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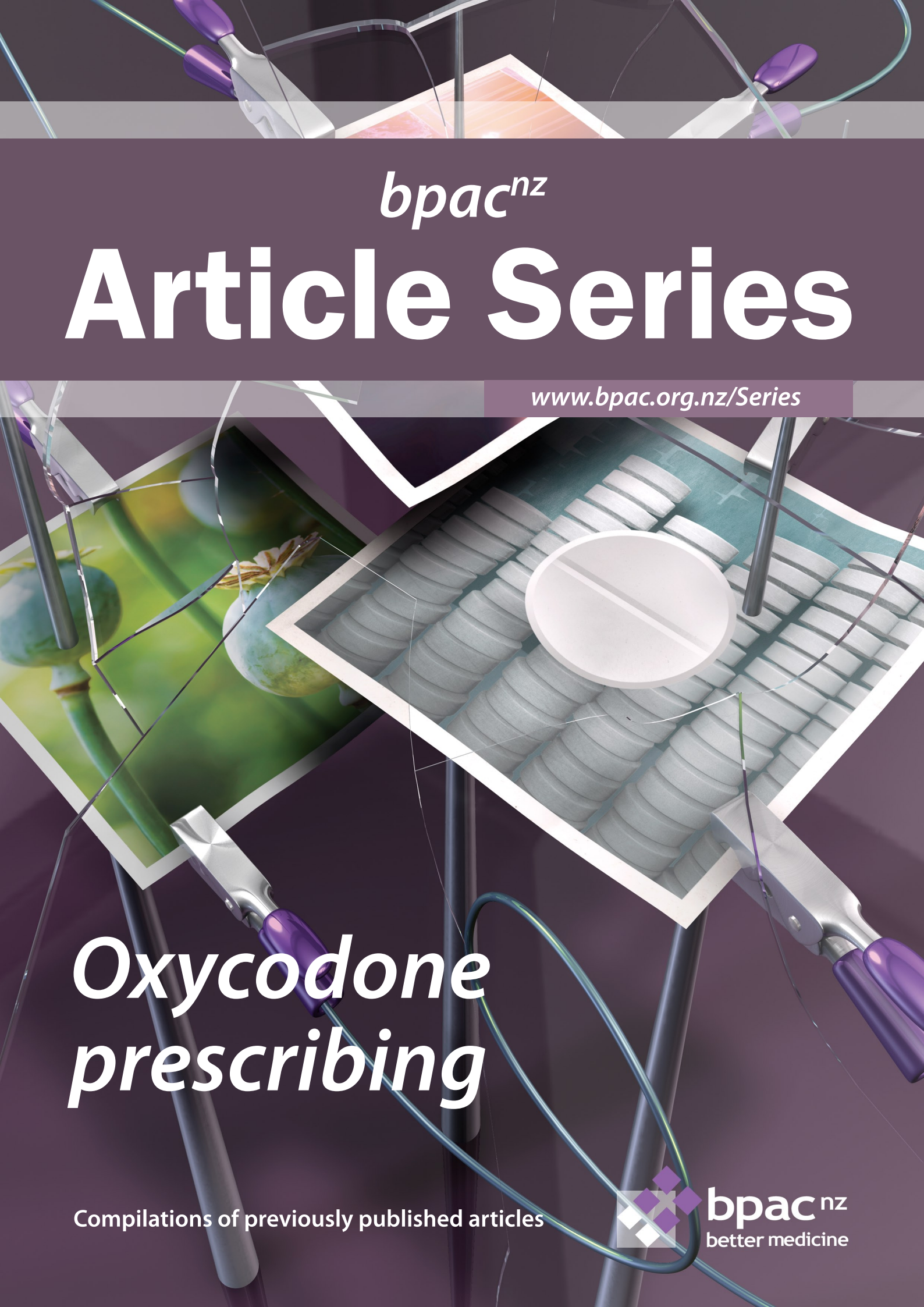

Oxycodone prescribing

Compilations of previously published articles

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"A disaster in the making": it's time to take action against misuse of oxycodone

Dr Jeremy McMinn is a consultant psychiatrist and addiction specialist at Capital & Coast DHB. He is also the Co-Chair of the National Association of Opioid Treatment Providers and the New Zealand Branch Chair of the Australasian Chapter of Addiction Medicine. We invited Dr McMinn to answer a series of questions about the role of oxycodone, both as a legitimate option for pain control, and a medicine with a serious potential for misuse. The time for debating who to blame has passed. Oxycodone, and opioid prescribing in general, is already out of hand and we need to collectively take action before it is too late.

How would you describe the current situation in New Zealand in terms of misuse of oxycodone?

With due heed to hyperbole, we are looking at a disaster in the making. We have been complacent about the warnings from the rest of the western world, with harms arising from pharmaceutical opioids overtaking those from heroin. This has reached epic proportions in the United States, with oxycodone particularly over-represented. Pharmaceutical opioids in the United States now kill more people than firearms or road traffic accidents, and more than the combined death rates from heroin and cocaine overdoses. This is shocking and shameful – how can it be possible?

In New Zealand, we have had the good fortune to be last off the starting line, with oxycodone coming to us later. Even so, it is clear from [national dispensing] data that our prescribing of oxycodone has followed comparable trajectories to that seen in Australia and the United Kingdom. There is no good reason for this – oxycodone is more expensive than morphine and more addictive, and is no safer in renal [impairment] or other conditions. And it is not as if we are even prescribing it for the right reasons – the literature on chronic pain increasingly indicates that opioids are harmful long term, not beneficial. Chronic pain is not acute pain – the "benefits" of opioids in chronic pain may be limited to a brief reduction in subjective pain, before tolerance and hyperalgesia negate this, leaving the patient neuro-adapted to a higher dose.

> ***"New Zealand's problem prescribing pharmaceutical opioids, with the predictable onslaught of oxycodone, is a national scandal that should be stimulating profound professional soul-searching."***
>
> *— Dr Jeremy McMinn*

How does oxycodone compare to other prescription drugs of misuse, e.g. morphine?

The appalling aspect of this is that New Zealand has had three decades already of seeing pharmaceutical opioid abuse and dependence rather than heroin addiction – we, as prescribers, have significant responsibility for these harms.

In New Zealand, patients that end up on opioid substitution treatment [i.e. the methadone programme] mainly initiate and maintain their pre-treatment addiction with morphine and methadone. The morphine mainly comes from pain specialists, general practitioners and palliative care physicians, and the methadone comes from opioid substitution treatment (OST). In recent years, OST services have recognised this, and increasingly adopted greater treatment supervision, more restrictive dispensing, and more explicit adherence to evidence-based dose ceilings. Other prescribers need to catch up.

What advice can you give to general practitioners for identifying patients who are drug-seeking? i.e. no legitimate reason for requiring oxycodone

General practitioners need to take control, and use their knowledge of health conditions, prescribing risks and clinical concern appropriately. Patient choice is not the primary reason to prescribe a drug (although it may be a factor in which drug is chosen). But if the condition presented is not sensibly treated with the drug requested, do not prescribe it. Opioids are very likely not to provide a true benefit in pain conditions lasting over a month – just as benzodiazepines are not justified in cases of anxiety lasting more than two weeks.

Worry about a complaint to the Health and Disability Commissioner should not influence the decision – drug-seeking patients know that implying they will complain makes doctors fold. If the patient is likely to move on to a different, "softer touch" doctor, general practitioners can protect their colleagues by making an application for a Restriction Notice and making sure any documentation reflects the doubts about the legitimacy of the drug request.

General practitioners may know the background history and social/family environment better than any other doctor involved. It is likely that most people abusing oxycodone, benzodiazepines, etc, are using medications that were prescribed originally for someone else. *Primum non nocere* (first do no harm) extends to society, not just the patient in the room.

Any patient that insists on an abusable drug by name, without sufficient diagnostic justification, without supporting documentation, with stories of lost prescriptions or stolen medications should not receive a prescription. Medical Council guidance allows for a three day prescription to ease a threatening patient out of an office, but then preparations for the next consultation must be made. This may include talking with colleagues, arranging a chaperone, and applying for a Restriction Notice. Overt threats of violence should be reported to the police. Threats of suicide can be discussed with local emergency psychiatric services.

Chronic pain, current or past addiction to any substance, current or past mental illness, childhood sexual abuse and family history of addiction are all important risk factors for addiction.

"Many GPs already know that we are fighting to retract an opioid tsunami" *— Dr Jeremy McMinn*

What advice can you give to general practitioners for identifying patients who may be addicted to oxycodone? i.e. a legitimate need for pain relief which has turned into a dependency

Oxycodone is highly addictive – between 25–33% of regular users will experience features of dependence. With this risk, all patients with courses lasting longer than one month should be examined for signs of addiction. Requests for increasing doses and early (or replacement) prescriptions are obvious warning signs. It is essential to consider appropriate urine drug testing and examining for injections sites. The perceived stigma of these can be reduced by making this a standard condition of Controlled Drug prescribing.

General practitioners will be alert to treatment that does not achieve a net improvement. Emerging addiction is a powerful, but sometimes opaque, reason that treatment is not as effective as originally predicted.

Are there any safeguard practices for prescribing oxycodone which can help to avoid inadvertently contributing to drug misuse or addiction?

Prescriptions of any abusable medications that may last longer than a month should be subject to the 10 Universal Precautions*[to be discussed in the next edition of Best Practice Journal]. The gist of these precautions is an explicit contract covering treatment duration, dose parameters, outcome measures, side effect safeguards and defined review dates.

Patients (and doctors) should be aware of the relative lack of good evidence that oxycodone is genuinely effective after one month, contrasted with the wealth of evidence of harm. Oxycodone dose ceilings in primary care should be no more than 60 mg per day (broadly the equivalent of morphine 100 mg per day). After this, specialist review or re-thinking is required. Outcome measures should be measurable change in function, not subjective pain score – the pain always eases with a dose increase, but temporarily, just as it always flares with a dose decrease, temporarily. Safeguards for oxycodone prescribing include universal use of urine screens, examination for injection sites and regular discussion with the dispensing pharmacist.

A key advantage of some degree of treatment contract is that it allows the prescriber to back out of prescribing that is getting out of hand. The subsequent re-think can include seeking specialist advice for pain and addiction.

* Gourlay D, Heit H, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005;6(2):107-12.

What issues are you seeing among patients as a result of oxycodone addiction?

I am seeing patients who tell me how easy it is to get oxycodone – and it is cheap. My impression is that most people find it straightforward to convince a doctor to prescribe for them, although clearly some doctors (and some regions) are easier than others. For the ones that do not go directly to a doctor, they can buy from other individuals or from doctor-shopping rings. These rings can include older women, who may not trigger the same suspicions. I have been surprised how much oxycodone seems to travel by New Zealand Post between regions. It is just a matter of time before the street oxycodone "market share" becomes evident.

People presenting voluntarily for treatment are still mainly presenting with morphine addiction, with methadone a close second. Virtually everyone has added some oxycodone into the mix of what keeps them going, but addictions driven only by street oxycodone are infrequent so far. However, I am not reassured by this – presentations for OST are usually very late: most people struggle with their own attempts to manage before they resign themselves to the restrictive rigours of OST.

