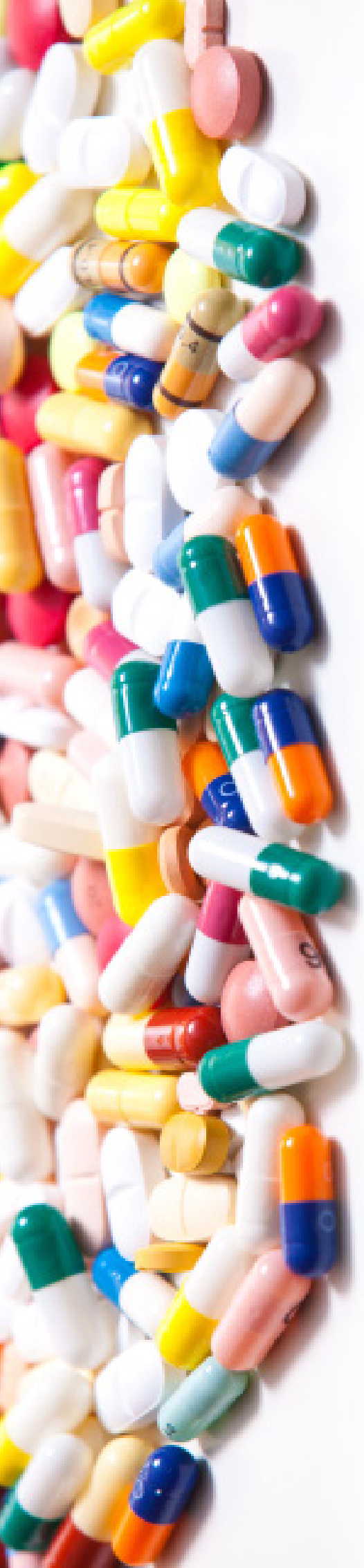


Pharmaceutical opioids in Australia: A double-edged sword

A literature review to support Australian prescribers to respond to patients with pharmaceutical opioid-related problems

Roger Nicholas

NCETA

Flinders UNIVERSITY

Suggested citation: Nicholas, R. (2019). *Pharmaceutical opioids in Australia: A double-edged sword.* National Centre for Education and Training on Addiction (NCETA), Flinders University, Adelaide.

ISBN: 13: 978-1-876897-67-3

Any enquiries about or comments on this publication should be directed to:

Professor Ann Roche
National Centre for Education and Training on Addiction (NCETA)
Flinders University
GPO Box 2100 Adelaide 5001
South Australia
Australia

Published by the National Centre for Education and Training on Addiction (NCETA).
www.nceta.flinders.edu.au

About NCETA

The National Centre for Education and Training on Addiction is an internationally recognised research centre that works as a catalyst for change in the alcohol and other drugs (AOD) field.

Our mission is to advance the capacity of organisations and workers to respond to alcohol- and drug-related problems. Our core business is the promotion of workforce development (WFD) principles, research and evaluation of effective practices; investigating the prevalence and effect of alcohol and other drug use in society; and the development and evaluation of prevention and intervention programs, policy and resources for workplaces and organisations.

NCETA is based at Flinders University and is a collaboration between the University and the Australian Government Department of Health.

About the author

Roger Nicholas is a Senior Project Manager at NCETA. He has worked in the alcohol and drugs field for almost 30 years in clinical, research and policy roles. He has a particular interest in public policy development and in psychoactive pharmaceutical drugs and enhancing their quality use.

Foreword

This literature review was undertaken by the National Centre for Education and Training on Addiction, Flinders University with assistance from HERA Partners. It was funded by Indivior Pty. Ltd.

The review informed the development of a resource to support prescribers assist patients experiencing difficulties with their use of pharmaceutical opioids. This resource – ***Responding to pharmaceutical opioid-related problems: A resource for prescribers*** *is available at nceta.flinders.edu.au.*

Prescribers are likely to see increasing numbers of patients experiencing difficulties with pharmaceutical opioid use. They are also likely to become more cautious about continuing to prescribe opioids (particularly in high doses) to their patients. There are three reasons for this.

First, in recent years, there have been increasing community and professional concerns about the burgeoning harms associated with pharmaceutical opioid use in Australia. These harms include hospitalisations, iatrogenic dependence, adverse physical effects and deaths. As a result, many prescribers and their patients are becoming hesitant about the ongoing use of these medicines.

Second, there is increasing community and professional awareness about the lack of efficacy of pharmaceutical opioids for the treatment of persistent non-cancer pain (PNCP). A very large proportion of pharmaceutical opioids use in Australia is for this condition. The use of opioids for PNCP is not only associated with the range of harms described above, but results in lost opportunities for more effective pain treatment approaches.

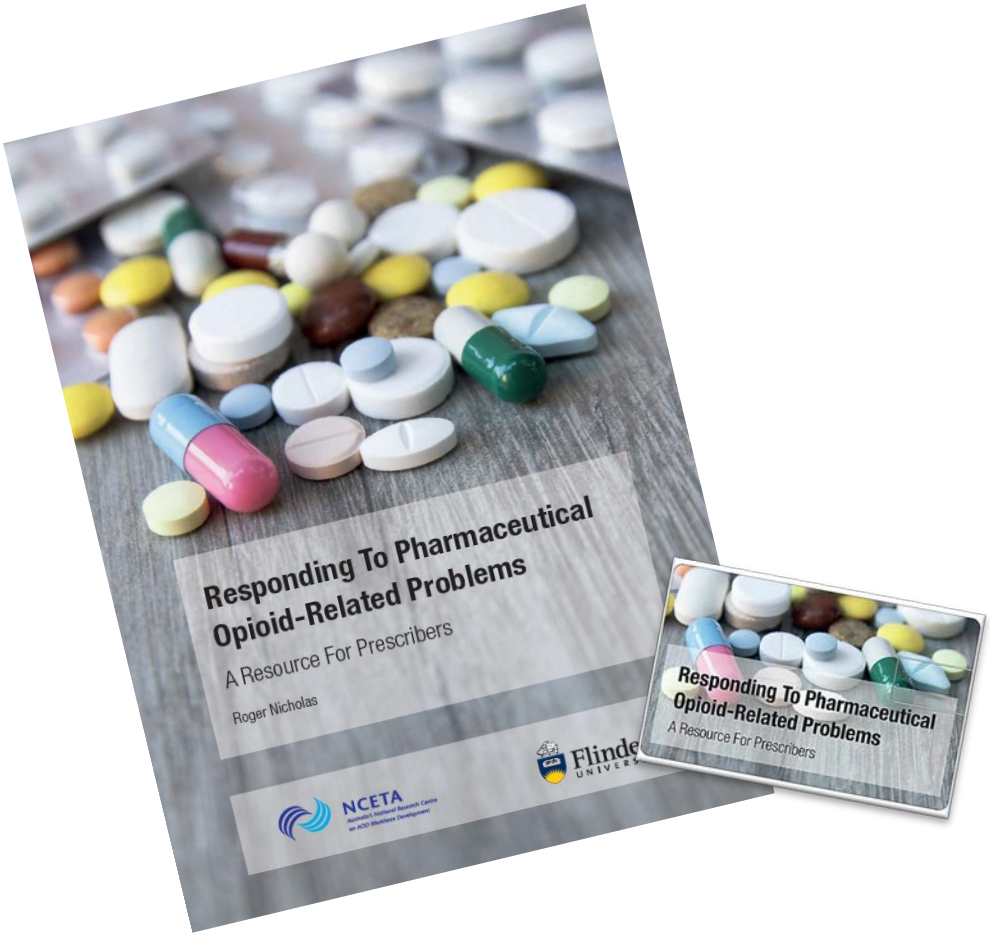
The third reason relates to recent regulatory changes impacting the availability of over-the-counter (OTC) codeine. On 1 February 2018, medicines containing low-dose codeine (most importantly compound analgesics) became unavailable from Australian pharmacies without a prescription. This stemmed from a growing awareness of:

- *Harms associated with codeine use*
- *Harms associated with exposure to high levels of paracetamol or non-steroidal anti-inflammatory medicines mixed with codeine in OTC analgesic preparations*
- *Evidence that codeine, at OTC dosage levels, is an ineffective analgesic*
- *The highly variable nature of codeine metabolism, meaning that some people derive no benefit from it while others are at risk of overdosing.*

The cessation of OTC codeine availability may mean that OTC codeine users, particularly those using larger doses, may require support to transition to other pharmacological and non-pharmacological pain management approaches. Some will also require support with codeine withdrawal symptoms or initiation of opioid dependence replacement therapy.

It is also important that opioids continue to be prescribed where their use is appropriate. Concerns about the effectiveness of opioids for the treatment of PNCP should not result in reduced use for conditions for which a strong evidence base exists, such as acute pain, palliative care and opioid substitution therapy.

In recognition of these factors the National Centre for Education and Training on Addiction developed a resource for prescribers to assist them to support these patients. The resource was derived from the evidence base identified in this literature review and is available at nceta.flinders.edu.au in electronic, hard copy or USB formats.



Contents

1 Introduction

1.1 The history of opioid use

Opium and its derivatives have been used for many centuries. Fossilised opium poppy seeds dating as far back as 30,000 years ago suggest the use of opium by Neanderthals.[1] Five thousand years ago, Sumerians (from what is now modern-day Iraq), called it the 'joy plant'. In the 8th century BC the Sumerians' direct descendants, the Assyrian-Babylonians, were aware of its analgesic effects as well as its sedative and hypnotic properties (Benedetti & Premuda, 1990; Sneader, 2005 as cited in Macintyre[2]).

The emotional analgesic effects of opium are mentioned in Homer's *The Odyssey* (composed near the end of the 8th century BC).

> *Then Jove's daughter Helen bethought her of another matter. She drugged the wine with a herb that banishes all care, sorrow, and ill humour. Whoever drinks wine thus drugged cannot shed a single tear all the rest of the day, not even though his father and mother both of them drop down dead, or he sees a brother or a son hewn in pieces before his very eyes.*[3]

Hippocrates (born 460 BC), and referred to as the father or western medicine, was known to have prescribed the drug.[2] The earliest written reference describing the use of opium as an analgesic is thought to have emanated from Theophrastus (born 371 BC), a pupil of Plato and Aristotle (Benedetti & Premuda, 1990; Sneader, 2005 as cited in Macintyre[2]).

Despite opium being in common use from early times for the treatment of pain and numerous other ailments, basic forms of investigation into the use of this drug did not start until the 17th century. In 1803/1804, Friedrich Sertürner discovered the major active ingredient of opium, which he named morphine and opioid pharmacology was born. Codeine was isolated from opium a few years later.[4] In 1898, heroin was synthesised and pronounced to be more potent than morphine and free from misuse liability. This was the first of several such claims for novel opiates. To date, none have proven to be valid.[4] Another 50 years on, the administration and efficacy of morphine was greatly improved by the introduction of the hypodermic needle and syringe.[2]

In 1939, the search for a synthetic substitute for atropine culminated serendipitously in the discovery of pethidine. This was the first opioid with a structure that is entirely different from that of morphine. This was followed in 1946 by the synthesis of methadone, another structurally unrelated compound with pharmacological properties like those of morphine.[4]

The major advances in the knowledge of opioid pharmacology came in the 1970s. By the 1980s, the use of epidural morphine for postoperative analgesia became commonplace and patient-controlled analgesia had become a routine part of (usually postoperative) pain management. By the 1990s, opioids had been administered by a wide variety of routes in attempts to treat acute pain, including

intravenously, spinally, intranasally, transmucosally, transdermally, by intra-articular injection and inhalation.[2]

Despite this extensive history of opioid use, a range of associated problems have yet to be resolved. For example, as a result of large interpatient variation in dose requirements, effective pain relief requires individual titration of opioid dose, regardless of the route of administration. In addition, issues related to the side effects of opioids as well as problems related to the development of tolerance and opioid-induced hyperalgesia remain.[2]

1.2 Opioids: Uses and mechanisms of action

Opioids act on an endogenous opioidergic system which is not only involved in setting pain thresholds and controlling nociceptive processing, but also participates in the modulation of gastrointestinal, endocrine and autonomic functions.[1]

The opioid system comprises four types of receptor:

- m- (MOP)
- d- (DOP)
- k-opioid
- nociceptin (NOP).[1]

Opioid analgesia occurs predominantly at the MOP receptor. Opioids bind to opioid receptors in the brain, spinal cord, and other areas of the body. They reduce the passage of pain messages to the brain and reduce feelings of pain.[1]

1.3 Tolerance, physical dependence, withdrawal, *substance dependence*[i]

Long-term opioid use can lead to tolerance, meaning that patients may need larger doses to maintain the same effect. Patients tolerant to one opioid will generally be tolerant to all other opioids, however the degree of cross-tolerance is difficult to predict.

Physical dependence on opioids means that if the opioid is antagonised, suddenly stopped, or abruptly reduced in dose, a withdrawal (or abstinence) syndrome can develop. This is most likely to occur if the patient has been taking opioids for more than 1 month. Opioid withdrawal syndrome symptoms include: tachycardia, hypertension, mydriasis, lacrimation, gastrointestinal upsets, anxiety or irritability, restlessness, perspiration, bone or joint aches, tremor, piloerection, rhinorrhoea and yawning.

