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Oxycodone:

**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.

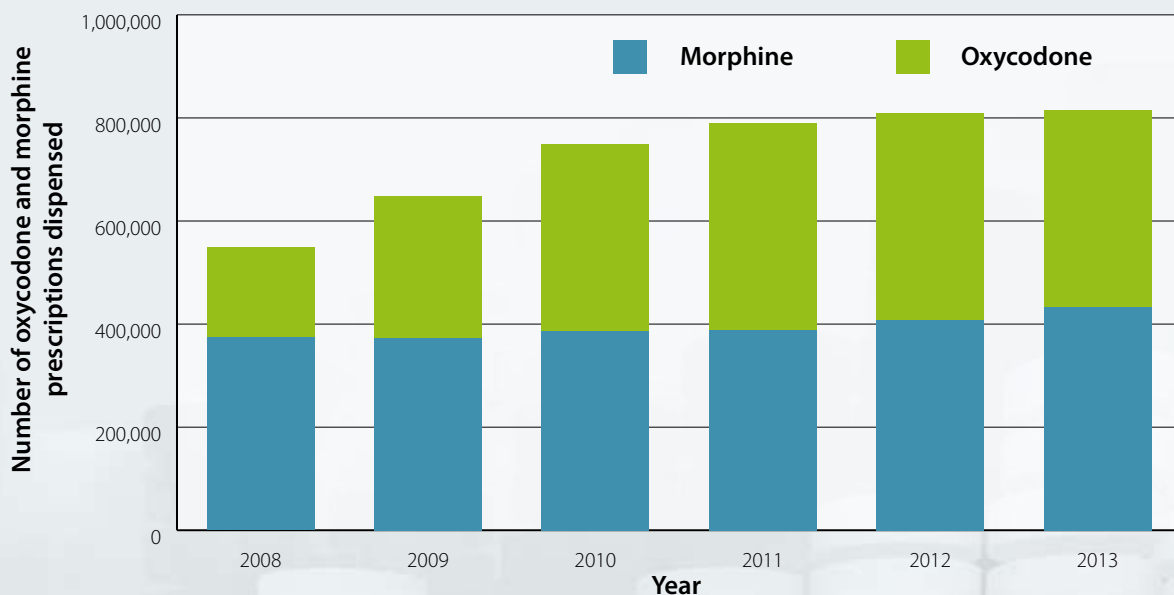


Figure 1: Number of oxycodone and morphine prescriptions dispensed (excluding injected preparations).⁵

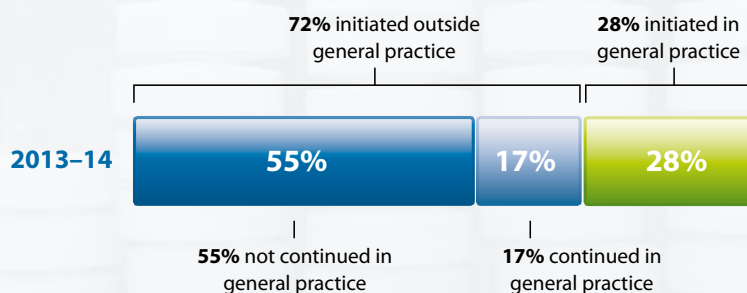


Figure 2: Source of oxycodone prescriptions for patients initiated in 2013/14 (Apr 2013 – Mar 2014)

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 m² (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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