I am also seeing a new cohort of patients, who are coming semi-voluntarily. These are the people who have received a long term prescription for pain which has tipped over into problematic use. Most have to see me because the original prescriber has become aware of problems and has wisely, if often belatedly, made further opioid prescription contingent on addiction assessment. Frequently, the problems arise from the short acting nature of the "pain", opioid-on/off effects, tolerance, aberrant use, etc. A transition to a longer acting opioid, i.e. methadone or buprenorphine (in the form of Suboxone) is usually required. Frequently these patients do not wish to characterise themselves as "addicts", but do nonetheless have features of opioid dependence. There may be some good prognostic factors present in this cohort, but a prolonged period of opioid substitution and related counselling still seem to be required.

It surprises me how often general practitioners seem to feel committed to continue a course of opioids started in hospital or recommended by a pain specialist – even though the use of opioids is clearly starting to go wrong. General practitioners usually have the best overall knowledge of the patient – in my opinion, this may trump the often more narrow and frequently time-limited recommendations of specialist care.

"General practitioners should not hesitate to bring their own knowledge to bear, even if this can be challenging initially to align with the specialist recommendations."

— Dr Jeremy McMinn

What advice can you give to a general practitioner managing a patient with an oxycodone addiction who wishes to withdraw?

The best advice is unhelpfully retrospective – do not get there in the first place. In opioid dependence, prevention is absolutely better than cure, as the opioid withdrawal failure rate without a period of substitution is nearly 100% - even if we had the best addiction resources, which we patently do not. Opioid substitution is the mainstay of managing opioid dependence, but funding exists for only around 5400 patients (with an expected need of at least 10 000 New Zealanders).

What is the recommended withdrawal regimen?

Withdrawal requires realism, compassion and determination on both the patient and doctor's part. Most people will require a stabilisation phase of two to four weeks to clarify the daily amount, which may include swapping to a longer acting opioid of the same equivalence. Given the Misuse of Drugs Act, general practitioners will have limited scope to use methadone or buprenorphine, but consolidating an Oxynorm and Oxycontin regimen into a set twice daily regimen of oxycodone as sensible pain management will be required.

After this stabilisation, a steady reduction should be agreed within a reasonable timescale. Factors such as prior treatment duration, size of total daily dose and important upcoming events, come into play when considering the rate of reduction. However, a reduction contained within one to three months should be agreed, with the reduction increments calculated back from this date setting.

Larger dose drops may be easier at the start of the reduction, with smaller drops later reflecting a larger proportion of the total daily dose. Neuro-adaptation plateaux, where the reduction is held for one to two weeks, may be sensible periodically, especially if the patient is struggling. Putting the dose back up is rarely sensible – a hold in reduction to allow the easing that comes with neuro-adaptation is more realistic than an oscillating rising and dropping dose.

What supportive treatments may be required?

The main support is one of compassion whilst maintaining a focus on the prize. Delaying a reduction restart, or providing unwise courses of other abusable drugs (benzodiazepines, zopiclone) will promote a sickness role and treatment failure. Patients need reminding that the discomfort is temporary and will abate. Levels of underlying distress need monitoring, and involving the educated support of family members may be useful. Excessive use of other substances from other sources (e.g. alcohol, cannabis, Nurofen Plus [containing codeine], a family member's opioids) should be addressed.

Loperamide for diarrhoea and non-opioid analgesics for withdrawal aching may be useful. Off-label use of clonidine may be considered for the hot/cold feelings and aching, but will require blood pressure monitoring: courses should be limited to two weeks. Quinine is no longer recommended.

What issues are there in terms of prescribing legitimate pain relief in the future?

Opioids are only part of the treatment of pain, and probably a much smaller part of chronic pain treatment than previously thought. Earlier problems with opioids mean that all potentially abusable future prescriptions may present risks, such that they should be avoided altogether or only provided within closely monitored parameters.

Patients who have experienced problems with opioids need more care, although commonly feel they receive less. A pain condition for which opioids were problematic could be framed as a "treatment resistant" condition and it may be legitimate to seek other less available treatments. In particular, access to non-pharmacological pain strategies may need to be emphasised.

Patients and prescribers should be explicitly discouraged from equating the removal of opioids with the removal of all pain management.

What other support systems are available for patients who have a prescription drug addiction?

Prescription drug addiction is a double act – both the patient and the doctor have, to some extent, entered into drug dyscontrol, drug salience (exclusive importance) and dysfunction. These need to be addressed, and prescription monitoring, dispensing restrictions, and use of the 10 Universal Precautions are good ways to achieve this. In particular, solid external controls on abusable medication availability are the keystones to preventing and managing prescription drug addiction.

For those who have ongoing opioid problems, the mainstay of opioid management will involve the local specialist Opioid Treatment Service, often with some degree of shared care with the general practitioner. Input from specialist Chronic Pain Services may also be required: in many regions there is regular liaison between Addiction and Pain services already in place.

Addiction support can also be available through non-government organisations, including the Alcohol & Drug Helpline, Salvation Army, CareNZ, 12-Step Programmes (e.g. Narcotics Anonymous, Alcohol Anonymous & Al-Anon) and Tranx.

The Alcohol & Drug Helpline (0800 787 797) and local DHB Addiction Services will usually be able to advise on local availability of addiction supports.

We would like to thank Dr McMinn for his willingness to speak out on these issues. We hope that this interview has challenged your thinking in terms of your own prescribing of oxycodone. We plan to publish a follow-up series of articles, expanding on some of the issues Dr McMinn has touched on, including examining the role of oxycodone in acute, short-term and long-term pain management and strategies for safe and rational prescribing of strong opioids.

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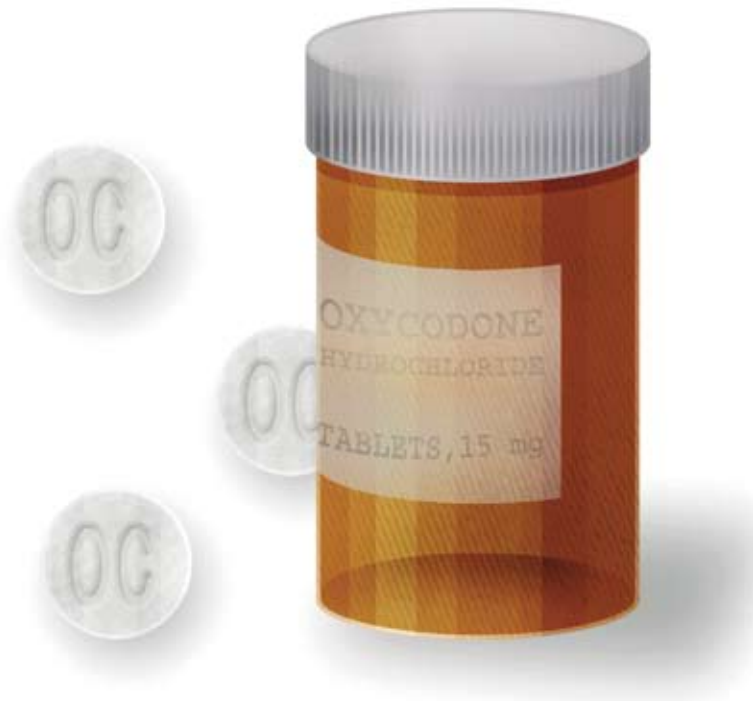

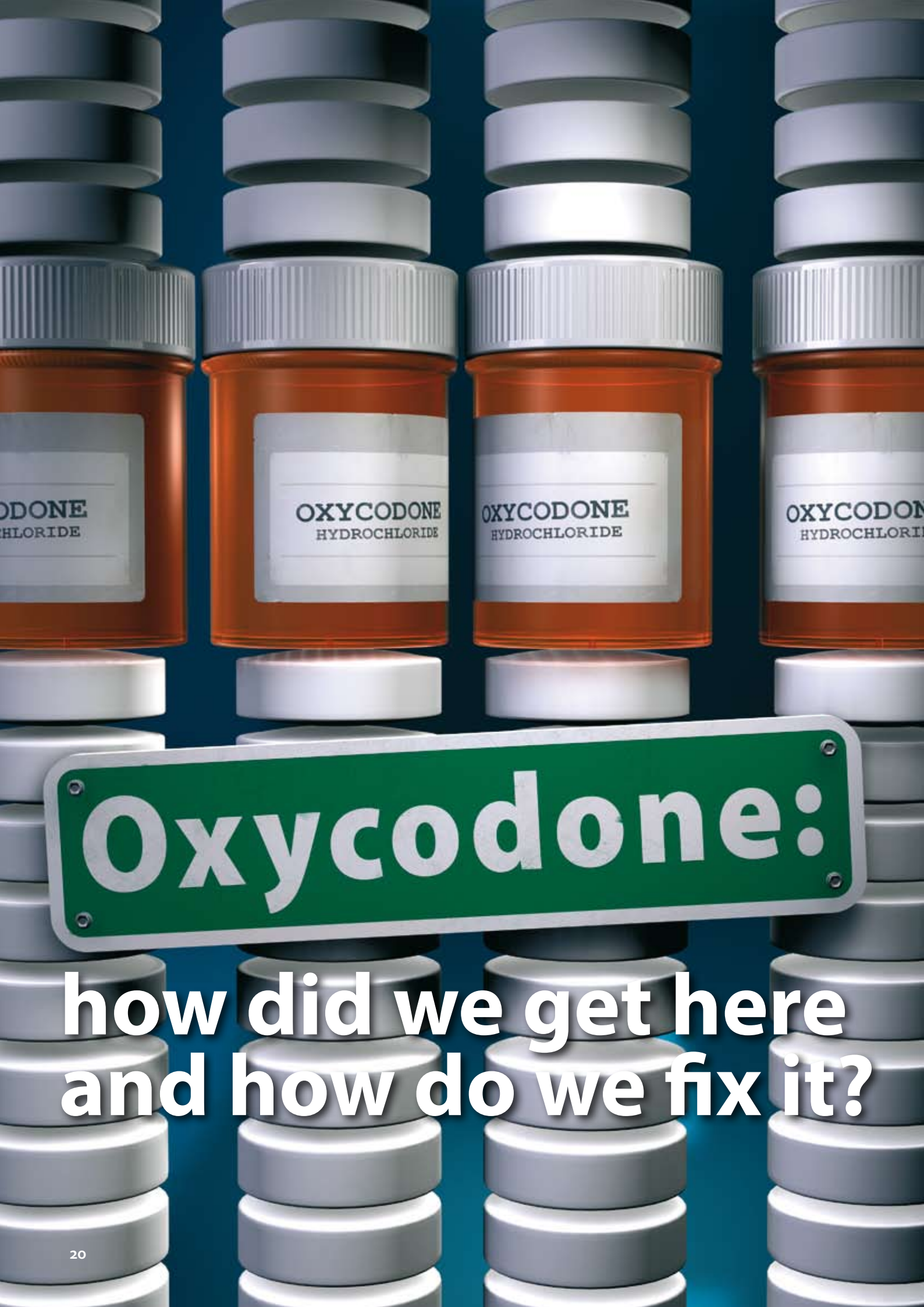

how did we get here and how do we fix it?