[i] To meet the ICD 11 diagnostic criteria for substance dependence, an individual must have two or more of the following features: Impaired control over substance use; substance use becoming an increasing priority such that it takes precedence over other interests or enjoyment; and physiologic features indicative of neuro-adaptation to the substance, such as tolerance, withdrawal or use of the substance to prevent and alleviate withdrawal. This definition aligns more closely with the medico-legal definitions contained in legislation concerning the prescribing of controlled drugs to dependent people, than does the DSM-5 diagnosis of Substance Use Disorder.

Opioid withdrawal can be assessed and recorded using tools such as the Clinical Opioid Withdrawal Scale (see Appendix 2 of the National Guidelines for Medication-Assisted Treatment of Opioid Dependence). In addition, some patients may be using multiple substances and may experience multiple withdrawals.

Tolerance and physical dependence are natural biological consequences of repeated opioid use and do not imply misuse or align with the ICD diagnosis of *substance dependence*. Some patients may not even be aware that they are physically dependent.

Substance dependence is a diagnosis in the revised ICD11 that refers to a pattern of drug-taking behaviours and compulsive drug use despite evidence of physical, psychological, or social harm.[3] It is not an inevitable effect of opioid use.

It is also important to note that some patients with pain who appear to be exhibiting drug-seeking behaviours may simply be seeking better pain relief.

Among people who use opioids for pain-related problems, some will have *substance dependence* problems (see Figure 1).

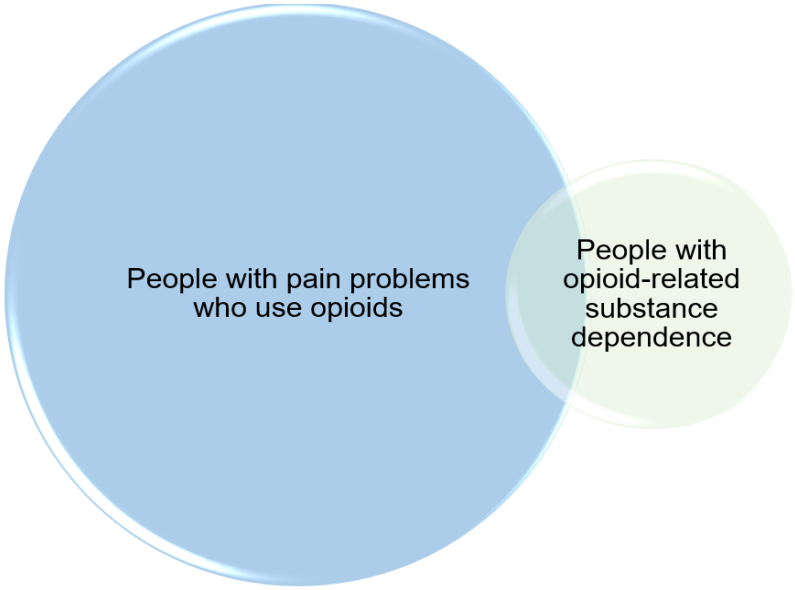


Figure 1: The overlap between people with pain problems who use opioids and people with opioid-related *substance dependence*. (Not to scale.)

2 Changes in opioid usage

Over the past two decades, many developed countries have experienced an increase in the use of pharmaceutical opioids. This increase has resulted largely from extending the use of opioids beyond the treatment of acute and malignant pain to include persistent non-cancer pain (PNCP[ii]).[5-7] This has occurred despite the strong evidence base suggesting that this is not an appropriate use of these medicines.[8]

Increased use of opioids for PNCP is of concern from a range of perspectives including higher levels of:

- Non-medical use[6]
- Pharmaceutical costs[9]
- Poisonings/overdoses[10-12]
- Opioid dependence[13, 14]
- Adverse effects such as constipation, sleep-disordered breathing, fractures, hypothalamic-pituitary-adrenal dysregulation[15]
- Lost opportunities for more effective treatment of PNCP.[7, 8, 16]

2.1 Different approaches to opioid use measurement

International rankings of levels of opioid use provide some context against which to consider utilisation levels in Australia. However, these rankings vary according to the calculation method[17], the particular drugs included in comparisons, and the data sources. An example appears in Table 1.

[ii] In this document, PNCP is defined as pain that is non-cancerous in origin which lasts for longer than the expected time for recovery of injured tissues, nominally 3 months. Persistent non-cancer pain also includes cancer survivor pain.

Table 1: Results of alternative approaches to opioid use calculation

Calculation method	Result
Using defined daily dose (DDD)[18, iii] per million persons per day of opioid utilisation and including: codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine, and trimeperidine, rates (in 2011-13).	• United States of America (USA) (43,879 DDD / million/day) • Germany (23,352) • Canada (22,941) • Australia (13,440).[19]
Using the measure of oral morphine equivalence (oMEDD)[iv] mg per capita / year, and including only the stronger opioids: fentanyl, hydromorphone, methadone, morphine, oxycodone and pethidine, in 2015 (noting the time-period is different from the DDD calculation cited above).	• Canada (853 oMEDD mg per capita / year) • USA (677) • Germany (612) • Australia (439).[21]

It has been argued that oMEDD measurement is preferable to the DDD approach because the latter does not accurately reflect opioid doses used in contemporary PNCP treatment.[22] An Australian comparison of DDD with actual levels of opioids used by PNCP patients revealed that the DDD ranged from 0.6 to 7.1 times the median opioid doses used by the sample. For transdermal fentanyl and oral hydromorphone, the median dose was comparable with the DDD. The DDD for methadone was 0.6 times lower than the median doses. In contrast, the DDD for oxycodone and transdermal buprenorphine, the most commonly used strong opioids for PNCP in Australia, was two to seven times higher than actual doses consumed.[22] This highlights the importance of clarity regarding the methods used to calculate opioid use.

Sources of pharmaceutical-related opioid data also vary. Data sources may include:

- Sales data
- Dispensing data
- Government-subsidised sales data (e.g., Pharmaceutical Benefits Scheme [PBS] and Repatriation Pharmaceutical Benefits Scheme [RPBS] data)
- Government-subsidised sales data that has been adjusted to reflect non-subsidised sales[v]

[iii] The DDD is the assumed average maintenance dose per day for a drug used for its main indication.[18]

[iv] Oral morphine equivalents are based on the notion that different doses of different opioids may give a similar analgesic effect. Where the doses of two different opioids are considered to give a comparable analgesic effect, they are deemed to be equi-analgesic doses. See Nielsen, Degenhardt, Hoban & Gisev (2014)[20] for a more detailed explanation.

[v] For example, pre-April 2012 Drug Utilisation Subcommittee (DUSC) data contained data on PBS/RPBS prescriptions submitted to the Department of Human Services (DHS) for payment of a subsidy plus an estimation of general under co-payment / private prescriptions based on dispensing data from a sample of pharmacies.

- Information provided yearly to the International Narcotics Control Board to estimate countries' opioid requirements.

Measuring the same phenomenon or trend within a given country using different data sources can lead to differing results. For example, Australian opioid sales data indicate that in 2013, 2.1 times more prescription opioids were actually sold than was indicated in PBS dispensing data. For methadone, the ratio of sales data to PBS dispensing data was 5.7:1.0. For prescription codeine this ratio was 3.2:1.0 and for over the counter (OTC) codeine, it was 1,579.5:1.0.[23]

As a result of these issues, caution is required in interpreting the data below relating to levels of, and trends in, opioid use.

2.2 Overseas trends in pharmaceutical opioid use

2.2.1 International patterns and trends

Worldwide, the DDD of opioids utilised per million inhabitants per day more than doubled between 2001-03 and 2011-13, from 1,417 to 3,565. Over this period, substantial increases occurred in:

- North America (16,046 to 31,453 DDD)
- Western and Central Europe (3,079 to 9,320 DDD)
- Oceania (2,275 to 9,136 DDD).[19]

This global increase in DDD of opioids used, fails to depict regional variations, as many other regions have shown no substantial increase in use. The absence of real growth in use in most of the world largely stems from inadequate provision of these essential medicines.[19, 24]

Opioid consumption rates vary substantially between developed countries (see Figure 2).

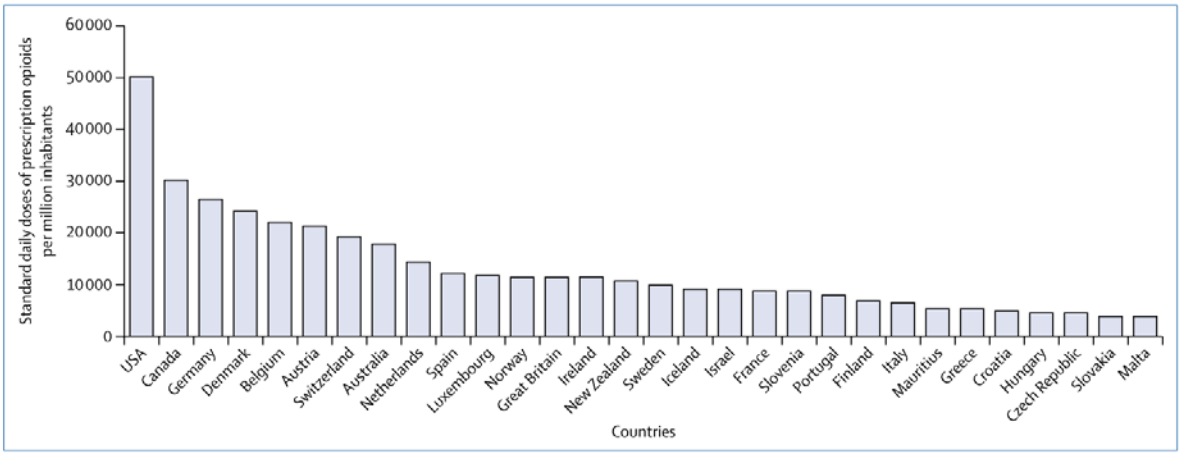


Figure 2: Top 30 opioid-consuming nations, 2012–14 using DDD/million inhabitants/day.
Source: United Nations International Narcotics Control Board, 2016 as cited in Humphreys (2017). This calculation includes buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, and other opioids.

Prescription opioid consumption rates in North America are more than double those of the European Union or the Australia/New Zealand regions and hundreds of times greater than those of China or India. The disproportionately high level of prescribed opioid use in North America has been explained by a multiplicity of drivers, including:

- A stronger cultural focus on pharmacotherapeutic interventions for pain
- A culture of high expectations on prescribers to meet patient demands
- Rewarding prescribers for volume of care, rather than quality of care
- Less rigorous regulatory frameworks for prescribing and drug promotion
- Aggressive pharmaceutical advertising in response to clinicians' legitimate concerns about poor pain management
- The commodification of health care and more pronounced 'for-profit' orientation of key elements of health care
- Greater reliance on community-based opioid dispensing approaches which facilitate greater availability and increase risk of diversion.[25-27]

Arguably, these factors have combined to contribute to patterns of medical care in which opioid pharmaceutical interventions are preferred over other interventions by prescribers and patients.[25, 26]

Given the high levels of opioid utilisation in North America, patterns of use and harms in the USA and Canada warrant particular attention.

2.2.2 The United States of America

The USA has experienced a dramatic increase in the use of prescribed opioids over the past three decades (see Figure 3).

