of the population who will benefit most.

PHARMAC considers that practice issues, such as prescribing of oxycodone over morphine, should be addressed by the medical profession and should be questions that health professionals should consider every time they prescribe a medicine – just because a medicine is available funded doesn't necessarily mean it is appropriate to prescribe in all circumstances.

We are open to further dialogue on this and other issues around appropriate prescribing. The more the medical profession questions the utility and appropriateness of medicines in certain circumstances, the better medicines management will be.

Dr John Wyeth

Re-infection with *H. pylori* does occur

Dear Editor,

As usual I appreciated your publication [Best Tests, May 2014]. My question: after an H. pylori *eradication programme on a patient from a high prevalence community, do they become re-infected? If not, why not? Presumably antibodies would have been present while they were infected.*

Dr J. L. Sarfati
General Practitioner
Wellington

Research has shown that humans do develop an antibody response to infection with *H. pylori*, however, this natural immune response is insufficient to either clear an infection or to prevent re-infection.[1,2]

Rates of re-infection with *H. pylori* vary widely throughout the world. In people who have had eradication treatment, re-infection rates range from 1% or less in developed countries to 11.5% or more in developing countries, reflecting the

underlying prevalence rate within those countries and therefore a varying risk of re-exposure.[3, 4] Factors associated with a higher risk of re-infection are similar to those that are reported to increase the initial prevalence of *H. pylori* and include lower socioeconomic status, overcrowding and poor sanitation, ethnicity, age and gender. Re-infection rates, for example, appear to be higher in children aged < 10 years and in adult males.[5, 6] Presumably the risk factors that increase re-infection within a high prevalence country will be similar to those that are at work within a high prevalence community.

There is limited data on re-infection rates in New Zealand, however, a small Auckland based study from 1998 reported a rate of 4% per year of follow up in patients treated for *H. pylori*.[7] The rate referred to in the study is the recrudescence rate (see below) because follow up of patients began at six months after eradication treatment. The authors acknowledge that in other studies if patients who are followed up less than one year since treatment are excluded, the rate decreases significantly and is likely to be due to re-infection rather than recrudescence.

Many studies looking at recurrence rates of *H. pylori* make a distinction, largely based on the time since initial eradication, between two distinct mechanisms – recrudescence and re-infection. Recrudescence refers to a reappearance of the original strain of *H. pylori*, usually within one year of initial eradication treatment.[3, 4] This generally reflects a failure of the eradication treatment* (estimated to be successful in approximately 80% of patients),[2] due to factors such as antibiotic resistance and poor patient compliance with the initial treatment regimen.[3, 4] Re-infection with *H. pylori*, at least one year after successful eradication, is regarded as the presence of a new infection usually with a new strain of *H. pylori* or with a true re-infection with the original strain (as determined by DNA analysis).[3, 6]

If a patient has a recurrence of symptoms within one year of eradication treatment, it is likely that this will reflect a relapse with the original strain of *H. pylori* and therefore an alternative treatment regimen should be considered, e.g. bismuth-based quadruple treatment. Ensure that the patient understands the importance of completing the course of treatment and that they are able to adhere to the dosing regimen. A further option is to refer the patient for endoscopy. There is limited advice on what treatment should be offered to patients who present again after more than one year since eradication and, depending on the individual circumstances, discussion with a Gastroenterologist is recommended.

For more information on *H. pylori* testing, see: "The changing face of *Helicobacter pylori* testing" Best Tests, May, 2014.

* New Zealand guidelines do not recommend routine confirmation of eradication after triple treatment, however, if patients have a recurrence of symptoms, important co-morbidities or complications such as peptic ulceration, confirmation of cure with faecal antigen testing can be requested.

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