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.

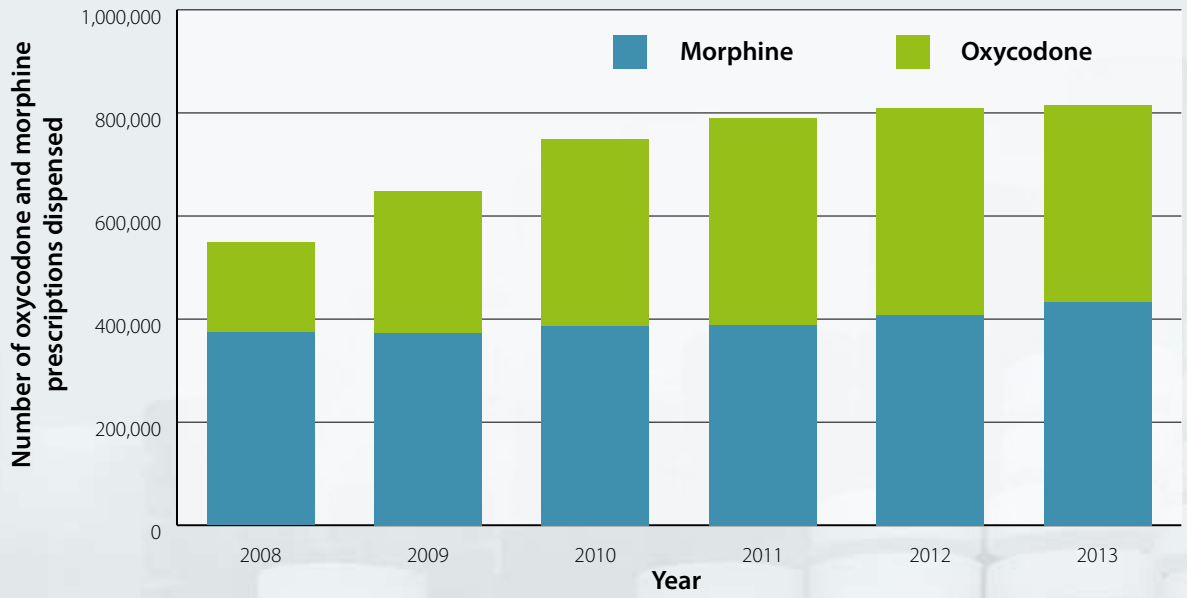

Figure 1: Number of oxycodone and morphine prescriptions dispensed (excluding injected preparations).[5]

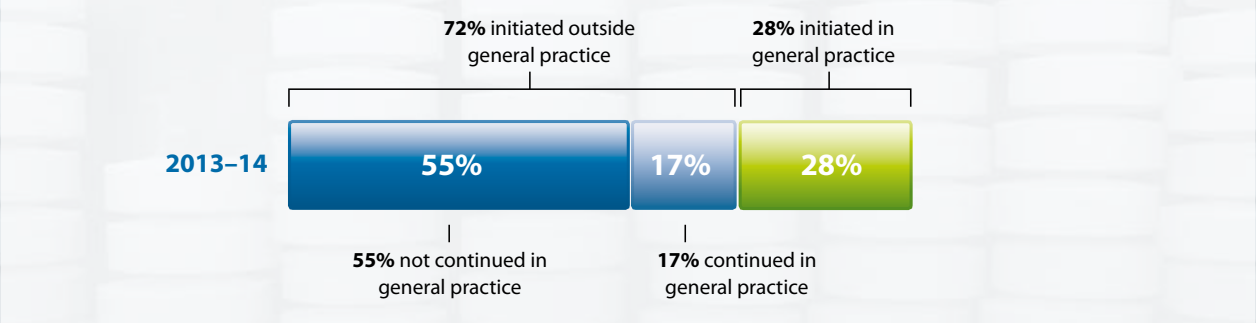

Figure 2: Source of oxycodone prescriptions for patients initiated in 2013/14 (Apr 2013 – Mar 2014)

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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Helping patients cope with **chronic non-malignant pain:** it's not about opioids

The role of opioids in the management of chronic non-malignant pain is a controversial subject due to concerns over the long-term efficacy and safety of treatment, including the risk of misuse and addiction. In the past, opioids featured prominently in many treatment guidelines for chronic non-malignant pain. However, this advice has been reconsidered in more recent times and the current opinion is that opioids have a very limited role in the management of patients with chronic non-malignant pain. Non-pharmacological methods for helping patients cope, and come to terms, with their pain should be the mainstay of treatment. Non-opioid analgesics may be considered for periods when pharmacological treatment for pain is necessary. Opioids should only be considered as a treatment of "last resort", and should be used for the shortest possible time, at the lowest effective dose, using the least potent opioid possible.

Why opioids should not be used for chronic non-malignant pain

Opioid analgesics are often used in the treatment of patients with chronic non-malignant pain, despite a lack of evidence supporting their effectiveness in this setting. There is now a growing, consistent body of evidence that suggests that opioids should play a much smaller role than previously thought in managing these patients.[1,2] This evidence suggests that the long-term efficacy of opioids is not proven and that opioid treatment is associated with a well established risk of adverse events and addiction.

Management of patients with chronic non-malignant pain involves a complex interplay of biological, psychological and social factors, therefore treatment needs to incorporate all of these aspects. Psychological factors in particular play a major role in determining the success or failure of treatment in patients with chronic non-malignant pain. It is important that clinicians understand and empathise with the emotions the patient is experiencing in order to best manage their pain (see: Recognising the importance of the patient's emotional wellbeing", Page 31).

The long-term effectiveness of opioids is not proven

Most clinical research on opioids has studied their effect on pain for relatively short-term treatment only. For example, a meta-analysis and a systematic review evaluated the effectiveness of opioids used to treat patients with chronic non-malignant pain.[3,4] The studies included in the analyses showed that patients were treated with opioids for a mean of five weeks (range 1 – 16 weeks). Opioids, which included oxycodone, morphine, fentanyl, tramadol and codeine, were associated with a modest short-term analgesic benefit, however, the authors cautioned that this finding should not be extrapolated to long-term treatment with opioids.[3,4] Opioid-induced hyperalgesia and tolerance have been found to be major limiting factors for long-term opioid treatment.[5] Another systematic review (that included 21 randomised studies) found that there was no evidence that opioids (including oxycodone, morphine and tramadol) were effective in managing chronic non-malignant pain in any of the conditions studied (including back pain and osteoarthritis). The only exception was "intermediate/fair" evidence for tramadol in patients with osteoarthritis.[6]

Opioids are associated with significant adverse events

The use of opioid treatment for the management of chronic non-malignant pain is associated with significant adverse events that affect multiple organ systems. These adverse events can occur with any use of opioids, but there is an increased risk in patients who use opioids long term.

Adverse effects of opioids include:[2]

- **Respiratory system** – respiratory depression, obstructive and central sleep apnoea, ataxic breathing, respiratory arrest and death
- **Central nervous system** – increased risk of falls, cognitive impairment, myoclonus, delirium, depression, somnolence and sleep disorders
- **Cardiovascular system** – orthostatic hypotension, bradycardia, vasodilation and an increased risk of cardiovascular events, e.g. myocardial infarction
- **Gastrointestinal system** – constipation, nausea and vomiting, gastric reflux, delayed gastric emptying, abdominal cramping and distension

Principles for managing patients with chronic non-malignant pain

- Communicate and listen to the patient and empower them to take a leading role in the management of their condition
- Focus on improving function and disability rather than just concentrating on pain outcomes
- Ensure that the patient has realistic expectations regarding treatment. Controlling or reducing pain rather than total elimination of pain is usually the goal.
- Treat any co-morbidities that are frequently associated with chronic pain, e.g. anxiety and depression. Non-pharmacological treatments, such as cognitive behavioural therapy and exercise, can play a major role in managing the psychological co-morbidities of pain. Short-term use of pharmacological treatments, e.g. selective serotonin reuptake inhibitors (SSRIs), can also be considered.
- Educate the patient that remaining active will be beneficial in managing their pain and encourage them to continue to do activities that bring enjoyment. A positive attitude or outlook can reduce the patient's perception of their pain. Focus on what the patient can do, as opposed to what they cannot do.
- If pharmacological treatment is used to manage pain, always have a plan to taper the dose (even if this is long term) and avoid increasing doses to "chase pain"

- **Immune system** – decreased wound healing, pruritus, altered cytokine production, increased histamine release, inhibition of macrophage, neutrophil and natural killer cell activity and recruitment, increased HIV replication and cancer progression
- **Endocrine system** – opioid-induced endocrinopathy (usually only with high opioid doses, long term), resulting in decreased libido, testicular atrophy, early menopause and sexual dysfunction

The sedative effects of opioid treatment can also add to psychological factors that patients with chronic non-malignant pain may be experiencing, and exacerbate feelings of helplessness and depression.

Opioids have high addiction rates

The rates of opioid misuse and addiction reported in the literature vary greatly for patients with chronic non-malignant pain. This is possibly due to different definitions and methods of measuring addiction and misuse. One systematic review reported that the rate of opioid addiction/misuse was relatively low (approximately 3%) but the rate of aberrant behaviour was much higher (approximately 12%) in patients with chronic non-malignant pain who received long-term opioid treatment.[7] However, other studies have reported much higher addiction/misuse rates. The retrospective TROUP study which investigated a number of factors associated with long-term opioid use, reported possible opioid misuse in 20% – 24% of patients with chronic non-malignant pain and probable misuse in 3% – 6%.[8] Another study reported even higher rates, with approximately 35% of patients with chronic non-malignant pain fitting the Diagnostic and Statistical Manual for Mental Disorders – fifth edition (DSM-V) criteria for a prescription opioid use disorder during a lifetime.[9]

Other treatment options are available

Clinicians may have a misconception that opioids are the only treatment option available for patients with chronic non-malignant pain. This can result in inappropriate prescribing of opioids, including switching patients from other treatments, e.g. NSAIDs, to opioids, which is generally not appropriate. Clinical judgement and individualised prescribing, which takes into consideration the risk and benefits of all treatments, are essential in managing patients with chronic non-malignant pain. Focusing solely on pharmacological treatments for these patients should be avoided.