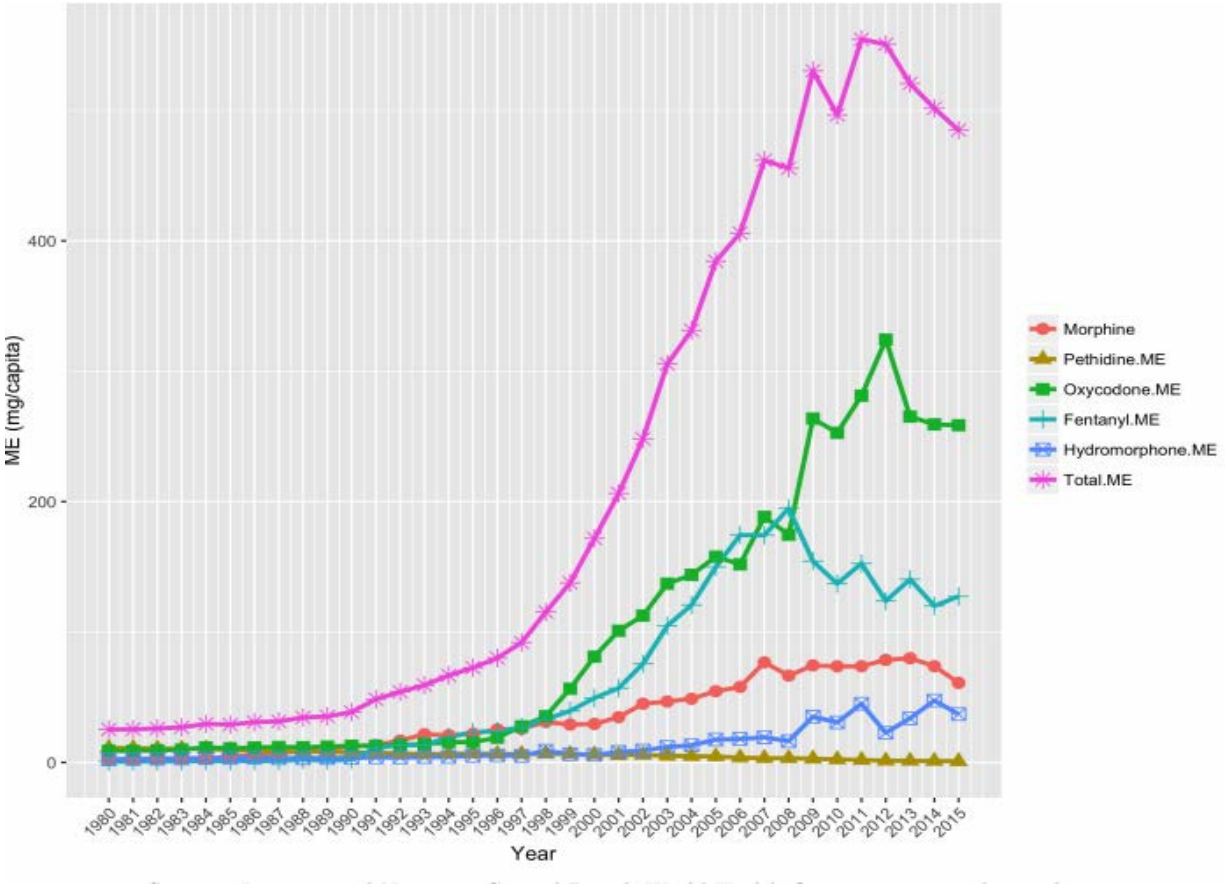


Figure 3. United States of America Opioid Consumption in Morphine Equivalence (ME) minus Methadone, mg per person / year 1980-2015. Source: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2017, Citing International Narcotics Control Board and World Health Organization population data.

In 2010, 11.8% of Americans received an opioid prescription. Between 2000 and 2010, each year was associated with a 6% increase in the likelihood of an individual receiving an opioid prescription. Despite the increase in use, there were no demonstrable improvements in the age- or sex-adjusted disability and health status measures of these opioid users.[28]

The per-capita level of opioids prescribed in the USA decreased by 13.1% between 2012 and 2015. Nevertheless, the level of opioid use in 2015 was more than three times that of 1999. Prescribing levels also varied substantially across the country with average per capita amounts prescribed in the top quartile of counties being approximately six times greater than those in the lowest quartile.[29]

County-level factors associated with high levels of opioid prescribing included having:

- A larger percentage of non-Hispanic whites
- A higher prevalence of diabetes and arthritis
- Less populous regions
- Higher unemployment levels
- Higher Medicaid enrolment.[29]

Two changes appear to be associated with recent decreases in opioid prescribing in the USA. First, the *average daily oMEDD per prescription* decreased. This followed publication of a range of opioid prescribing guidelines and accumulating research evidence demonstrating increased overdose risk at higher dosages. Second, the *rate* of opioid prescribing decreased, probably also reflecting growing awareness among clinicians and patients of opioid-related risks. Throughout this period, the average *duration* of opioid therapy increased. This was, at least in part, due to the continuation of opioid prescribing to existing patients and a substantial decrease in the total number of shorter prescriptions initiated after 2012. In other words, fewer patients were initiated into opioid therapy after 2012, while patients already prescribed opioids continued to receive them.[29]

In 2014:

- 4.3 million Americans engaged in non-medical use of prescription analgesics in the last month
- 1.9 million Americans met criteria for a substance use disorder, based on their use of prescription analgesics in the past year
- 1.4 million Americans used prescription analgesics non-medically for the first time in the past year[30]

In calendar year 2016, provisional data[vi] indicated that drug overdoses accounted for 64,070 deaths in the USA; a 21% increase over the preceding year. Approximately 83% of these deaths involved an opioid, signifying a continuing trend in opioid-related deaths observed since 1999.[31, 32] At the time of writing, drug overdose deaths were currently at their highest level ever recorded. In every year since 2009, drug overdose deaths have outnumbered deaths by firearms, motor vehicle crashes, suicide, and homicide.[33]

Age-adjusted opioid poisoning death rates increased by 15.6% from 2014 to 2015. This increase was driven by opioids other than methadone (most likely heroin and illicitly-manufactured fentanyl).[31] Fentanyl, in its licit form, is also diverted from legitimate markets for personal use or sale, although on a smaller scale compared to the use of illicitly manufactured fentanyl. Illicit fentanyl, predominantly manufactured in Mexico or China, is smuggled into the USA. It is usually mixed with heroin or pressed into counterfeit prescription pills. This adulteration often occurs without the consumers' awareness, increasing the risk of overdose incidents. The tripartite opioid threat of controlled prescription drugs, fentanyl, and heroin has risen to epidemic levels and is ranked by the US Drug Enforcement Authority as the most significant drug threat to the USA.[33]

Between the year 2000 and 2015, the specific drugs most commonly involved in prescription opioid overdose deaths in the USA (see Figure 4) were:

- Natural and semi-synthetic opioids (e.g., codeine, morphine, hydrocodone and oxycodone)
- Synthetic opioids (e.g., fentanyl)
- Methadone.[34]

[vi] Provisional counts may be incomplete and causes of death may be pending investigation. Detailed trend information is not available from provisional counts.

.

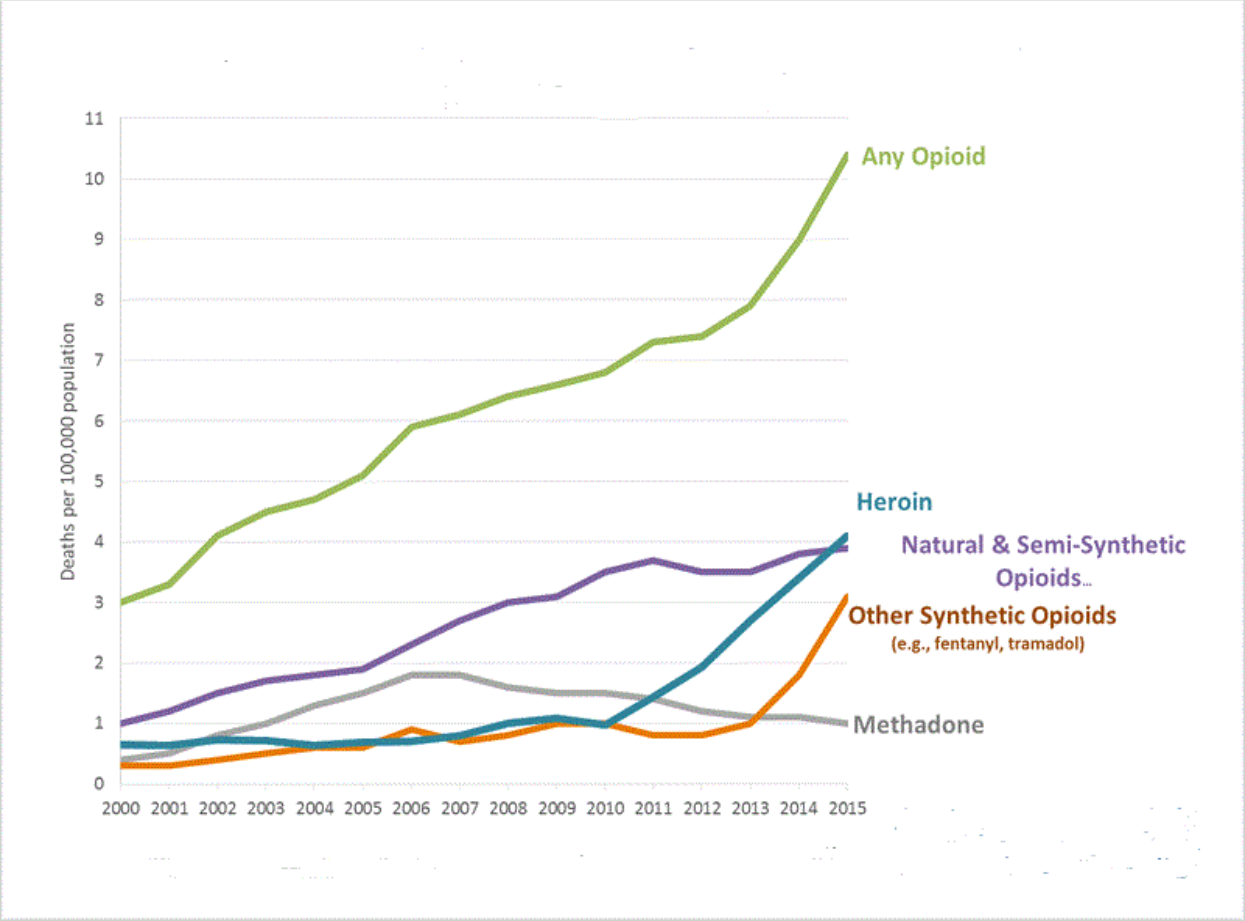


Figure 4: Overdose deaths involving opioids by drug type in the United States of America, 2000 to 2015.
Source: CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

Although men are still more likely to die from prescription opioid overdoses in the USA, the gap between men and women is closing. Deaths from prescription opioid overdose among women have risen more sharply than among men (see Figure 5). Between 1999 and 2010 there was a 400% increase in prescription opioid deaths among women compared to a 265% increase among men.[35]

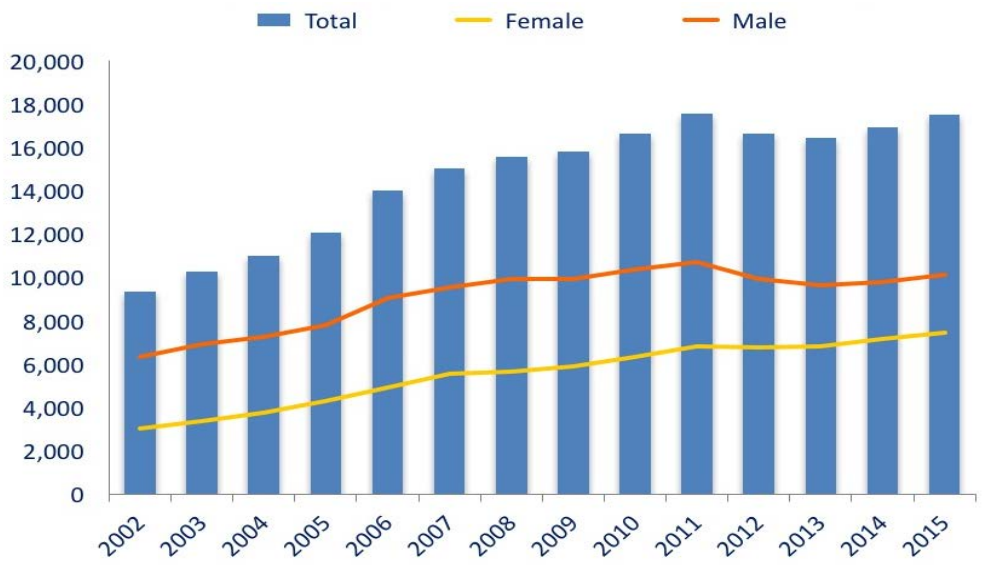


Figure 5: Number of deaths from prescription opioids (excluding non-methadone synthetics[vii]) in the United States of America 2002-2015 by gender.
Source: CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

In contrast to other demographic groups in the USA, and the population of other Organisation for Economic Co-operation and Development countries, white non-Hispanic Americans are currently experiencing greater increases in midlife (45-54 years) mortality. The change in all-cause mortality for this group is largely accounted for by increases in drug and alcohol poisonings and suicide. Prescription opioids are a particularly strong contributor to this trend.[36]

Between 2005 and 2014, the national rate of opioid-related inpatient stays increased by 64% and the national rate of opioid-related emergency department (ED) visits almost doubled[37] (see Figure 6). Prescribed opioids were major contributors to these increases. Across states, the rate of opioid-related inpatient stays in 2014 varied more than five-fold. The highest hospitalisation rates occurred in Maryland with the lowest rates in Iowa (403.8 vs 72.7 stays per 100,000 population, respectively). The rate of opioid-related emergency department (ED) visits in 2014 varied approximately 10-fold between states. The highest rates occurred in Massachusetts with 450.2 visits per 100,000 population and the lowest rates occurred in Iowa (45.1) (see Figure 6).[37]

[vii] Non-methadone synthetics is a category dominated by illicit fentanyl, and has been excluded to more accurately reflect deaths from prescription opioids.