For further information see **www.aci.health.nsw.gov.au**

Recognising the importance of the patient's emotional wellbeing

Psychological factors have been shown to play a major role in how patients experience and tolerate pain, but are often not considered when management plans for chronic non-malignant pain are implemented.[10] Recent research in patients with chronic pain has identified dysfunction and dysregulation in a several key brain structures.[11] This dysfunction is associated with changes in the patient's emotional and cognitive functioning, including increased activity, anxiety, depression, fear, addiction, altered attention and cognition (Figure 1).[11] These changes are also related to the phenomenon of "pain catastrophising", which can be defined as repetitive negative thoughts during actual or anticipated pain.[10] Pain catastrophising has been recognised as one of the major psychological determinants of the negative outcomes associated with chronic non-malignant pain.[10]

Clinical experience has shown that a "collaborative partnership" approach between patient and clinician is best when managing chronic non-malignant pain. For most patients, it is essential to them that the clinician believes that they are experiencing pain and recognises that their life has been significantly changed by this pain.[12]

Patients frequently report an "adversarial struggle" within themselves or with others when dealing with chronic non-malignant pain, which can result in:[12]

- A struggle with self-perception and self-worth – the patient may describe feeling alienated from their body and that they cannot meet other people's expectations and hide their pain in an attempt to appear normal
- Altered perceptions of the future – the day-to-day unpredictability of pain can mean that the patient changes their plans, expectations and dreams for the

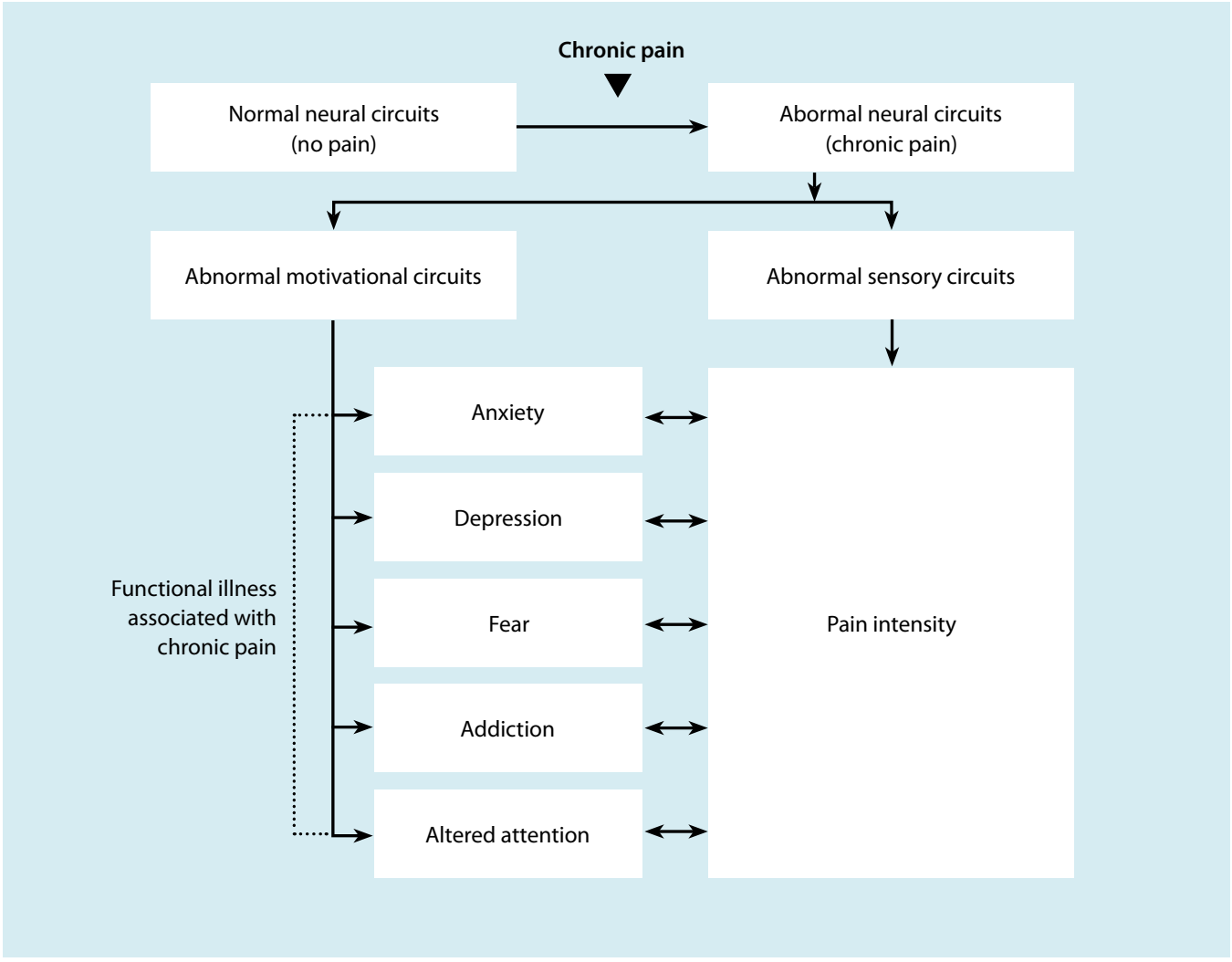


Figure 1: Chronic pain results in changes to emotional state, with resultant psychological symptoms. These effects are bi-directional, i.e. negative emotional states can augment the perceived intensity of pain. Adapted from Elman *et al*, 2011.[11]

future, resulting in an inwardly focused perspective on life

- A feeling that people do not understand or believe their pain – resulting in emotions of worthlessness, fear, guilt and doubt, which may influence the patient's work and relationships, as well as impacting on their likelihood of seeking help
- Problems with negotiating the healthcare system – the patient may feel as if they are being referred back and forth between clinicians and they are "trapped in the system"

Clinicians should aim to counsel the patient through these adversarial struggles and help them to move forward "alongside their pain".

Ways to achieve this include:[12]

1. Encourage the patient to recognise the type, intensity and duration of pain they are feeling and how this can vary throughout the day and between days. The aim is for the patient to feel increasingly more in control of their body and their pain.
2. Encourage the patient to redefine a "new normal" that does not focus on the losses which the pain has caused but reinforces positive self-images and plans for the present and the future
3. Encourage the patient to become part of a group and to share their pain experiences with others. This can help them realise that they are not the only person dealing with pain issues.
4. Reassure the patient that they do not have to hide their pain or seek the approval of others (i.e. convincing others that their pain is real). Patients should be encouraged to work with their pain to accomplish achievable and realistic goals and not to set goals based on other people's expectations.
5. Ensure that the patient understands that there may be no cure for their pain and that managing their pain and improving function are the goals of their management plan.
6. Help the patient to understand their pain condition and take a more active role in their health care. Patients should be given the confidence to experiment with different methods of managing their pain and the opportunity to make their own decisions about their treatment.

Pain is often complicated by a number of other factors, including anxiety, depression, substance use disorders and sleep difficulties.[13] Managing these co-morbidities is essential in gaining overall control of the patient's pain condition.

Further reading: Toye F, Seers K, Allcock N, et al. A meta-ethnography of patients' experience of chronic non-malignant musculoskeletal pain. Health Serv Deliv Res 2013;1(12). Available from: **www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0010/94285/FullReport-hsdr01120.pdf**

Finding treatments for pain

When managing patients with chronic non-malignant pain, the aim is to maximise use of non-pharmacological treatments and non-opioid analgesics, and to avoid using opioid analgesics where possible. Most patients can be managed in primary care, but discussion with, or referral to, a specialist pain clinic may be required in some cases. This may include patients with pain that is difficult to treat or when multiple treatment failures have occurred.

A treatment approach that incorporates both pharmacological (non-opioid) and non-pharmacological interventions is recommended. This method has been found to be more effective in managing chronic pain than single treatment modalities. This is supported by a 2008 systematic review, that included 35 randomised studies (2407 patients), which investigated the use of multidisciplinary treatments* in patients with chronic musculoskeletal pain (mostly chronic back pain or fibromyalgia). The review reported that there was "moderate" evidence of better effectiveness of multidisciplinary treatments compared to single treatments in the treatment of this patient group.[14]

There are a wide range of social, psychological, non-pharmacological and non-opioid pharmacological treatment options available for patients with chronic non-malignant pain. The best combination of treatments will vary between patients depending on a number of factors. These include the underlying pain complaint, e.g. nociceptive versus neuropathic pain, the mind-set and demographics of the patient, e.g. older and younger patients may have different expectations and preferences for different treatments, the severity and duration of the pain, and the availability and affordability of different treatment options. It may be necessary to trial different combinations of treatments in order to find the best combination that suits the individual patient.

* Multidisciplinary treatments in the studies included cognitive behavioural therapy (CBT), psychotherapy, exercise programmes (including stretching and hydrotherapy), patient education, muscle relaxation, nutritional counselling, and vocational and occupational therapy.

Non-pharmacological treatment options for chronic pain

Exercise therapy

Physical activity is beneficial for people with pain as it can improve, or stop deterioration, in a number of parameters, including range of motion and flexibility, and the pain associated with these. The choice of exercise programme will vary depending on the patient's pain condition and physical capabilities. A patient may choose a structured exercise programme, or may prefer self-directed activities such as walking or swimming; these activities may be particularly beneficial in patients with osteoarthritis of the lower limbs or chronic back pain. Patients who are initially reluctant to begin exercise can be advised to gradually increase their level and duration of activity.

A Cochrane systematic review reported that exercise therapy was slightly effective in decreasing pain and improving function in adults with chronic low-back pain, and at least as effective as other conservative treatments, e.g. behavioural approaches.[15] The positive effects of exercise programmes were most pronounced in patients who presented to healthcare providers and received individually-designed programmes that commonly included strengthening or trunk-stabilising exercises.[15]

Pilates: A systematic review concluded that regular sessions of pilates (one to three times per week) resulted in greater improvements in pain and function than usual care and physical activity in the first 4 – 15 weeks in patients with chronic low-back pain.[16]

Yoga: A randomised trial that investigated the efficacy of the addition of yoga to usual care in patients with chronic low-back pain found that pain and function were both improved (at three, six and 12 months) in patients who underwent at least three yoga sessions.[17]

Tai Chi: A systematic review found that regular sessions of Tai Chi (on average one to two times per week for 6 – 15 weeks) had small positive short-term effects on pain and disability in patients with chronic musculoskeletal pain due to arthritis.[18] However, the studies included were generally of low quality.

Brisk walking and home-based quadriceps strengthening exercises have both been reported to significantly reduce pain and disability in patients with osteoarthritis of the knee.[19] Weight reduction in overweight patients with osteoarthritis of the knee has also been shown to improve pain and function scores.[20]

Massage

Massage therapy may have some benefits compared with placebo and relaxation in patients with chronic low-back pain in the short term, according to the results of a systematic review.[21] However, there were conflicting and contradictory findings regarding the effectiveness of massage therapy when compared to other manual therapies (such as mobilisation) and acupuncture.[21] The use of topical rubefacients during massage can also be recommended, e.g. heat rubs.

Acupuncture and nerve stimulation techniques

A systematic review and meta-analysis reported that acupuncture improved pain outcomes in patients with four chronic pain conditions – back and neck pain, osteoarthritis, chronic headache and shoulder pain.[22]

Transcutaneous electrical nerve stimulation (TENS) is a form of nerve stimulation for pain relief and involves delivery of low-voltage electrical current to the skin via surface electrodes. However, systematic reviews have found variable and inconclusive results for TENS in patients with chronic pain.[23]

Cognitive behavioural therapy (CBT)

CBT (individual or group) is one of the more commonly used behavioural approaches for treating patients with chronic pain. CBT focuses simultaneously on the environment, behaviour and cognition. The efficacy of CBT has been investigated in a number of chronic pain conditions including fibromyalgia and low back pain. A randomised study conducted in patients with chronic low-back pain in England reported that six sessions of group CBT resulted in significantly better pain and disability scores ($p < 0.001$ for both) compared with the control group (no CBT).[24] Another study reported that CBT improved the patient's ability to cope with pain, reduced depressive moods and reduced the number of follow-up appointments in patients with chronic pain due to fibromyalgia, but had no significant effects on the actual pain, fatigue, sleep and quality of life.[25]

Cognitive behavioural therapy for pain

The principle behind CBT is in examining the relationship between a person's thoughts, feelings and behaviours, and understanding that these factors are dependent on each other.

The patient may begin with:
"If I move, I will hurt more" (thoughts)
"This makes me feel anxious about doing anything" (feelings)
"I will avoid doing anything that might hurt" (behaviour)

This then progresses to:
"No one cares about my pain, and no one can fix me" (thoughts)
"I feel angry that no one cares, and fearful that I cannot be fixed" (feelings)
"This makes me tense and irritable" (behaviour)

The purpose of CBT is to help patients avoid feeling overwhelmed by the pain they are experiencing, and instead come to terms with their pain and feel that it is manageable. This means that the patient moves from a passive to an active role in their care, focusing on increasing their function and quality of life.

The goals of the clinician are to:

- Actively listen to the patient's experience of their pain
- Provide education about the cause of pain (if possible) and possible treatments
- Help patients find additional resources and support groups
- Set goals for the patient to achieve
- Solve problems that happen along the way
- Encourage engagement
- Positively reinforce any successes

For further information, see: Promoting mind-body approaches to pain self-management, by Debra Hughes. Available from: **www.empr.com**

The access to, and cost of, CBT in New Zealand varies throughout the country and can be a significant barrier to treatment. Some primary care clinicians may be trained in this technique, but referral to a Clinical Psychologist or Pain Specialist may be required.* When access to specialist CBT is not possible, there are some internet-based programmes available which have been shown to be effective in helping patients manage their pain (see below for details). A US-based study that examined the effectiveness of an internet-based CBT chronic pain management programme (mostly in patients with joint, back and osteoarthritic pain) reported positive results.[26] The study found that pain intensity was significantly reduced from baseline after both one and six months, and quality of life was also improved after six months.

An example of on online CBT programme that can be recommended for patients is available at: **www.getselfhelp.co.uk/chronicfp.htm**

Other treatment options and useful advice that can be given to patients

Other non-pharmacological treatment options for chronic non-malignant pain that can be considered include:

- Hot or cold compresses, depending on the pain condition and specific benefit, e.g. hot packs can be beneficial in patients with chronic back pain and cold packs can be beneficial in patients with pain due to osteoarthritis of the knee
- Biofeedback (the process of gaining greater awareness of many psychological functions, e.g. pain perception) and mind-body activities such as meditation, mindfulness and relaxation can also be considered, mostly in combination with other treatments
- Encourage the patient to engage in activities they enjoy or that make them laugh
- Referral to an Occupation Therapist who can assist with postural problems, e.g. in a patient with a repetitive strain injury due to work
- Referral to a Physiotherapist, Chiropractor or Osteopath who can perform massage, strapping, mobilisation and manipulation (where appropriate)

* The Aotearoa New Zealand Association for Cognitive Behavioural Therapy (AnzaCBT) offer courses and workshops on CBT, and more information is available at: **www.cbt.org.nz**

Pharmacological treatment options for chronic pain

Pharmacological treatment should not be the sole focus in managing patients with chronic non-malignant pain and should be used in combination with non-pharmacological interventions. As with non-pharmacological treatments, the most appropriate treatment (or combination of treatments) will vary between patients, and individual treatment trials should be undertaken. When undertaking a trial, use the pre-intervention level of pain and function to assess whether the medicine(s) is working.

Analgesic treatment options for chronic non-malignant pain may include*:[27]

- Paracetamol
- NSAIDs: naproxen (up to 1000 mg per day) or ibuprofen (up to 1200 mg per day) are the recommended first-line choices if NSAIDs are required for longer periods of time, due to the lower risk of cardiovascular events occurring when these medicines are taken at these doses, compared to other NSAIDs.[28] N.B. ibuprofen may be taken up to 2400 mg per day, but this is associated with increased cardiovascular risk.
- Tricyclic antidepressants, e.g. amitriptyline, nortriptyline (less sedating)
- Other neuromodulators, e.g. gabapentin, carbamazepine
- Topical analgesics, e.g. NSAIDS, capsaicin

Referral to secondary care to investigate surgical options, permanent nerve blocks, epidural steroid injections and spinal cord stimulation may be appropriate for some patients.

The use of opioids in chronic non-malignant pain

Opioids have a limited role in the treatment of chronic non-malignant pain and should only be used after other treatment options have failed. When considering using any opioid treatment it is recommended that there are strict protocols in place to minimise the associated risks. One method that has been proposed for the safe use of opioids for chronic non-malignant pain is the "10 universal precautions" approach (see: "The 10 Universal Precautions approach to pain management", over page).

When opioids must be used some considerations include:

- Use the weakest opioid possible, e.g. use codeine or tramadol before considering morphine
- Use opioids for the shortest possible time at the lowest possible dose
- Have a plan in place to decrease the opioid dose, e.g. ensure the patient knows that the dose will gradually be stepped down and then ceased
- Regularly review opioid treatment for efficacy, tolerability and signs of addiction. Re-evaluate opioid treatment at every consultation and only continue treatment if there is a very good reason for doing so.
- Have a system in place to identify and manage opioid misuse and addiction

Weaker/atypical opioid treatment options

Codeine, tramadol and dihydrocodeine can be considered as treatment options in combination with non-pharmacological and non-opioid analgesics in patients with chronic non-malignant pain.

Codeine is a pro-drug which is metabolised to morphine by the liver enzyme CPY2D6 to achieve its analgesic effect. Genetic differences mean that there is variation in how people metabolise codeine (either fast or slow metabolisers). Dihydrocodeine is similar to codeine in both its structure and analgesic effect. Tramadol is classed as an "atypical" opioid as it is both a relatively-weak mu opioid receptor agonist and a noradrenaline and serotonin reuptake inhibitor.[29]

Codeine, dihydrocodeine and tramadol are not recommended for use in patients with renal impairment. Use of all opioids is associated with constipation, but this can be particularly problematic with codeine. Co-prescription of a laxative is recommended. Tramadol may be more associated with nausea, vomiting, dizziness and sedation than codeine.

Strong opioids are ideally a "last resort"

When all other treatment options have failed, the clinician may decide that a strong opioid is the only treatment option available when the patient has moderate to severe chronic non-malignant pain. When a strong opioid is indicated, morphine is the first-line choice. Fentanyl patches are sometimes considered in patients with severe chronic pain. However, they are best reserved for patients with constant and stable opioid requirements.

* A number of these medicines are not subsidised or approved for use in pain management in New Zealand. For example, tricyclic antidepressants are not approved for neuropathic pain (but are frequently used for this indication) and capsaicin is subject to subsidy restrictions. Pregabalin and duloxetine are sometimes used for chronic non-malignant pain, but are not subsidised in New Zealand. Refer to the New Zealand Formulary for further information on approved indications and subsidies.

Take home messages

- Chronic non-malignant pain takes time to treat and the management plan needs to include not only physical treatments, but also acknowledgement of the patient's pain and emotional wellbeing, and support to help them self-manage their condition
- Use combinations of non-pharmacological interventions and non-opioid analgesics as the mainstay of treatment
- Only use opioid analgesics as a last resort
- If it is absolutely necessary to use opioids, consider weaker opioids such as codeine or tramadol before using strong opioids such as morphine, and use the opioid at the lowest possible dose, for the shortest possible time

Coming up: In the next edition we look at the growing problem with opioid addiction in New Zealand, and discuss strategies for withdrawing patients from opioids.

The 10 Universal Precautions approach to chronic pain management

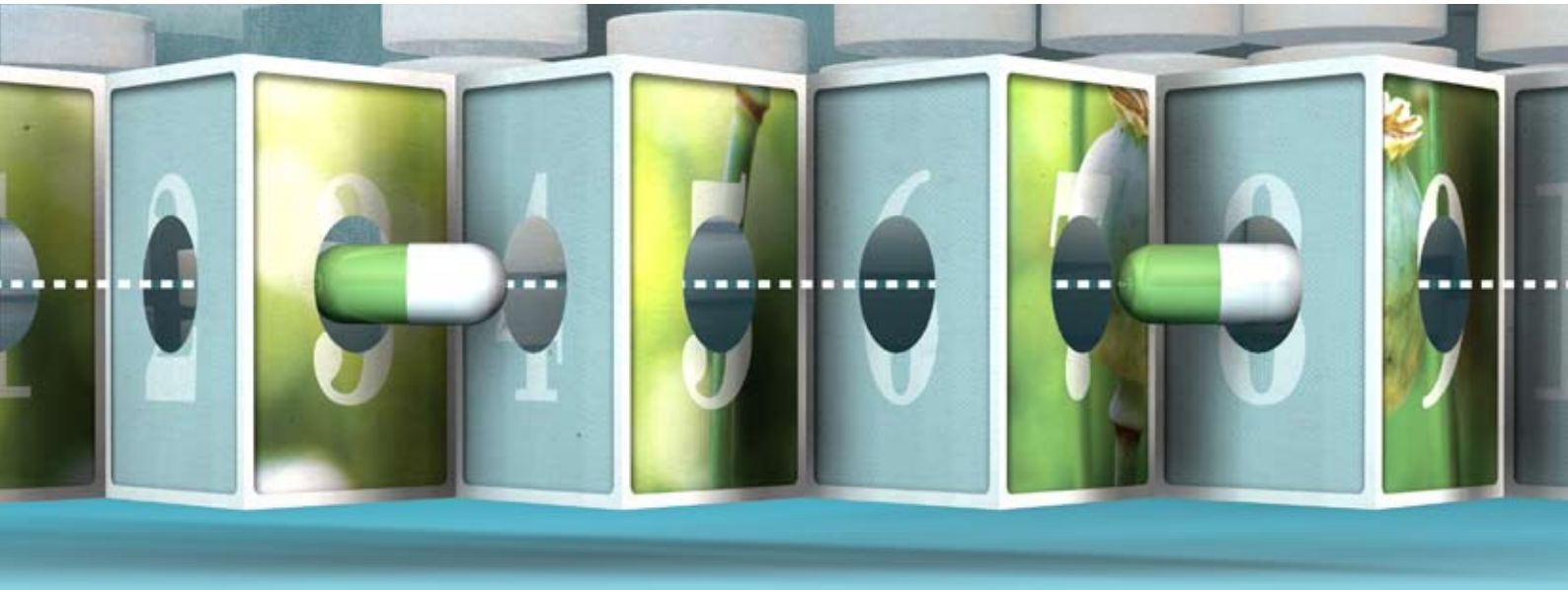
The "10 universal precautions" are a set of guiding principles which can be applied to the management of long-term pain. Opioids are not recommended for long-term use when treating chronic non-malignant pain. However, if there is no other treatment option and they must be used, these principles can help determine which patients may be at risk of opioid misuse, to guide opioid treatment and ensure appropriate review.[30]

The 10 Universal Precautions are:[30]

1. **Aim to diagnose the underlying cause of the pain**, considering differential diagnoses. If there is no clear diagnosis, and an absence of objective findings, treatment can be initially aimed at managing the patient's symptoms. If the pain persists the patient should be reassessed for a diagnosis, and their analgesic requirements reviewed, with the aim of stepping down from the use of a strong opioid, if appropriate.