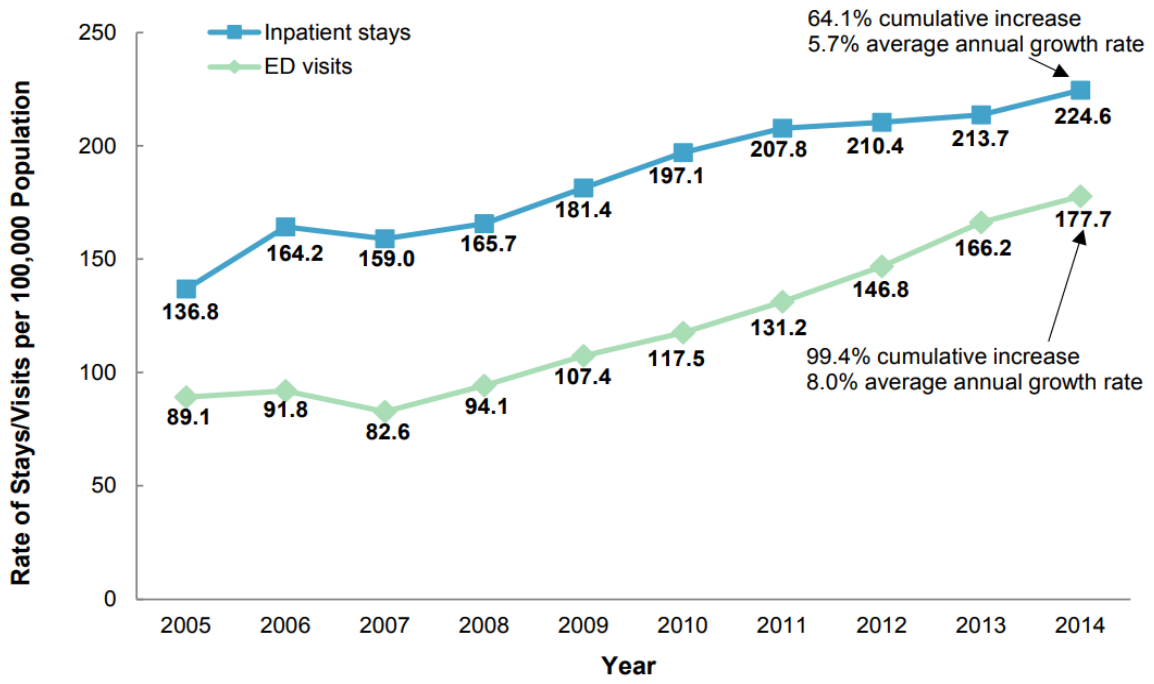


Figure 6: United States of America's rate of opioid-related inpatient stays and emergency department visits, 2005–2014.
Source: Weiss et al. (2017).

2.2.3 Canada

As with the USA, Canada has seen a dramatic increase in the use of pharmaceutical opioids over the past three decades (see Figure 7).

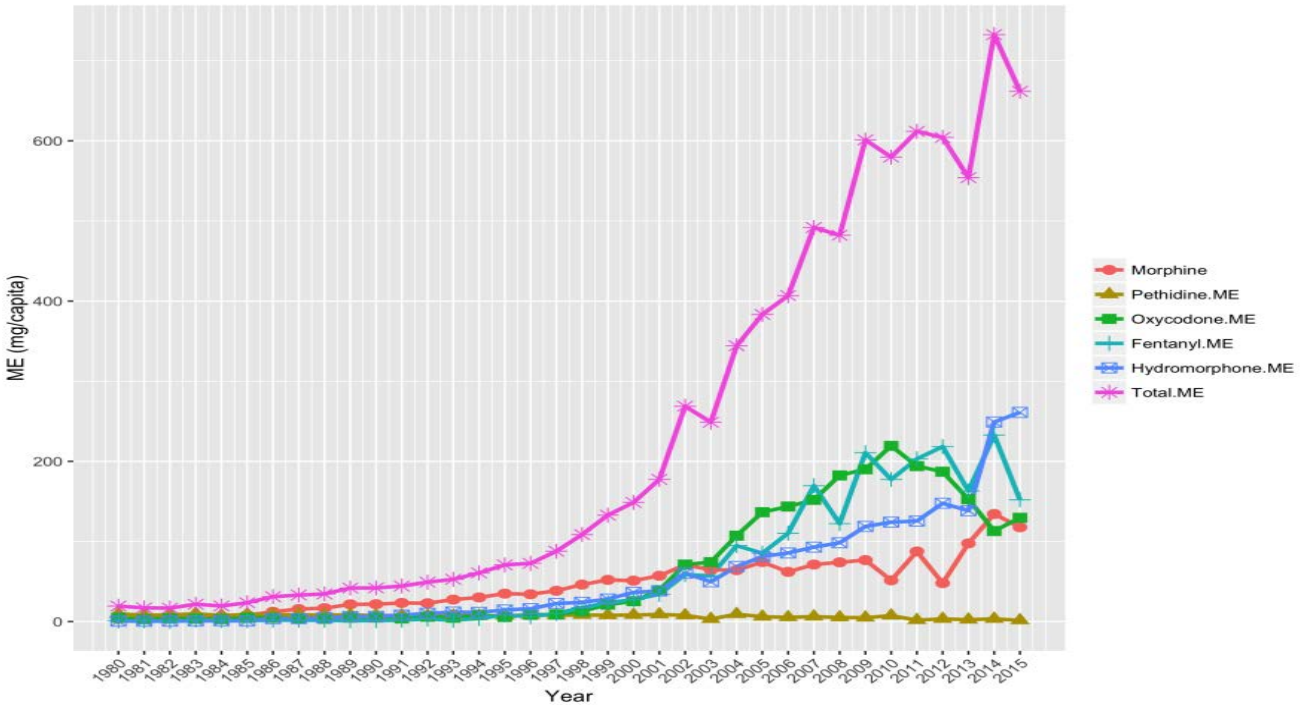


Figure 7: Opioid Consumption in Canada - morphine equivalence (excluding methadone), mg per capita 1980-2015.
Sources: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2017, Citing International Narcotics Control Board; World Health Organization population data.

There are substantial gaps in data related to understanding the extent, nature and trends in pharmaceutical opioid use and related harms in Canada. The information about pharmaceutical opioid-related harms is predominantly limited to Ontario-based indicator data**.** Data are largely absent for most other provinces.[26, 38]

There were 2,458 apparent opioid-related deaths in Canada in 2016[viii], although this figure may change as more up-to-date data become available. Based on this, the apparent opioid-related death rate in Canada in 2016 was 8.8 per 100,000 population. Western Canada experienced the highest rates, with apparent opioid-related death rates of over 10.0 per 100,000 population for Yukon, Northwest Territories, British Columbia and Alberta.[39]

[viii] It should be noted that these data do not include all Canadian provinces / territories and some of the data is extrapolated from 2015 sources.

2.3 Patterns and trends in pharmaceutical opioid use and harms in Australia

2.3.1 Patterns and trends in pharmaceutical opioid use

Over the past three decades, there has been a substantial increase in prescribed opioid dispensing in Australia.[6, 40, 41] From 1985-2000, methadone was the main contributor to increased opioid dispensing, whilst between 2000-2015 oxycodone[6] and fentanyl[41] contributed most to the increase. Between 1992 and 2012, opioid dispensing episodes increased 15-fold (500,000 to 7.5 million) and the corresponding cost to the Australian government increased 32-fold ($8.5 million to $271 million).[9]

Oxycodone has been the main contributor to the increase in Australian opioid utilisation in the last few years. This trend is likely due to inclusion of PNCP as an indication for the use of PBS-subsidised opioid analgesics.[9] The most concerning recent trend has been the increasing use of buprenorphine and fentanyl for treatment of pain. The cost to the PBS of buprenorphine and fentanyl combined now exceeds that of oxycodone.[9]

Consumption of prescribed opioids, expressed as oMEDD, increased exponentially between 1980 and 2015, the most recent data available (see Figure 8). Use of prescribed opioids peaked at approximately 500 oMEDD (mg/capita) in 2014.

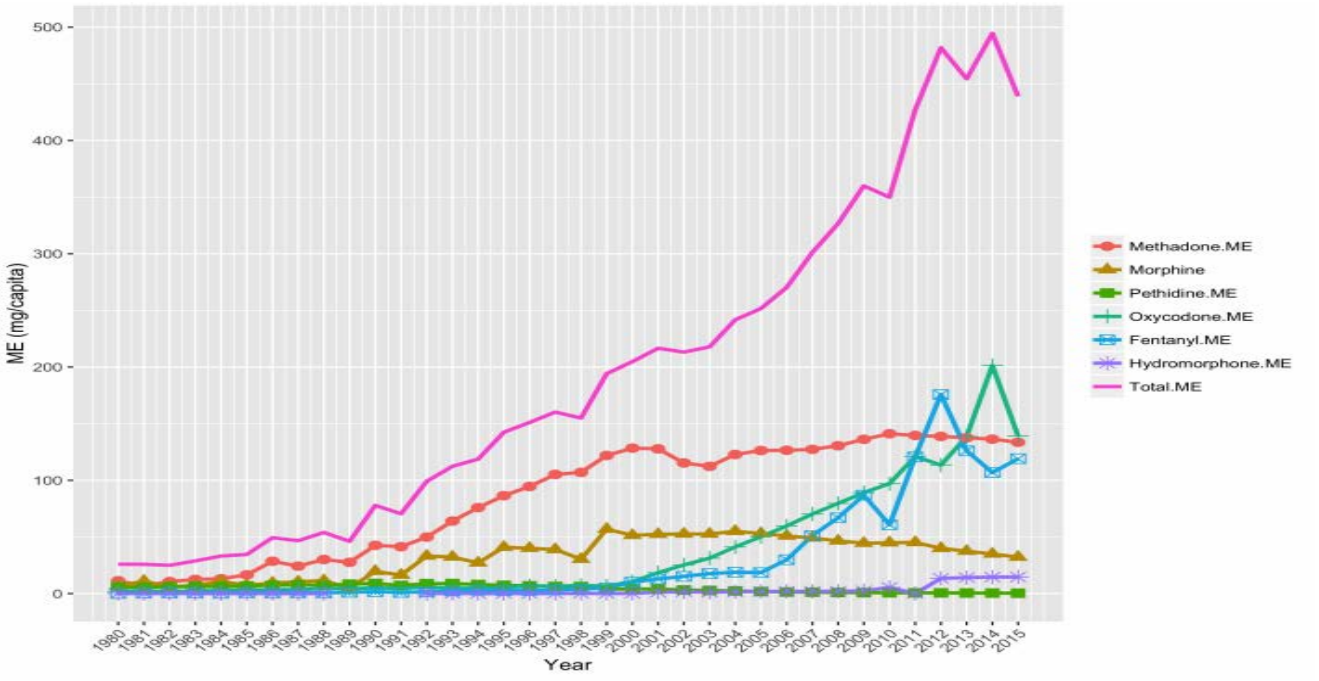


Figure 8: Opioid Consumption in Australia – oral morphine equivalence, mg per capita 1980-2015.
Source: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2017, Citing International Narcotics Control Board and World Health Organization population data.

In the Australian context, possible reasons for recent increases in opioid prescribing include:

- An ageing population
- Insufficient access to non-pharmacological treatments for PNCP
- Insufficient emphasis on pain management in medical education
- Longer cancer survival periods
- A growing group of elderly people with PNCP
- Changing community expectations of living with PNCP
- Undertreated mental health issues
- Aggressive promotion of these drugs by pharmaceutical companies.[42, 43]

Research conducted using Australian opioid sales data which included OTC codeine and prescription opioids (buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, tapentadol and tramadol) estimated usage for 2013 at 481 oMEDD mg per capita.[23]

There were approximately 15 million packs of opioids sold in Australia in 2013. Over the counter codeine was the opioid most commonly sold and was the most accessible opioid in the community pharmacy setting.[23] This is despite concerns about the effectiveness of codeine, particularly at lower doses, and variations in rates of codeine metabolism.[44-47]

The metabolism of codeine into morphine relies on cyctochrome p450 (CP450) enzymes. Genetic variations in CP450 result in some people experiencing very little opioid effect from codeine while others experience close to 1:1 conversion to morphine.[48] There is also strong evidence regarding adverse events associated with its use, particularly in combination with other medicines such as paracetamol and ibuprofen.[49-55]

In 2013, rates of oMEDD opioid utilisation varied widely across Australia.[23] These are outlined in Table 2.

Table 2: Rates of opioid utilisation in Australian jurisdictions by oMEDD per person in 2013.
Source: Degenhardt et al. (2016).[23]

Jurisdiction	**oMEDD mg per person per year**
Tasmania	641
South Australia	605
Queensland	552
New South Wales	479
Victoria	434
Western Australia	431
Australian Capital Territory	419
Northern Territory	272

In 2013, Australians used an average of 0.5 pack of stronger prescription opioids per person. While codeine use was very prevalent in Australia in that year, the majority of oMEDD consumption was derived from stronger opioids.[23]

An breakdown of the number of packs of opioids sold in 2013 (using sales data) appears in Table 3.

Table 3: Number of packs of opioid medicines sold in Australia in 2013.
Source: Degenhardt et al. (2016).

	Packs sold	
	Number	**% of pack sold**
Strong prescription opioids	*10,096,112*	*23.8*
Buprenorphine	*1,881,695*	*4.4*
Fentanyl	*859,518*	*2.0*
Hydromorphone	*224,840*	*0.5*
Morphine	*775,568*	*1.8*
Methadone	*541,701*	*1.3*
Oxycodone	*5,812,790*	*13.7*
Other prescription opioids	*16,762,307*	*39.6*
Codeine	*12,290,027*	*29.0*
Dextropropoxyphene	*464,247*	*1.1*
Tapentadol	*5,074*	*0.1*
Tramadol	*4,002,959*	*9.5*
Total prescription opioids	**26,858,419**	**63.4**
Over the counter codeine	**15,490,207**	**36.6**
TOTAL OPIOIDS	**42,348,626**	**100**

There are major geographic and demographic differences in patterns of pharmaceutical opioid utilisation in Australia. Areas outside of major cities have higher utilisation rates for all types of opioids (see Figure 9). This map shows sub-jurisdictional variation in utilisation at the unit of Statistical Local Areas (SLAs). As can be seen, there is also considerable variation in utilisation within jurisdictions.

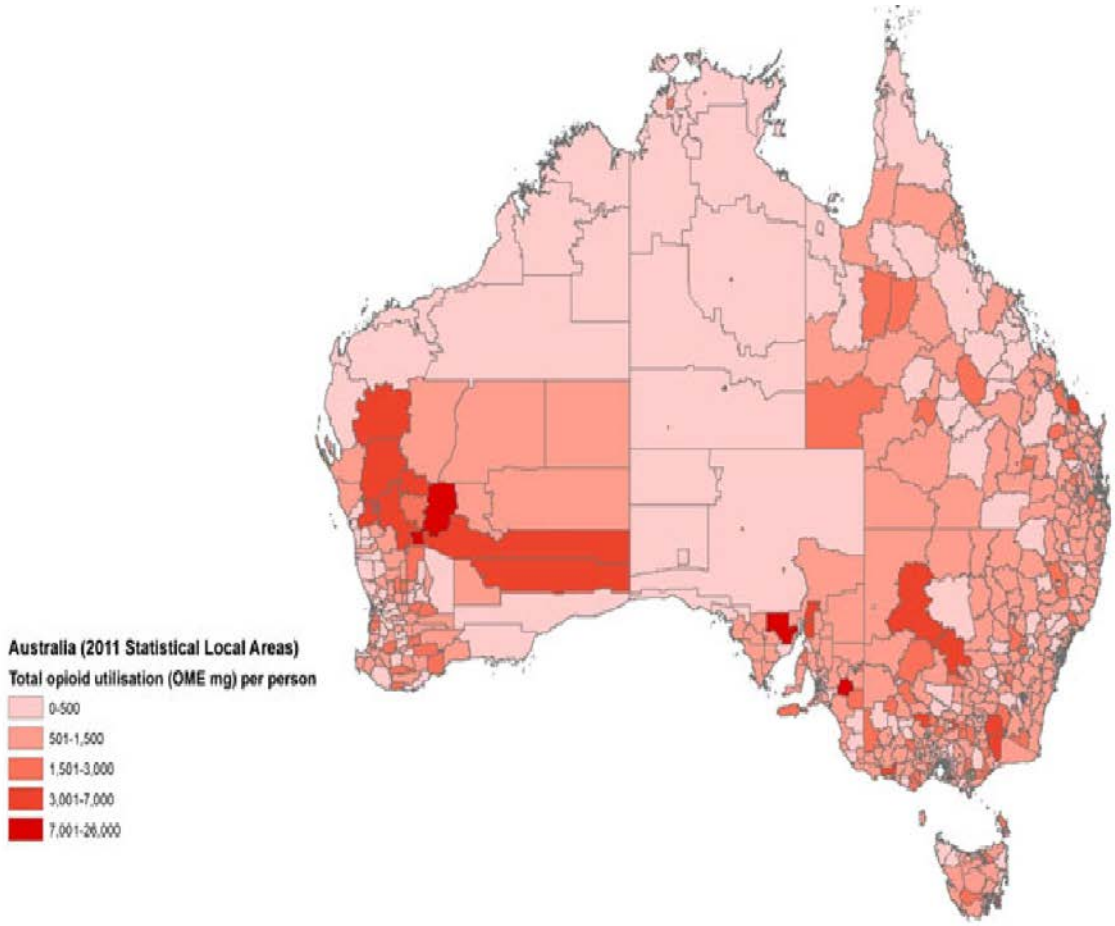


Figure 9. Total opioid utilisation per person (oMEDD mg/person) in 2013 by Statistical Local Area.
Source: Degenhardt et al. (2016).

In addition, areas with indicators suggestive of greater disadvantage (e.g., more physical labourers and higher unemployment rates) had higher rates of opioid utilisation. The rates of utilisation were also higher in regions with:

- A greater proportion of males
- A greater proportion of people over 65 years
- More low-income households
- Lower population density.

A 2010-11 Australian general practitioner (GP) survey found that opioids were prescribed in 4.9% of consultations. Opioids accounted for 5.8% of all medications prescribed or supplied by GPs. Among opioid prescriptions, 43.9% were for PNCP, 3.5% for malignant neoplasm, and the remainder for acute conditions, musculoskeletal and back problems predominantly.[56]

As noted, PNCP is a key reason for opioid prescription. A 2012-13 study of 1,424 Australians prescribed opioids for PNCP found that the oMEDD of opioid consumption varied widely. Over half of opioid prescriptions to PNCP patients had

an oMEDD of 21-90mg/day (Table 4). Approximately one in seven patients with PNCP were prescribed opioids of 200 oMEDD mg/day or higher.[57] These dosage levels are inconsistent with contemporary approaches to the use of opioids in PNCP which indicate that dosages should not exceed 40 oMEDD mg/day.[58]

Table 4: Dosage of opioids prescribed in Australia for persistent non-cancer pain 2012-13.
Source: Campbell et al. (2015).[57]

Opioid morphine equivalence mg/day	Proportion of opioid prescriptions
≤20	8.8
21-90	52.1
91-199	24.3
≥ 200	14.8

Consumption of higher levels of daily oMEDD by patients with PNCP was associated with higher odds of:

- Multiple physical and mental health issues
- Aberrant opioid use
- Problems associated with opioid medication
- Opioid dependence.[57]

A substantial minority of this group of PNCP patients met the criteria for lifetime, or past year ICD-10 pharmaceutical opioid dependence (8.55 and 4.7% respectively). Past year dependence was independently associated with being younger, exhibiting more aberrant behaviours and having a history of benzodiazepine dependence.[57]

There are also complex inter-relationships between social disadvantage and the use of opioids to manage PNCP. Among Australian patients receiving long-term opioid therapy for PNCP:

- Most had low income levels
- Two-thirds reported that their pain had impacted on their employment status
- Half were moderately-to-severely depressed
- 1 in 5 had made a lifetime suicide attempt
- Over half the sample reported a history of childhood abuse and/or neglect, most commonly emotional abuse
- Younger patients experienced higher levels of pain and pain interference, more mental health and substance use issues, and barriers to treatment, compared with older patients
- Over 30% of the sample had a lifetime alcohol use disorder, and just over 10% had a cannabis use disorder.[59]

2.3.2 Pharmaceutical opioid-related harms

2.3.2.1 Deaths

An examination of Australian National Coronial Information System[ix] data indicated that between 2001-2012 deaths caused by pharmaceutical opioid overdose increased from 21.9 to 36.2 per million population per year, an average increase of 6% annually. In 2012, pharmaceutical opioid overdose deaths occurred at 2.5 times the rate of heroin overdose deaths (see Figure 10).

Increases in pharmaceutical opioid deaths were largely a result of accidental overdoses. They were more likely to occur among males than females and were highest among Australians aged 45–54 years. Rates of fentanyl deaths in particular showed an increase over this period.[60]

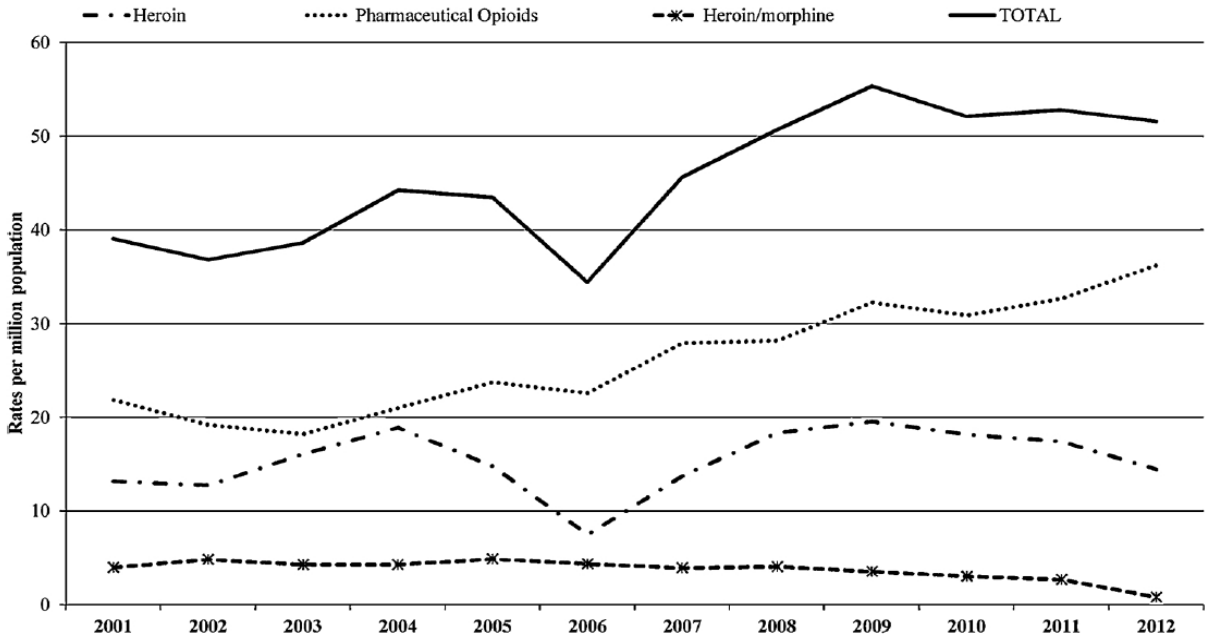


Figure 10: Rates per million population 15–74 years of heroin, pharmaceutical opioid and heroin/morphine[x] overdose deaths, 2001–2012.
Source: Roxburgh et al. (2017).

Death rates from fentanyl, oxycodone, and methadone all increased significantly between 2001 and 2012, by approximately 40%, 16% and 3% yearly respectively.[60]

[ix] This approach is likely to underestimate opioid-related deaths because opioid overdose may not be recognised as a cause of or major contributor to death.

[x] The heroin/morphine category refers to deaths where there was not enough information to determine whether the death was due to heroin or morphine.

A comparison of pharmaceutical opioid deaths by opioid type and according to levels of utilisation (i.e., rates of deaths per 100,000 oMEDD grams utilised) demonstrated that only fentanyl deaths increased disproportionately between 2001 and 2012. That is, fentanyl deaths continued to increase after taking into account the amount and relative potency of each opioid dispensed in the community. In contrast, oxycodone and morphine[xi] deaths per 100,000 oMEDD grams utilised showed no change over time (see Figure 11).

This suggests that while rates of oxycodone deaths have followed trends in increased prescribing, the increase in rates of fentanyl deaths appears to exceed the increased levels of prescribing. This may be indicative of extra-medical use.[60]

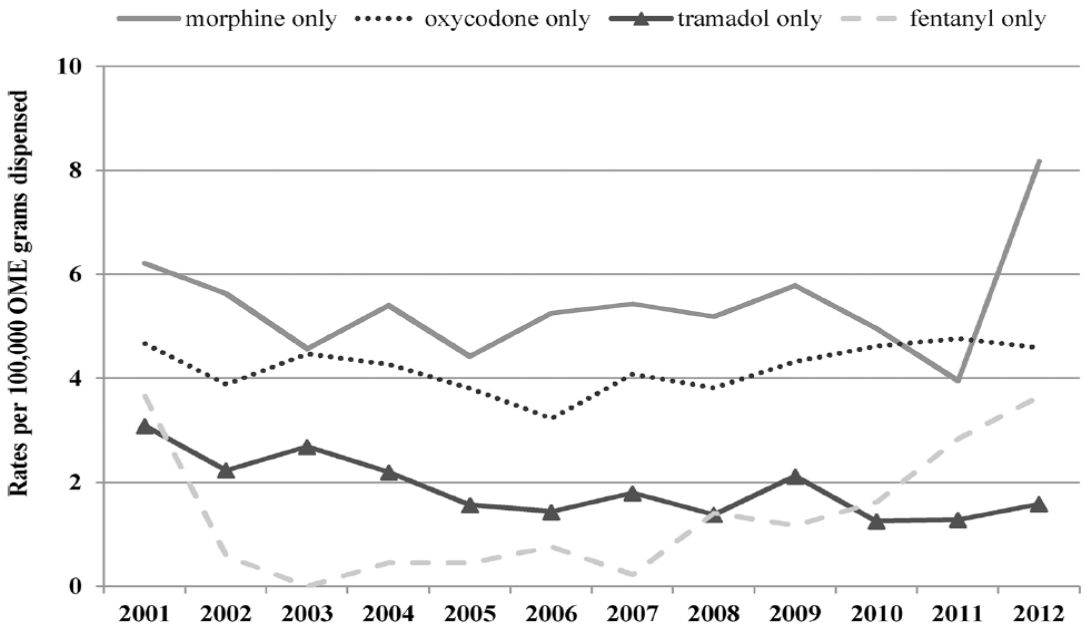


Figure 11: Death rate per 100,000 oMEDD grams utilised by opioid type 2001–2012, Australia.
Source: Roxburgh et al. (2017).