2. **Conduct a comprehensive psychological assessment** including the risk of addiction. Question the patient about past or present alcohol or illicit drug use. In addition ask about any family history of substance misuse or addiction (including alcohol) as this increases the risk that the patient may misuse opioids. Other psychological factors, such as the patient's expectations and mood, and social aspects, e.g. sleep, work, family and social support should also be considered.

3. **Gain informed consent** from the patient. Discuss the proposed treatment with them, including the anticipated benefits and the possible adverse effects and risks of physical dependence, tolerance and addiction. Ensure the information has been delivered at an appropriate level and that the patient understands the information that has been discussed. Some patients may wish to include family members, a support person or caregivers in the decision making process.



4 **Obtain a treatment agreement**. The concept of universal precautions relies on clear communication between the clinician and the patient and is ideally based on mutual trust and respect. The expectations and obligations of both the patient and clinician need to be clearly understood and either agreed verbally or more formally in a written treatment agreement or opioid contract.*

5 **Record a measure of the pre- and post-intervention pain level and function**. In order to assess the success of a treatment trial, it is necessary to have a baseline measure of the patient's pain (e.g. pain score) and level of function. These aspects can then be monitored and documented periodically during treatment and at the conclusion of the trial treatment period, to determine whether functional goals have been met and pain has been reduced. This then forms the basis of a decision on continuation of treatment.

6 **Conduct an appropriate trial of opioid treatment**, ideally with adjunctive medicines. Prescribing an opioid should not be routinely thought of as the first step when choosing a pain treatment. Before opioids are considered, ensure there has been an adequate trial of both non-pharmacological and other pharmacological treatments that are appropriate for the patient's condition.

7 **Regularly reassess the patient's pain scores and level of function**. A regular reassessment of the patient to check how well their pain is being managed and their level of functioning will help the clinician to decide whether to continue or modify the current treatment. Ensure that the patient has realistic expectations of the treatment, i.e. that they may have an increase in their level of function and their ability to cope, but not a complete resolution of their pain.

8 **Regularly assess the "5 A's" of pain management:** analgesia (how much relief has the medicine provided?), activity (progress in functional goals), adverse effects (especially constipation, nausea and sedation), aberrant behaviours (signs or suspicion of medicine misuse) and affect (impact of pain on mood and psychological wellbeing)

9 **Periodically review the pain diagnosis,** co-morbidities and addictive disorders. The underlying illness can evolve during treatment and it is important to periodically re-assess the original condition for which analgesia is being used. In addition, a patient's co-morbidities can influence the success of pain management strategies, so where possible, other conditions need to be optimally managed.

10 **Carefully document** every step of the patient's treatment protocol.

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* There are a number of standard opioid contracts available online, e.g. www.hnehealth.nsw.gov.au/__data/assets/pdf_file/0017/108701/Opioid_treatment_agreement_Mar_2013.pdf

www.wps.ac.nz/Portals/9/Documents/Opioid%20Contract%20formv2%200-2012.pdf www.icsi.org/_asset/dyp5wm/Opioids.pdf (Appendix A)

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Identifying and managing **addiction to opioids**

The increased use of opioid analgesics in recent years, particularly oxycodone, has resulted in misuse and addiction issues associated with prescription opioids becoming more evident in New Zealand. Clinicians need to be aware of what these issues are, and how to identify and manage patients with inappropriate opioid use. All patients with non-malignant pain who have been taking opioids for longer than a few weeks should be reviewed, to consider whether treatment is still appropriate and how adequate controls can be ensured.

There are a number of issues associated with the long-term use of opioid analgesics for the treatment of patients with chronic non-malignant pain, including an unproven efficacy for this use, adverse effects, tolerance, aberrant behaviour and addiction (see: "Definition of terms related to opioid misuse", over page). Patients initially start taking opioids to manage pain, but become increasingly reliant on the opioids, not only for pain relief, but also to manage emerging issues that overlap with addiction. Pain and addiction have inter-related symptoms and are often present at the same time. If one disorder is untreated, effective treatment of the other will not be possible. This adds to the complexity of managing patients with pain and addiction. It also further reinforces that opioids should be a treatment undertaken with considerable caution in patients with chronic non-malignant pain, and subject to careful and ongoing oversight.

The international experience with oxycodone misuse

Although not the only opioid that is misused, the well-documented global experience with oxycodone demonstrates the problems that occur when large volumes of strong opioids are available in the community.

Canada has led the world in publicising the misuse and addiction problems associated with oxycodone. After controlled-release oxycodone (OxyContin) was approved by Health Canada in 1996, and added to the Ontario provincial drug formulary in 2000, it rapidly became widely prescribed and then misused, particularly in Ontario. It soon became evident that the controlled-release characteristics of this formulation of oxycodone could be overcome by chewing or crushing the tablet, therefore making it an attractive medicine to misuse.

Between 2005 and 2011, there was a strong and significant correlation between prescription oxycodone dispensing levels and opioid-related mortality in Ontario. The number of oxycodone-related deaths increased from 0.54 deaths per 100 000 people in 2005 to 1.24 deaths per 100 000 in 2011.[5]

The oxycodone problem readily extended to remote communities and Canada's First Nations People. Some communities in Northwest Ontario have reported addiction rates as high as 70% in their adult populations.[6] In addition to adverse health effects, this has had significant economic implications with single 80 mg tablets selling for $80 – 800.[6]

The problems experienced from 1996 – 2012 resulted in a number of changes to how oxycodone is supplied and prescribed in Canada. Despite the manufacturers replacing OxyContin with the "crush-deterrent" formulation OxyNeo in 2012, legislation was passed in Ontario to delist oxycodone from the province's public drug benefit programme. This was a first for any province to delist a medicine based on addictive properties. The new law prohibits prescriptions for OxyNeo except to certain patients under an Exceptional Access Programme, which includes use for patients in palliative care and patients who have other extenuating circumstances.

At this stage the strategy appears to be working. It has been reported in the media that a year after the change, the number of OxyNeo prescriptions in Ontario was approximately 60% lower than the number of OxyContin prescriptions in the year before it was replaced.

Oxycodone was introduced to Australia in 1999 and, like in Canada, use of this medicine rapidly rose. The number of prescriptions for oxycodone increased by 152% over a five year period, from 3530 prescriptions per 100 000 people in 2002/03 to 8902 per 100 000 in 2007/08.[7] Of the 465 oxycodone-related deaths that were reported during this period, 53% were in patients who had been prescribed oxycodone (as opposed to obtaining it from other sources).[7]

A crush-deterrent tablet formulation of controlled-release oxycodone was released in Australia in April, 2014 and conventional OxyContin formulations were withdrawn, with the aim of reducing the misuse issues associated with oxycodone.[8] It is too early to tell what impact these changes have had, but it is hoped that it will result in positive changes similar to those seen in Canada.

Definitions of terms related to opioid misuse

Aberrant behaviour: any behaviour that raises concerns about addiction in opioid-treated patients, including:[1]

- Recurrent prescription losses
- Undertaking unauthorised dose escalations rather than adhering to scheduled dosing
- Repeated, and often aggressive, requests for higher doses of opioids
- Accessing opioids from other sources, e.g. from friends and relatives, "doctor shopping" and from the street
- Altering the route of delivery, e.g. injecting or snorting oral formulations

Addiction: Characterised by an inability to consistently **a**bstain (from taking opioids), impairment in **b**ehavioural control, **c**raving, **d**iminished recognition of significant problems relating to behaviour and interpersonal relationships, and a dysfunctional **e**motional response; the "ABCDE of addiction".[2]

Dependence: a state of physiological adaptation that can be unmasked by abrupt cessation, rapid dose reduction, decreasing blood levels of the opioid or administration of an opioid antagonist.[1] The terms addiction and dependence are frequently used interchangeably, depending on the medical context. Pain specialists tend to refer to dependence to mean neuroadaption (tolerance and withdrawal) by itself; addiction specialists use the term dependence to mean neuroadaption plus behavioural change.

Opioid-induced hyperalgesia: occurs when prolonged administration of opioids results in a paradoxical increase in atypical pain that may be unrelated to the original cause of pain.[3] The typical presentation is a patient with increased sensitivity to pain (sometimes at a different location to the original pain site), with different characteristics to the original pain.[4]

Tolerance: occurs when repeated administration of opioids results in a diminished clinical effect.[1]

Withdrawal: physical and psychological symptoms that occur when patients stop taking opioids.[1]

What is happening in New Zealand?

In New Zealand the dispensing rate of oxycodone increased by 249% between 2007 and 2011, before slowing in 2012 – 13.[9] The misuse problems seen in other countries are now starting to become apparent in New Zealand. Obtaining an accurate estimate of the rate of opioid dependence/addiction in New Zealand is difficult as there is limited data available. However, data from a number of sources show that the rate of opioid misuse in New Zealand is increasing. Anecdotally, addiction specialists across the country have raised concerns about the frequency at which oxycodone is found to be a factor, or the driving force, in new patient presentations.

Statistics on oxycodone misuse in New Zealand

The 2014 Global Drug Survey was conducted in 20 countries, with nearly 80 000 respondents, typically aged in their 20s and 30s. It was found that opioid analgesics had been used in the previous year by 8.7% of all respondents. This figure was substantially higher among respondents from New Zealand (19.1%) and second only to the USA (21.5%).[10]

It was estimated in a 2012 study in New Zealand that 0.3% (9100) of people aged 15 – 64 years were dependent on opioids.[11] However, the authors acknowledged that this figure is lower than previous estimates and should be considered as a minimum estimate of opioid dependence.[11]

The results of a 2010 survey that was sent out to a random sample of 300 New Zealand general practitioners, revealed that 66% of respondents had diagnosed at least one patient with prescription drug misuse in the last year.[12] Benzodiazepines and opioids were the most problematic medicine classes. Of the 111 general practitioners who had prescribed oxycodone in the preceding 12 months, 30% reported that they had at least one occasion where they had declined to prescribe oxycodone to a patient or had concerns about prescribing it due to issues of misuse.[12] As was reported in BPJ 62 (Jul, 2014), 72% of prescriptions for oxycodone in New Zealand in 2013 were initiated in secondary care.[9] This means that general practitioners frequently encounter patients discharged from hospital on oxycodone and face the challenge of negotiating withdrawal of oxycodone treatment.