Aboriginal and Torres Strait Islander people in Australia are substantially over-represented in pharmaceutical opioid-related deaths, as they are in deaths associated with the use of a range of other substances.[61]

The per capita death rate associated with pharmaceutical opioid use during 2011-2015 varied substantially across Australian jurisdictions. This ranged from 1.6 deaths per 100,000 persons in the Northern Territory to 4.0 deaths per 100,000 persons in Western Australia[62] (see Figure 12).

The difference in per capita death rates between jurisdictions was at variance with their relative levels of pharmaceutical opioid utilisation. For example, in 2013

[xi] This statement applies to morphine-related deaths up until 2011. However, in 2012, the rate of morphine deaths per 100,000 grams oMEDD dispensed jumped substantially to be well above the death rates per 100,000 grams oMEDD of oxycodone, fentanyl and tramadol dispensed. There appears to be no obvious explanation for this sudden increase in morphine-related deaths and it is a trend that requires close monitoring.

Tasmania had an opioid utilisation rate of (641 oMEDD mg/person/year)[23] and between 2011 and 2015 there were (a total of) 1.7 deaths per 100,000 population in that jurisdiction.[62] In 2013, Western Australia had an opioid utilisation rate of (431 oMEDD mg/per person/year)[23], yet between 2011 and 2015 there were (a total of) 4 deaths per 100,000 population.[61]

A possible explanation for this is that while much of Western Australia has low levels of pharmaceutical opioid use, it also has several regions with very high levels of use (see Figure 9). It is possible that many of the Western Australian deaths occurred in the relatively few regions with very high levels of opioid consumption.

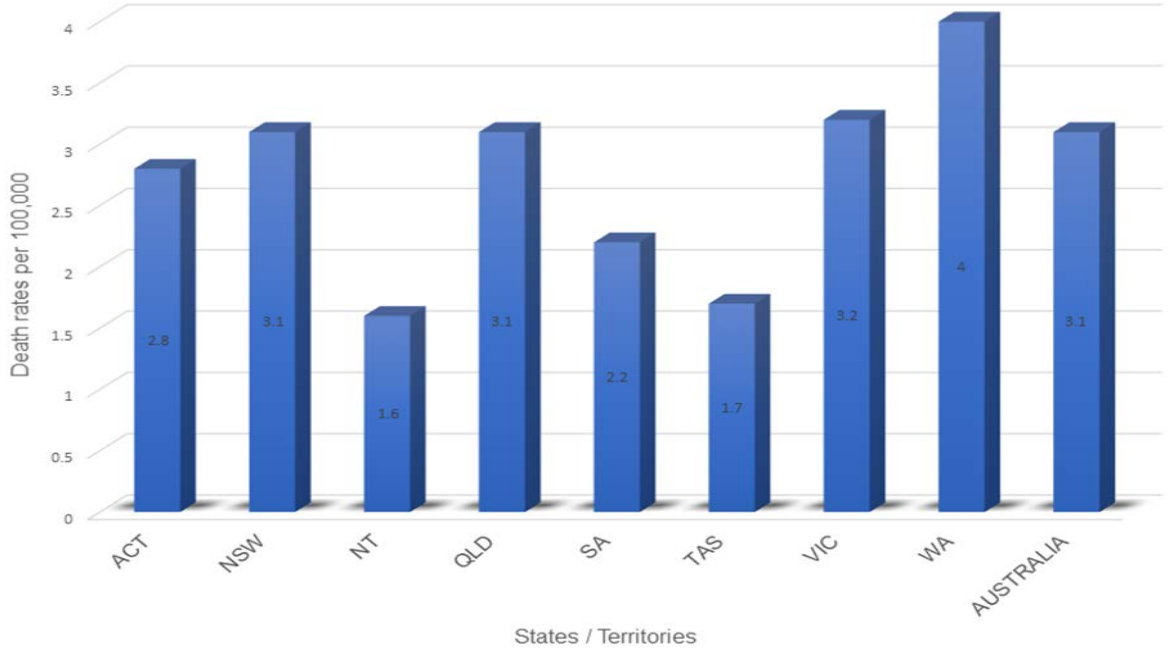


Figure 12: Per capita rates of accidental deaths due to pharmaceutical opioids Australia 2011-15.
Source: Pennington Report (2017).[61]

3 Adverse effects of longer-term opioid use

A number of adverse effects of longer-term opioid use have been identified. The most common are discussed below.

3.1 Respiratory system and sleep disturbances

Respiration is predominantly controlled via medullary respiratory centres with peripheral input from chemoreceptors and other sources. Opioids inhibit chemoreceptors in the medulla. Respiratory depression, especially in the presence of pre-existing sleep apnoea, is a key adverse effect of opioid use.[63, 64] A number of characteristics are associated with serious respiratory depression among people using prescribed opioids. These include:

- Being diagnosed with a substance use disorder
- Having mental health disorders
- Having obstructive sleep apnoea
- Impaired liver, renal, cardiovascular and pulmonary function
- Cardiac dysrhythmia, hypertension or coronary artery disease or diabetes
- Being prescribed fentanyl, methadone or morphine
- Higher daily opioid doses
- Concurrent use of other psychoactive medications particularly benzodiazepines and other anxiolytics, hypnotics and sedatives, antipsychotics, anti-epileptics, antihistamines and anaesthetics.[65-67]

Sleep disturbances (such as sleep apnoea) can have a significant impact on general health and wellbeing, and an estimated 20-35% of Australian adults are affected.[68] Prevalence increases to 50% for patients with PNCP.[69, 70] The prevalence of sleep-disordered breathing among long-term opioid users is higher at 70% (range 42%–85%).[71]

Sophisticated sleep monitoring suggests an opioid dose-response relationship between respiratory depression and sleep disorders, particularly among normal weight individuals.[15, 70, 71] Rates of respiratory depression vary between opioid medications,[72] with fentanyl, methadone and morphine leading to greater depression.[65, 66]

The International Classification of Sleep Disorders recognises five distinct types of sleep apnoea, including central sleep apnoea (CSA) which is due to drug or substance use.[73] A systematic review of eight studies involving 560 patients found that 24% of patients taking long-term opioids were affected by CSA.[71]

A recent systematic review of seven observational studies of patients with obstructive sleep apnoea, also found that longer-term opioid use worsened CSA; but the review acknowledged the potential for confounding factors.[74]

The available evidence highlights that opioid-related respiratory depression and sleep disturbances are frequent adverse effects of longer-term opioid therapy. However, this has not yet been widely studied.[75]

3.2 Gastrointestinal system

3.2.1.1 Constipation

Constipation is one of the most common adverse effects of opioid use, with approximately half of all patients likely to be affected.[70, 72, 76-82] Opioid-related constipation has substantial implications for patient quality of life and health service utilisation.[15] Constipation in frail elderly patients is a major problem in long-term therapy for PNCP pain, often lasting beyond the initial titration period and requiring use of laxatives.[83] Mu-opioid receptor activation in the gastrointestinal tract leads to constipation, and antagonists targeting this receptor form the basis of new pharmacological treatments aimed at alleviating this side effect of opioid therapy.[84] However, reviews of trial data for these new drugs indicate that despite some alleviation of constipation, they are associated with increased abdominal pain, nausea and diarrhoea, flatulence, vomiting and headaches.[84, 85]

3.2.1.2 Nausea and vomiting

Nausea and vomiting are also commonly associated with the gastrointestinal effects of mu-receptor agonists, albeit less so than constipation.[15, 72, 76, 78, 79, 81, 86] This affects approximately 25% of patients however, slow titration of opioid medication can help avoid this adverse effect.[15, 87]

3.3 Cardiovascular system

Interactions between opioid use and cardiovascular outcomes have been studied, but the evidence is generally of poor quality and inconclusive. However, a high-quality systematic review based on outcomes from more than 300,000 patients, concluded that there was consistent, albeit low level, evidence that current opioid therapy versus non-use was associated with a dose-related moderate increase in odds for myocardial infarction.[88]

Observational studies have previously implicated opioid use with cardiovascular events.[15] However, a review of recent literature[89] argued that few studies suggest chronic opioid administration is associated with increased risk of cardiac-related adverse effects. The authors reported that while most opioids have little direct negative effect on cardiac contractility, their use can nonetheless decrease cardiac function when administered in combination with other medications, including benzodiazepines. Opioids can also lead to bradycardia and vasodilation and, as a result, can occasionally lead to oedema, hypotension, orthostatic hypotension, and syncope when used at analgesic doses. While most opioids have no effect on cardiac conductivity, methadone and buprenorphine can prolong QTc[xii], especially when used in patients at increased risk of this.[89]

[xii] In electrocardiography, this refers to the duration of the QT interval adjusted for the patient's heart rate. Prolonged QTcs are associated with an increased risk of ventricular dysrhythmia and sudden death.

Among frail elderly people, possible associations between opioids and hypotension, and between methadone and prolongation of the QTc interval, suggest the need for caution when prescribing opioids.[90]

From a clinical perspective, the lack of evidence concerning the impact of opioids on cardiovascular function is a major research gap. More robust studies are required to address the potential relationship between opioid use and cardiovascular problems. This is particularly the case among patients with multiple morbidities and those at elevated risk for cardiovascular events.[91]

3.4 Endocrine system

The established strong impact of opioids on male and female physiological hormonal activity are referred to as opioid endocrinopathies.[15, 70] Reduced levels of gonadotropin-releasing hormone with subsequent reductions in testosterone, estrogen and adrenal androgens occur with opioid use and normal hormonal feedback is disrupted. This occurs irrespective of opioid route of administration.[70, 92]

Symptoms include infertility, hypogonadism, decreased sexual function, loss of muscle mass and anxiety and/or depression. Osteoporosis may result from long-term opioid therapy, leading to fractures and their associated morbidity, and human and financial costs.[93]

Typical opioid endocrinopathy presentations in men include decreased libido, erectile dysfunction, depression and lethargy; and in women: dysmenorrhea, sexual dysfunction, depression and decreased bone mineral density.[70]

A high-quality systematic review of sexual dysfunction among male recipients of methadone or buprenorphine maintenance treatment found a 52% prevalence of sexual dysfunction. Clinical factors associated with sexual dysfunction included:

- Older age
- Hormone assay results
- Longer duration of treatment
- Methadone dose
- Psychiatric illness
- Other current substance use
- Familial status
- Methadone versus buprenorphine treatment (dysfunction was more frequent with methadone).[94, 95]

A study of more than 11,000 men found a relationship between opioid use and increased use of medications for erectile dysfunction or testosterone replacement. Patients prescribed daily opioid doses of ≥120 oMEDD, had greater use of medication for erectile dysfunction or testosterone replacement than patients without opioid use, regardless of duration of opioid therapy.[96] The true incidence of opioid-induced androgen deficiency is likely to be very high but under-reported, as there are no evidence-based guidelines for diagnosis.[92]

Prescribers should therefore inform patients about the potential long-term effects of opioids on the endocrine system before therapy is commenced and regular monitoring should be performed. The benefits of opioid therapy should be carefully assessed against the risk of opioid endocrinopathies. If therapeutic goals have not been achieved, opioids should be tapered and withdrawn. If it is necessary to continue opioids, hormone replacement therapy should be initiated and monitored by an endocrinologist.[92]

3.5 Fractures

There is an increased risk of bone fracture in patients using opioids.[93, 97] There are many risk factors for decreased bone mineral density and osteoporosis in patients treated with opioids, including possible poor nutritional status, hypogonadism, inhibition of osteoblasts, decreased osteocalcin synthesis, abnormal calcium and parathyroid hormone and increased bone resorption, mediated by interleukin.[93] Sedation and dizziness might also increase the likelihood of falls.

A high-quality systematic review of eight cohort studies with more than 800,000 participants found that opioid use was associated with an 88% increase in all fracture risk. The risk of hip fractures increased two-fold.[97]

3.6 Central nervous system

3.6.1 Opioid-associated cognitive effects

Opioid-related changes in cognitive function can range from mild to major and represent a challenge in terms of balancing patient needs with treatment risks.[70]

Use of methadone to treat people with drug dependence issues is common practice; but recent studies suggest that high-dose treatment may impact cognitive function. In a systematic review of cognitive function among patients receiving methadone maintenance treatment for drug dependence[98], 85% of the studies found associated cognitive function impairment. Although this was a consistent finding, the overall quality of evidence was low.

The impact of opioid use, if any, on cognition related to driving performance also remains uncertain. One good-quality controlled study (5,300 patients)[99], identified an increased odds of road trauma with oMEDD daily doses above 20mg per day. This level of use was associated with a 21% to 42% increased odds of road trauma.

A recent high-quality systematic review of 27 case control and cohort studies covering 53 specific medications[100] found evidence in support of a significant interaction between motor vehicle collisions and use of 15 specific medications, including buprenorphine, codeine, dihydrocodeine, methadone, and tramadol.

However, a slightly earlier literature review[101] found the evidence to be too limited to draw precise conclusions regarding opioid maintenance therapy and driving ability. The reviewers found a range of studies demonstrating that low doses of both

methadone and buprenorphine may cause driving impairments among opioid-naïve subjects. The authors also found that some opioid maintenance therapy patients experienced improvements in cognitive and psychomotor functioning, when compared to control groups or baseline. They reported that this improvement could be the result of a less harmful lifestyle, a reduction in the use of other (illicit) drugs, or the stabilisation and benefits associated with maintenance therapy. Overall, they determined that the scientific literature did not allow any clear-cut conclusions to be drawn as to whether opioid maintenance therapy patients, or certain subgroups of patients, should or should not be allowed to drive. They recommended an individual evaluation of the driving performance among opioid maintained patients as the most informative procedure in approaching the question of ability to drive.

3.6.2 Opioid-associated delirium

Delirium is a syndrome characterised by depression of the highest mental functions. Symptoms occur acutely, fluctuate (often worsening at night) and in most cases resolve without sequelae.[102, 103] Although multifactorial in aetiology, opioid use has been implicated in delirium.[70, 102, 103] A moderate-quality systematic review of six studies investigating eight different opioid medications identified a potentially increased risk for perioperative delirium in elderly patients using pethidine compared to placebo.[102] [xiii] The reviewers also found that tramadol may increase risk of delirium.

3.7 Hyperalgesia

Opioid-induced hyperalgesia (OIH) is a state of nociceptive sensitisation caused by exposure to opioids. The condition is characterised by a paradoxical response in which patients receiving opioids for pain treatment can become more sensitive to certain painful stimuli. The increased pain sensitivity experienced can be the same as, or differ from, the underlying pain. Opioid-induced hyperalgesia appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients.[15, 43, 104, 105]

Opioid tolerance and opioid sensitisation are similar concepts to opioid-induced hyperalgesia. However, tolerance occurs when there is a progressive lack of response to a drug, thus requiring increased dosing. Opioid-induced hyperalgesia cannot be overcome by increasing the opioid dosage as this is likely to increase pain sensitisation. Conversely, pain may be improved by reducing or eliminating opioids.[104]

3.8 Depression

The links between the use of opioids and mental health problems such as depression have been well-established.[106] Since opioids are prescribed for pain, it can be difficult to disentangle the complex relationship between opioid use, pain and depression.[107] That is, it is difficult to determine whether depression is a *cause* or a *consequence* of opioid use (or the conditions for which opioids were prescribed). In support of the former hypothesis (depression is a *cause* of opioid use), patients with

[xiii] Pethidine is rarely used in Australia.

depression and / or anxiety are more frequently prescribed opioids and are more likely to use them on a long-term basis.[108-111]

More recent evidence[106, 107, 112-114] suggests that opioid use may also be a causal factor in the *development* of depression. There is a range of plausible neurobiological evidence that supports this link.[107]

The finding that opioids can contribute to depression has led to calls for the potential for opioid depressogenic effects to be considered in risk-benefit analyses regarding their use, and for patients initiating opioid treatment to be monitored for the development of depression.[106]

3.9 Immune system

Opioid drugs decrease the effectiveness of both natural and acquired immunity. They interfere with intracellular pathways involved in immune regulation, both directly and indirectly via the activation of central receptors. Opioids such as morphine and fentanyl impair the function of macrophages, natural killer cells and T-cells and weaken the gut barrier. In epidemiological studies, high doses and the initiation of opioid therapy have been correlated with a higher risk of infectious diseases such as pneumonia, sepsis, meningitis/encephalitis, cellulitis, endocarditis, pyelonephritis and infective arthritis/osteomyelitis.[115]

The impact of opioid use on the immune system is receiving increased research attention because of concerns that opioid-induced immune system changes may affect the outcome of surgery or a variety of disease processes, including bacterial and viral infections and cancer. These opioid-mediated immune effects could be particularly dangerous in vulnerable populations, such as the elderly or immunocompromised patients.

In addition, not all opioids induce the same immunosuppressive effects.[116] Among commonly used opioids, several suppress the immune system (e.g., morphine, codeine and fentanyl), while others appear not to appear to do so (e.g., hydrocodone and oxycodone).[117, 118]

4 The role of opioids in the treatment of persistent non-cancer pain

Persistent non-cancer pain refers to pain that has persisted beyond normal tissue healing time. It can be continuous or interrupted by pain-free intervals. In the absence of other criteria, PNCP pain is usually understood as pain that has persisted for three months or more.

4.1 History

The role of opioids in treating acute and malignant pain and opioid dependence is well established and relatively uncontroversial. There were substantial advances in the use of opioids for these purposes in the 1980s and 1990s. These successes led many clinicians to believe that opioids could be equally effective in the treatment of PNCP.

The history of the use of opioids for PNCP in the US provides a valuable insight into factors that influenced opioid prescribing practices in Australia.

Dr Russel Portenoy, a US-based pain specialist was a key proponent of the use of opioids for PNCP. Dr Portenoy authored an influential paper in 1986[119], based on the treatment of only 38 PNCP patients. The paper concluded that opioid therapy could be a safe, salutary and a more humane alternative to the options of surgery, or no treatment, in those patients with PNCP and no history of substance use problems.

At the same time, in the US and elsewhere, there was increasing recognition that pain was being widely under-treated. Other research at that time also suggested that addiction to prescribed opioids was rare.[120, 121]

In the early 1990s, the American Pain Society determined that pain should be classified as the 5th vital sign. That is, along with pulse, temperature, respiration and blood pressure, pain levels should be measured for all patients. The difficulty with this approach was that the other vital signs are objective, numerical and clinical measures. The experience of pain, on the other hand, is highly subjective and influenced by a range of factors. In order to objectify the experience of pain, a number of scales were developed, such as those with a numerical value (pain score out of 10) or faces pain scale.[122] In early 2000, the Joint Commission on Accreditation of Healthcare Organizations mandated that hospitals in the US assess each patient for pain.[123]

In 1998, the US Federation of State Medical Boards made a clear statement that physicians would not receive excessive regulatory scrutiny if prescribing large doses of opioids for the treatment of pain, a concern that had previously reduced the willingness of doctors to prescribe opioids for PNCP.[124] Further, some groups called for the under-treatment of pain to be punishable by Medical Boards.[125] In 2001, the

Drug Enforcement Agency (DEA) also agreed to adopt a more liberal approach to examining opioid prescribing practices.[123]

All these factors had the effect of encouraging use of opioids to relieve pain and reduce regulatory oversight of practitioners with high rates of opioid prescribing.[123]

In clinical practice, having pain as the 5th vital sign proved to be more complex to assess, evaluate, and manage than originally anticipated. As a result of ascribing pain as a vital sign, prescribers became obliged to treat patients with subjectively high scores on pain scales. Many doctors feared professional sanctions if they did not treat pain adequately. The increased obligations on doctors to treat pain, coupled with inadequate medical training regarding pain management, led many to take the least complex approach to patients in pain, namely to prescribe opioids.[122, 125, 126]

Clinical experience and multiple studies have also found that the use of pain severity ratings is a poor basis for selection of patients for opioid prescription. Pain ratings are well-known to be influenced by multiple psychological and contextual factors.[111] Patients with mental health and substance abuse problems are more likely to be prescribed chronic opioid therapy ("adverse selection") and at higher doses than people without those risk factors.[127]

Once established, dependence on opioids makes it hard to wean and cease them, despite lack of analgesic benefit. Later studies demonstrated that routinely measuring pain as the 5th vital sign did not increase the quality of pain management. Rather, under this approach, patients with substantial pain often had inadequate pain management.[128]

In the late 1990s and early 2000s, manufacturers of opioids such as oxycodone were also engaging in aggressive marketing campaigns promoting the use of these medicines for PNCP. The main impetus for this was that the market for these products was very much larger for PNCP patients compared with malignant pain patients. A central message of the marketing campaigns was that the use of prescribed opioids carried very little risk of iatrogenic dependence.[129]

Misrepresenting this risk subsequently proved costly for Purdue Pharma, the manufacturer of OxyContin. In 2007, an affiliate company of Purdue Pharma, along with three company executives, pleaded guilty to criminal charges of misbranding OxyContin by claiming that it was less addictive and less subject to abuse and diversion than other opioids, and paid $US634 million in fines.[129]

By the early 2000s, concern was being expressed in relation to opioid prescribing and related harms. Across the US from 1997 to 2002, there was a 226%, 73%, and 402% increase in fentanyl, morphine, and oxycodone prescribing, respectively (in terms of grams per 100,000 population). During that same period, emergency department mentions for fentanyl, morphine, and oxycodone increased 641%, 113%, and 346%, respectively.[130]

Among Americans who initiated illicit drug use in 2005, more reported that prescription opioids were the first drug they tried. This exceeded the number of new

initiates to cannabis.[131] By 2002, unintentional overdose deaths from prescription opioids surpassed those from heroin and cocaine nationwide.[132]

In 2010, prescription opioid analgesics were responsible for more deaths than both suicide and motor vehicle accidents or deaths from cocaine and heroin use combined. Among prescribed opioid-related deaths in 2010 in the US:

- The majority (60%) occurred in patients receiving prescriptions based on medical board prescribing guidelines
- 20% were prescribed 100mg of morphine equivalent dose or less per day
- 40% occurred in individuals with substance use disorders who obtained opioids through multiple prescriptions, doctor shopping, and drug diversion.[133]

4.2 Contemporary approaches to the management of persistent non-cancer pain and the role of opioids

While a 'cure' for PNCP may not be possible, it is generally feasible to reduce pain and achieve and maintain an acceptable level of function in personal, social and occupational life, if patients adopt active self-management measures. It is critical to adopt multidisciplinary and multidimensional approaches to PNCP that do not pivot on pharmacotherapy. If drug therapy is required, non-opioid therapies are preferred.

Treating patients with PNCP is always challenging. In addition to medico-legal considerations, all prescribers should consider what is in the best interests of their patient. Opioids, may have a role to play in some patients' pain management, but they should be prescribed in accordance with established guidelines and good clinical practice.[134]

In recent years, research has highlighted the limitations of, and harms associated with, the use of opioids to treat PNCP. A recent large systematic review [8] that examined the evidence of long-term opioid efficacy and risk, concluded that there was insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. It also found that there was a dose-dependent risk of serious harms especially when opioids are combined with other psycho-active agents including alcohol.

Tolerance and other adverse effects limit the effectiveness of long-term opioid use.[135, 136, 8, 137] At best there is only weak evidence of modest analgesic benefit and inconclusive data concerning improvement in physical function and quality of life for PNCP patients.[137] In addition, long-term opioid therapy for PNCP is significantly associated with severe pain, poor self-rated health, not being engaged in employment, higher use of the health care system, and a poorer quality of life.[138]

Therefore, the use of opioids for the treatment of PNCP does not appear to fulfil any of the key outcome opioid treatment goals: pain relief, improved quality of life or improved functional capacity.[138]

In response to concerns regarding the efficacy of opioids for the treatment of PNCP and increasing awareness of the associated harms, a number of countries and

jurisdictions have developed guidelines concerning the role of opioids in the treatment of PNCP.

Recent comparisons of Australian, Canadian, German and US guidelines for the management of PNCP[139, 140] revealed a number of similarities. These included the need:

- For comprehensive patient evaluation
- To use non-pharmacological and non-opioid treatments in the first instance
- To only use opioids in conditions with a clear nociceptive or neuropathic cause
- To avoid monotherapy with opioids (where opioids are used, they should be part of a multi-modal and interdisciplinary approach)
- For exploration and clarification of opioid treatment expectations
- To define goals of opioid therapy (e.g., a 30% reduction in pain / and or improvement in function is as much as can realistically be expected)
- For regular clinical assessment
- To titrate opioids to the individual response of the patient
- To use the minimum dosage of opioids possible.

Key international evidence-based guidelines concerning the role of opioids in managing PNCP include:

- Opioids aware: Faculty of Pain Medicine Royal College of Anaesthetists
- The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain
- The US Centers for Disease Control Guideline for Prescribing Opioids for Chronic Pain — United States, 2016
- Chronic pain: supporting safer prescribing of analgesics (2017): British Medical Association
- Guidelines for the Chronic Use of Opioid Analgesics (2017): Federation of State Medical Boards 2017.