The Illicit Drug Monitoring System (IDMS) is a survey which is conducted annually to provide a snapshot of trends in the use of illicit substances in New Zealand. The latest IDMS results are available from the 2012 survey which involved interviews with 330 frequent illegal substance users from Auckland, Wellington and Christchurch.[13] The report revealed that each

year, oxycodone becomes more widely used for recreational purposes. The proportion of frequent injecting-drug users who had used oxycodone in the previous six months increased from 9% in 2008 to 25% in 2012. The proportion who had used oxycodone at any time increased from 21% in 2008 to 54% in 2012.[13]

The implications of opioid misuse in general practice in New Zealand

The increase in use and misuse of oxycodone and other strong opioids in New Zealand highlights two main points – firstly, that these medicines should be avoided in patients with chronic non-malignant pain, and secondly, that patients who are taking opioids long-term, with no plan for stopping or controls around dispensing should be re-assessed.

The efficacy, tolerability and addictive potential of opioids make them a generally unsuitable treatment option for patients with chronic non-malignant pain. However, prescribing data shows that many patients in New Zealand are receiving strong opioids long term.[9] Clinicians should re-assess opioid use in these patients, and consider whether their pain condition is being ideally managed. This involves first gaining an understanding of the patient's experience of their pain, and the factors that may be contributing to their pain. Chronic non-malignant pain is best managed with a combination of non-pharmacological treatment interventions, e.g. cognitive behavioural therapy, exercise and lifestyle activities, and non-opioid pharmacological treatments. Even optimal pain treatment may need to allow for the continued experience of manageable pain.

 For further information on understanding pain and why opioids are not an appropriate treatment, see: "Helping patients cope with chronic non-malignant pain: it's not about the opioids", BPJ 63 (Sep, 2014).

How to withdraw opioid treatment

Although prevention is better than cure when it comes to opioid misuse and addiction, clinicians should be aware of appropriate treatment pathways when patients need to be withdrawn from opioids. This may be because the patient is showing signs of aberrant behaviour or addiction, or because long-term use of a strong opioid is no longer considered appropriate.

The features of opioid addiction are not always obvious and can be difficult to clearly define. Some signs and symptoms may include:

- Physical symptoms – flushing, vomiting, dizziness and lack of stability resulting in falls, loss of appetite, dry mouth, compromised mental function, breathing difficulties, headaches and migraines, impaired liver function, seizures, decreased blood pressure and sleep apnoea
- Psychological issues – altered perception of reality, anxiety, depression, mood swings, personality shifts, low self-esteem and negative body image, feelings of rage and bursts of anger, confusion, disorientation and paranoia
- Social issues – withdrawal and isolation from friends and family, loss of interest in activities normally enjoyed, damaged relationships with loved ones

Management of patients with addiction issues can be challenging and a decision needs to be made whether to attempt to withdraw the opioid in primary care or refer to a specialist pain or addiction service (see: "When to attempt opioid tapering in primary care", Page 21). Patients taking high doses of opioids for prolonged periods and patients with signs of aberrant behaviour are usually best referred to a specialist service. Other factors to consider are the patient's level of motivation to withdraw from treatment, how amenable they are to dose reduction and the nature of their underlying pain condition, e.g. what other options are available to manage their pain? The decision to refer to specialist services will also be dependent on the general practitioner's expertise in treating addiction.

General practitioners should not be deterred from referring a patient to an addiction specialist (or seeking a second opinion), if they have an aggressive or negative response to withdrawing treatment. It can be explained to patients that opioids cannot continue to be prescribed to them without a review of their case by an addiction specialist, as there would be concern that further prescriptions would contravene the Misuse of Drugs Act. Linking the ongoing prescribing of opioids with the date of the specialist assessment will encourage attendance at the appointment.

Managed opioid withdrawal

The two general approaches to managed withdrawal from opioids are abrupt cessation and gradual dose reduction. The preferred method depends primarily on the dose the patient has been taking and the duration of opioid use.

Abrupt cessation

Patients treated with lower doses of opioids (e.g. morphine 20 – 40 mg/day or oxycodone 10 – 20 mg/day) and for short periods

of time (one to two weeks) can generally stop treatment abruptly without experiencing withdrawal symptoms.[14] This is most likely to be patients discharged from hospital on opioids and patients with acute injuries who have received short-term opioid treatment.

Some patients may prefer not to stop opioid treatment abruptly but to rapidly reduce their dose, e.g. by 25% of their total daily dose per week (this is termed rapid tapering).[15] This approach may also be suitable for patients who have been taking lower doses of an opioid for longer periods of time, e.g. one to two months, who are highly motivated to discontinue the opioid.

Gradual dose reduction (tapering)

Patients who have been receiving higher doses of opioids or long-term opioid treatment are likely to require gradual tapering of the opioid dose. The rate of reduction of the opioid dose depends on a number of factors. These include the length of time the patient has been taking the opioid, their total daily dose, the underlying condition being treated, co-morbidities, e.g. depression and other psychological conditions, and upcoming important events.

Opioid-tapering protocol

Tapering regimens for opioids vary. Discussion with a pain or addiction service is recommended before beginning a taper, particularly if patients are taking high doses of an opioid.

A suggested protocol is as follows:[1]

Set goals prior to initiation of opioid taper

1. Emphasise that the goal is to reduce the pain intensity and improve patient function and mood
2. Have a written clinician/patient treatment agreement that clearly defines the aims and method of opioid tapering. Make sure the patient understands all the conditions documented in the agreement.
3. Recognise that frequent and supportive review will be required. Continuity of care is important and where possible a single clinician should conduct follow up and prescriptions should be collected from the same pharmacy. Formal counselling may not be necessary, but regular contact to "keep the faith" is valuable.

Consider the treatment regimen

1. Have a stabilisation phase of two to four weeks to clarify the daily dose of opioid the patient is taking; this will require an honest and open discussion for the patient to reveal the actual extent of their opioid use – do not assume that the patient's opioid requirements are what has been prescribed to them. Enquire about use of over-the-counter medicines which contain codeine and opioids from friends or family members. Consider a urine drug test and an examination for injection sites.

   N.B. Oxycodone, fentanyl, buprenorphine and tramadol are not included on a standard drug screen – list the medicine(s) you specifically wish to test for on the requesting form.
2. Prescribe scheduled doses. Consolidate long- and short-acting regimens and "as required" use into a set twice-daily regimen.
3. Prescribe frequent dispensing intervals, e.g. daily, alternate days or weekly, depending on what level of control the patient has over their opioid use; do not refill the prescription if the patient runs out and be especially cautious about claims of accidental losses. Addiction services often require that the patient has their opioid dispensed daily during this phase of treatment, and lost or vomited doses are not usually replaced.
4. Do not co-prescribe benzodiazepines – if the patient has been taking benzodiazepines, consider stopping these before withdrawing the opioid. N.B. Specialist advice for withdrawal of benzodiazepines may be required.
5. Discourage use of alcohol and cannabis during the opioid withdrawal.

Be flexible on the rate of taper

1. The rate of taper can vary from a 10% reduction in the total daily dose every day, to a 10% reduction every one to two weeks. The decision on the rate of tapering should be jointly agreed between clinician and patient and can be varied, e.g. with larger dose reductions initially or a slowing of the rate of reduction due to an important upcoming event.
2. As doses are recalculated, they may not be able to be easily made up using available medicine formulations therefore clinical judgement is required in selecting an appropriate dose.
3. A reduction in the total daily dose can be equally divided into the two daily doses although this may only be practical in patients starting their taper from a higher starting dose of opioid. For patients on lower total daily doses, a suggested approach may be to start the taper by reducing the patients' dose at the time of day when their pain is less. For example, in a patient taking 20 mg of oxycodone, twice daily (i.e. total daily dose of 40 mg), reduce the morning dose to 15 mg if this is when their pain is best controlled and leave the evening dose at

20 mg. Although this is slightly more than a 10% dose reduction (12.5%), it represents a practical "patient focused" solution given the available tablet sizes of oxycodone.

4. Slower rates of taper, e.g. 5% dose reductions, may be more appropriate in some patients, e.g. those who have significant co-morbidities, are anxious about tapering or who may be psychologically dependent on opioid treatment.
5. Once the patient has tapered to one-third of their original dose, the taper can be slowed to half or less of the previous rate.
6. Be prepared to hold the dose when necessary, including when the patient experiences reduced function, severe withdrawal symptoms or has a significant worsening in mood or pain (referred to as the neuro-adaptation plateau). Reassure the patient that their symptoms will resolve as neuro-adapation occurs, and the reduction in opioid will then resume.

Regularly monitor the patient during the tapering period

1. Schedule frequent contact, e.g. weekly, during the tapering period. Be aware that the cost of consultations may be prohibitive for some patients. Face-to-face consultation is preferred, but contact by other means, e.g. phone call or text message, can be considered and is often well received by the patient.
2. At each consultation ask the patient about withdrawal symptoms and their functional status (function rather than pain should be the focus) as well as any possible benefits they may be experiencing, e.g. improvements in energy levels, mood or alertness. A return of a more normal emotional range may initially be unsettling to the patient, but can also be very rewarding.
3. Check for injection sites and consider requesting urinary drug testing to assess adherence.

Endeavour to complete the taper

1. Be aware, and advise the patient, that the tapering period can take a variable length of time, e.g. from two weeks to four months.
2. Be prepared to keep patients on low doses of opioids for an extended period if they are unable to complete the taper, as long as their mood and functioning improves and they are willing to follow the opioid withdrawal agreement.
3. Avoid any dose increase, except for a brief return to a previously manageable dose – a "reducing" schedule that is actually oscillating up and down should be re-thought.

When to attempt opioid tapering in primary care

One of the more challenging aspects of withdrawing opioid treatment is deciding whether the patient can be successfully managed in primary care or whether they require more specialised support. In general, it may be worth considering the following broad categories when assessing the most appropriate treatment setting:[16]

1. Patients who can be managed in primary care – no personal or family history of substance use disorder and no major or untreated psychiatric disorders.
2. Patients who can be managed in primary care with specialist support* – a past history of substance use disorder, a significant family history of problematic drug use or a past or concurrent psychiatric disorder, but no active addiction
3. Patients best managed in a speciality pain service – active substance use disorder or major untreated psychiatric disorder

* Specialist support may be formal, i.e. the patient is co-managed in a pain/addiction clinic, or the patient can be referred for reassessment as required.

Managing symptoms during opioid withdrawal

Many of the symptoms classically associated with withdrawal may not be seen in patients who undergo a gradual taper.[17] Symptoms also vary between individuals. Withdrawal from opioids is not considered a life-threatening situation (except in neonates), in contrast to withdrawal from alcohol and benzodiazepines, which can be. The physical symptoms of withdrawal generally resolve within five to ten days after opioid dose reduction/cessation; whereas, psychological symptoms, when present, may take longer to resolve, e.g. weeks to months.[17]

Early symptoms (hours to days after withdrawal) include: restlessness and anxiety, rapid short respirations, sweating, yawning, sniffing, rhinorrhoea, lacrimation, musculoskeletal pain and dilated reactive pupils.[17]

Late symptoms (days to weeks) include: continuation of early symptoms (as above), along with tremor, diffuse muscle spasms and aches, abdominal pain, nausea, vomiting, diarrhoea, tachypnoea, pilo-erection, fever and chills. Patients who rapidly withdraw from opioids may have a transient increase in white blood cell count (although testing WBC is not generally required during opioid withdrawal).[17]

Prolonged symptoms (weeks to months) include: craving, reduced tolerance to stress, irritability, insomnia, fatigue, bradycardia and decreased body temperature.[17]

How to manage withdrawal symptoms

Symptomatic management is important for successful opioid withdrawal, along with compassionate acknowledgement of what the patient is experiencing. The patient can be reassured that their discomfort is temporary and will resolve. The patient's underlying levels of distress during the opioid withdrawal should be monitored and they can be referred for specialist addiction treatment if agitation or anxiety is severe. Involving family members to support the patient during their withdrawal is also recommended – as for any mental health condition, family support enhances the prognosis.

Symptomatic treatments that may be required include:[17]

- Paracetamol and/or NSAIDs for withdrawal aches and pains and general pain
- Topical rubefacients, e.g. menthol + methyl salicylate (Deep Heat) and massage for muscle pain and aches
- Mebeverine for abdominal cramping
- Loperamide for diarrhoea
- Antiemetics, e.g. prochlorperazine or metoclopramide, for nausea and vomiting
- Oral or transdermal clonidine (off-label use) for hot/cold sensations (not routinely required if the taper is gradual), however, be aware that clonidine has misuse potential also. Blood pressure monitoring is required after the first dose and for at least 72 hours or until a stable dose is achieved and then again after discontinuation. Reassess treatment after one week and taper to stop.

A short-acting benzodiazepine or zopiclone should only be considered if the patient has insomnia that cannot be managed with non-pharmacological treatments (e.g. "sleep hygiene" and relaxation techniques) and the insomnia is compromising the success of the withdrawal. These medicines have significant misuse potential and should only be used for a short time.

Quinine is no longer used to treat symptoms of withdrawal.

Refer to NZF for dosing instructions for these medicines: **www.nzf.org.nz**

How to manage pain in patients undergoing opioid tapering

During the opioid taper, patients are likely to report that their pain has increased as the opioid dose was decreased. An increase in pain when withdrawing opioids does not mean that the opioid was effective in providing pain relief, only that removing it makes the pain worse for a short period of time. When pain occurs, the rate of taper can be slowed and other pharmacological (e.g. paracetamol, NSAIDs) and non-pharmacological treatments (e.g. exercise, massage, cognitive behavioural therapy) added to maximise pain relief.

Preventing relapse

Naltrexone may be considered for relapse prevention in people who have ceased opioid use. It is approved in New Zealand for this indication, but is only subsidised for the treatment of alcohol dependence. However, the evidence of effectiveness of naltrexone in maintaining opioid abstinence is low, as the majority of patients stop taking it, especially during risk periods. The risk of fatal overdose may then be increased as the patient relapses without any tolerance for opioids. If relapse occurs, or is very likely to occur, a period of opioid substitution (specifically with a long-acting opioid, i.e. methadone or buprenorphine) is the treatment best supported by the evidence.

Opioid substitution treatment (OST) in New Zealand

OST is the evidence-based treatment of choice in patients with opioid misuse and addiction problems who have not achieved opioid withdrawal or for whom tapering is an unsuitable withdrawal method, e.g. due to complex co-morbidities. Substitution with a long acting opioid, i.e. methadone or buprenorphine, allows the patient to move away from the reinforcing effects of shorter acting opioids. The "on-off" effects of opioids with shorter half-lives means that the expected return of pain (or associated opioid withdrawal symptoms) becomes a powerful disincentive to completing a successful taper.

By law (the Misuse of Drugs Act 1975) OST can only be carried out by specialist services in New Zealand and some general practitioners that are trained and authorised by the specialist service to administer OST.

Methadone or buprenorphine can be used for OST

The rationale behind opioid substitution stems from the fact that the majority of patients who have been dependent on opioids for a year or longer, will not be able to remain abstinent from opioids, even with optimal support.

Methadone and buprenorphine are used as opioid substitutes.[18] These medicines both have gradual onsets of effect with longer durations of action than the opioids being misused, e.g. oxycodone and morphine, resulting in more stable serum levels. As a result of this, patients taking methadone or buprenorphine do not experience a "rush" or marked withdrawal symptoms, and have a reduced desire to use other opioids. For patients with pain, this longer action ameliorates the sudden onset and rapid wearing off of pain relief of shorter acting opioids and therefore improves pain cover.

Methadone is the more commonly used substitute, as it is more effective in retaining patients in treatment, has been available for longer and is substantially cheaper than buprenorphine. Buprenorphine is a useful alternative choice, although its partial agonist action means that it may not achieve enough protection against relapse in all patients. In New Zealand, only the buprenorphine combined with naloxone (Suboxone) is funded, subject to Special Authority criteria. The naloxone does not act unless injected – its inclusion in Suboxone is to deter injection (although some drug users will do so anyway).

Long-acting morphine and sustained relapse oxycodone preparation are not effective opioid substitutes.

Treating acute pain in opioid-dependent patients

Using opioids for acute pain in patients who are, or have been, opioid dependent has risks and should be done with caution. If needed at all, opioids should only be prescribed for an acute, clearly defined condition in combination with regular review. The treatment plan should be agreed on with the patient and include regular follow up and a plan to rapidly taper and stop the opioid treatment. Course length will be between three and 14 days, depending on the condition treated. Dispensing safeguards need to be addressed. In patients with a significant risk of relapse or with an active opioid addiction discussion with specialist pain/addiction services is strongly recommended if pain relief is required, and as a courtesy if the patient is undergoing opioid substitution treatment.

Some best practice principles for acute pain management in this patient group include:[18, 19]

- Consult with specialist pain/addiction services and consider early referral for assessment and management
- Maximise the use of non-opioid analgesics and non-pharmacological treatments
- If an opioid is required, it may be best to use it in combination with a non-opioid analgesic to reduce the dose of opioid needed
- If opioid substitution is already in place, the addiction service may suggest a temporary increase of the opioid substitute as a pragmatic solution, with dispensing controls already in place
- Alternatively, patients on opioid substitution who have been stable in treatment for a year or more may find it psychologically easier to separate the opioid prescriptions into the opioid substitute for addiction, and a closely supervised, reducing dose of a shorter acting opioid for pain. This only generally works for short periods of time, i.e. less than 14 days, because of the degree of supervision (dispensing restriction and close review) involved

When patients first begin OST, the opioid substitute is dispensed daily as this becomes an external control that takes the place of the patient's diminished internal control. This phase of treatment may last for three to six months. Dispensing restriction is then gradually relaxed to aid rehabilitation as the patient regains the confidence and ability not to use doses in advance or by injection.

Patients usually require a minimum of two years of opioid substitution for it to be effective, reflecting how profoundly opioid dependence affects individuals. Any duration of treatment less than one year would be considered to represent an opioid detoxification, where the chance of relapse is high. For these reasons alone, prevention of opioid dependence by careful opioid prescribing is far more preferable than having to treat dependence.

Referral of patients to OST services

The decision of whether to refer a patient for OST will depend on a number of factors. OST is offered nationwide and there should not be significant waiting lists for treatment. Patients in rural areas can also access OST, although alternative dispensing procedures may have to be put in place (e.g. involving a district nurse) if the patient has to travel a significant distance to a pharmacy.

Red flags for referral for OST in patients taking opioids include:[18, 19]

- Higher doses of opioids (e.g. greater than oxycodone 60 mg/day or morphine 100 mg/day)
- Signs of aberrant behaviour, e.g. injecting or snorting oral formulations, recurrent prescription losses, accessing opioids from other sources, requests for pethidine
- Repeated failure of opioid tapering
- History of significant psychological and/or substance use disorders
- Aggressive or intimidating behaviour
- Feedback from pharmacies about problem behaviour, including presenting prescriptions from different doctors, intoxicated or intimidating behaviour, or contact with other people with opioid dependence

General care of patients undergoing OST

Most general practitioners will not be involved in the day-to-day administration of OST, but there are a number of potential issues to be aware of when patients receiving OST present in general practice.

Adverse effects

Methadone is associated with a number of significant adverse effects. Patients have an increased risk of methadone overdose in the first two weeks of treatment.[18] Titration to an effective dose of methadone can take two to six weeks, and during this time patients may resort to using alternative supplies, with the potential for fatal misjudgement of dose. Loss of consciousness through cardiorespiratory depression will require emergency treatment with injectable naloxone.

The most troublesome adverse effects associated with methadone include excessive sweating, dental cavities resulting from decreased saliva production, sleep apnoea, constipation, osteoporosis, drowsiness and reduced sexual function through either impotence or loss of libido.[18] In general, these adverse effects can be managed symptomatically or with dose reduction.[18] QT prolongation is a recognised risk of methadone treatment, especially in patients with a family history of QT prolongation, those taking higher doses of methadone and those concurrently taking other QT prolongating medicines, e.g. antidepressants and antipsychotics. The risk of QT prolongation is also increased in females, and with increasing age.[20]

Buprenorphine is not generally associated with overdose, unless the patient is opioid naïve (i.e. inappropriately in OST). Adverse effects include constipation, nausea, reduced sexual function and drowsiness.

Medicine interactions

Methadone and buprenorphine have potentially significant interactions with a number of other medicines such as antibiotics (e.g. ciprofloxacin and erythromycin), antifungals (e.g. fluconazole) and antivirals (e.g. ritonavir).[18]

Refer to the New Zealand Formulary for full details: **www.nzf.org.nz**

Safe storage

Not all patients receiving OST will be given "take away" doses. However, those that do should be educated on safe storage of their medicine. Even small doses of methadone in children can be life-threatening and deaths have been reported in adolescents who have inadvertently taken methadone when looking for an analgesic at home. Pharmacists should dispense all opioids in child-resistant packing whenever possible.

Managing pain

Be aware that methadone and buprenorphine provide little, if any, analgesia for acute pain due to increased opioid tolerance or hyperalgesia. As a result, opioid analgesics are often less

effective in managing acute pain in patients undergoing OST and these patients require higher doses more frequently than usual.[18] If a patient has a need for acute pain relief for a clearly defined condition, discuss appropriate options with their OST provider.

The partial agonist action and high opioid receptor affinity of buprenorphine creates particular challenges for using additional opioids for analgesia. Because stopping the buprenorphine can destabilise the opioid substitution control, prescribers are usually faced with providing sufficient short-acting opioids to achieve analgesia. Given that this may involve substantial doses, inpatient oversight is commonly required.

Further resources

The 2014 New Zealand Practice Guidelines for OST contain practical and evidence-based information for clinicians on the clinical assessment and treatment of people with opioid dependence. This document is available from: **www.health.govt.nz/publication/new-zealand-practice-guidelines-opioid-substitution-treatment-2014**

The Alcohol & Drug Helpline (0800 787 797) and DHBs can advise on local availability of addiction support.

Community and Alcohol Drug Services (CADS) are offered in most main centres around New Zealand. Resources are also available from: **www.cads.org.nz**

Addiction support is also be available through non-government organisations, including the Salvation Army, CareNZ, 12-Step Programmes (e.g. Narcotics Anonymous, Alcohol Anonymous & Al-Anon) and Tranx.

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