A number of Australian jurisdictions and organisations have developed similar guidelines:

- NSW
- South Australia
- Victoria
- Western Australia
- Queensland
- RACGP
- RACP
- NPS Medicinewise
- Faculty of Pain Management: Australian and New Zealand College of Anaesthetists.

Key aspects of the Australian guidelines concerning the role of opioids in managing PNCP[141, 142] appear below.

The first principle is the importance of a comprehensive sociobiomedical assessment. This includes:

- Family, life events, housing, sleep activity and nutrition
- Patient beliefs, mood state, behaviours and responses
- Psychological assessment (the pain experience is affected by mood, stress, coping skills, fear avoidance, and catastrophising)
- Risk of opioid misuse.

A comprehensive pain assessment is also required which includes a:

- General assessment and pain-specific history (that explores the pain type, severity, functional impact, context, and the meaning of pain to the patient, and expectations and fears)
- Physical examination (assessing for signs of tissue damage or disease that might indicate nociceptive and/or neuropathic mechanisms of pain).

A comprehensive assessment will inform the selection of treatment options most likely to be effective. The assessment may need to be repeated frequently, particularly while establishing a diagnosis and appropriate pain management.[141]

Most patients with PNCP are physically deconditioned from inactivity. Movement and exercise therapies, regardless of their form, are recommended in the management of patients with PNCP. Physiotherapists and exercise physiologists with an interest in chronic pain can be extremely beneficial.[141]

Pharmacotherapy should be conceptualised, at best, as a partial response to PNCP. Non-drug therapies should include:

- Education
- Pacing of painful activities
- Addressing postural issues
- Structured exercise programs
- Sleep hygiene
- Psychological therapies.[143, 144]

Where pharmacotherapeutic approaches to PNCP are to be used, non-opioid approaches should be trialled first. Drug therapy for patients in pain is mainly for symptom control. Symptom control itself is important, not only to reduce distress but also as an adjunct to non-drug therapy to enhance quality of life. In some situations where the mechanism of pain can be confidently determined, such as inflammatory or neuropathic conditions, anti-inflammatory or anti-neuropathic agents respectively may be helpful.[142]

Historically, paracetamol has been recommended as a first line treatment for PNCP. However, recent research[145] has found that paracetamol is ineffective in the treatment of low back pain and provides minimal-short term benefit for people with osteoarthritis, key causes of PNCP.

Non-opioid adjuvant agents should be considered before opioids, especially for treatment of neuropathic pain. These include tricyclic antidepressant drugs (amitriptyline, nortriptyline), serotonin-noradrenaline reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine) and anticonvulsants (gabapentin, pregabalin).[142]

Invasive medical procedures (injections, implants) in parallel with the above approaches may be considered in selected cases to support active self-management. However, evidence of long-term benefit is weak and there is significant risk of harm.[142]

4.2.1.1 Opioid therapy in PNCP

The Therapeutic Goods Administration has approved a number of indications for opioids listed on the Pharmaceutical Benefits Scheme (see Table 5).

Table 5: Approved indications for opioids listed on the Pharmaceutical Benefits Scheme.
Source: Pharmaceutical Benefits Scheme (2014).[146]

Opioid	Indication
Codeine	Mild to moderate pain
Buprenorphine	Moderate to severe pain
Fentanyl	Moderate to severe acute or chronic pain
Hydromorphone	Moderate to severe pain
Methadone	Pain requiring opioids
Morphine	Moderate to severe pain
Oxycodone	Moderate to severe pain
Tapentadol	Moderate to severe chronic pain
Tramadol	Moderate to severe pain

It is important for prescribers to seek specialist advice from a pain specialist if they are uncertain about the advisability or conduct of a trial of opioids.[142]

Where patients are already on >100mg oMEDD, this dose should be tapered to more appropriate levels.[142]

Time-limited opioid use for PNCP aims to create a “breathing space” in which the patient can develop active management approaches.[144] Before starting opioid therapy, prescribers should discuss known risks and realistic benefits of opioid therapy with patients and patient/clinician responsibilities for managing therapy.[147] If the commencement of opioid therapy, in conjunction with other approaches, is considered appropriate, an agreement between the prescriber and patient is required regarding an opioid trial. Such an agreement involves:

- Establishing clear goals, identifying the trial’s duration and the next steps if those goals are not reached (e.g., ceasing opioid therapy)
- Establishing a therapeutic contract (verbal or written) involving issues such as:
    - Having only one opioid prescriber and dispenser

    - No early repeats / replacement prescriptions
    - Urine drugs screening if required

- A timed maintenance period before staged withdrawal of opioid therapy.[142]

See Appendix A for an example of a written agreement.[148]

In conducting an opioid trial for PNCP:

1. Opioids should only be prescribed for a maximum of 90 days at a maximum of 40mg oMEDD
2. Use lower doses for older patients and those with co-morbidities: 'start low and go slow'
3. Longer acting opioids should be used (avoid or wean off short-acting preparations)
4. Injectable opioids are not recommended
5. Beware of increased opioid sensitivity in renal and hepatic impairment
6. Opioid rotation can be used to treat tolerance or other adverse effects and start the new opioid at 50% of equivalent dose
7. Negotiate an appropriate timeframe to wean the patient off opioids which limits opioid withdrawal symptoms and minimises patient distress
8. Monitor the effectiveness of opioid therapy, for example using the 5As Opioid therapy monitoring tool (Analgesia, Activity, Adverse effects, Affect and Aberrant behaviour) with repeat prescriptions contingent on satisfactory 5 As assessments
9. Titrate the dose according the 5As Assessment
10. Closely monitor oMEDD and keep below 40mg. If doses are escalating, seek assistance well before 100mg is reached
11. Avoid fentanyl patches, but if using, adopt particular caution as the lowest dose (12mcg/hr) is close to 40mg oMEDD
12. Undertake intermittent planned reductions of opioid dosage.[58, 142]

Opioids should be avoided in patients with an active or past substance use disorder (SUD)[xiv] or unstable psychiatric disorders. At the same time, there may be occasions when opioids may be suitable for such patients. Nevertheless, the management of these patients should be approached cautiously.[142]

Prescribers should incorporate strategies to mitigate risk into the management plan, including consideration of offering naloxone when factors that increase risk for opioid overdose are present (such as history of overdose, history of substance use disorder, higher opioid dosages [50 mg oMEDD] or concurrent benzodiazepine use).[147]

[xiv] If opioids are required for patients with a SUD, evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with other therapies) is preferred. Referral to specialist substance use services is advised, particularly in the context of regulatory restrictions concerning the prescribing of opioids to patients with opioid dependence.

Opioids should be withdrawn if:

- Pain episodes have resolved
- There is no improvement in function during the trial
- Adverse effects or other risks of therapy outweigh any benefits
- Aberrant behaviours develop.[142]

A successful trial of opioid therapy is indicated by improved function and quality of life. Ongoing treatment should be renegotiated on a regular basis to include goals, duration and lowering of dose.[142]

5 Medico-legal issues related to opioid prescribing

Important medico-legal issues must guide decisions concerning opioid prescribing. Many prescribers are not aware that seeking an Authority from the Pharmaceutical Benefits Scheme (PBS) differs from seeking an authority, or a permit, from the state-based pharmaceutical services unit or equivalent.[134]

All Australian states and territories place restrictions on prescribing to patients who are drug dependent. It is important that prescribers use clinical judgment to determine whether the patient is drug dependent in accordance with the relevant legislative definition. Definitions vary between states and territories, but usually relate to the patient's behaviour (e.g., drug seeking) rather than the presence of physical dependence. In many instances, determining if a patient is dependent is not a simple task. Prescribers are often limited in their ability to identify this problem as a result of systemic issues such as the absence of real-time prescription monitoring.[134]

Figure 12 depicts a flow chart concerning the safe, effective, responsible and lawful prescribing of opioids.

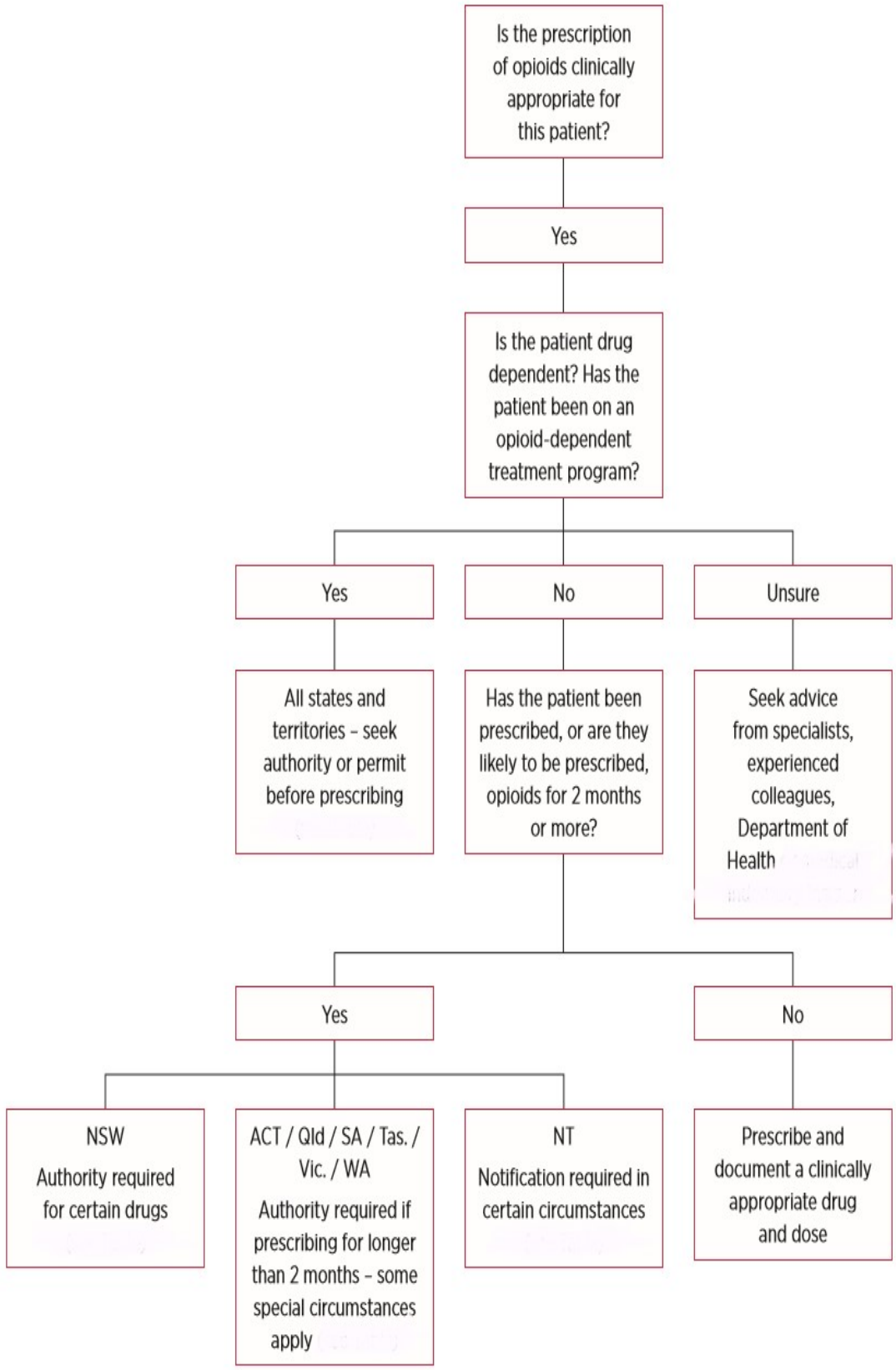


Figure 12: Guide to the steps required to lawfully prescribe opioids.
Source: Jammal & Gown (2015).[134]

6 Responding to patients presenting with pharmaceutical opioid-related problems

At times prescribers will be required to respond to patients who are already experiencing difficulties with their pharmaceutical opioid use. These difficulties could stem from OTC or prescribed pharmaceutical opioid use.

6.1 Assessing opioid use

As with other medical conditions, assessing patients with problems associated with their opioid use is an important part of patient-doctor engagement.[147] A comprehensive biopsychosocial assessment of the patient is necessary. Also important is an examination of indicators of potential opioid problems and the patient's willingness to change their opioid use.[142]

It is essential to explore the use of pharmaceutical opioids in terms of the amount and pattern of use, the social consequences of use, and the experience of compulsion/craving/loss of control.[142]

Do not assume that what is being prescribed is what is being taken – patients may be using more or less than what is prescribed. Also check if the patient has been hoarding or diverting opioids (e.g., lending, giving, selling, bartering or stealing opioids), or if use has been other than as prescribed, (e.g., in response to stressful situations or for emotional escape). This may include over- or under-consumption, topping up with other drugs or pills, or tampering with tablets or patches. Tampering turns slow release formulations into immediate acting ones for smoking, swallowing or intranasal or intravenous consumption. [142-147]

Careful assessment will assist clinical decisions about treatments such as whether there is a need for opioid pharmacotherapy. Physical signs such as opioid intoxication or withdrawal as well as biochemical testing (such as urine drug screens) may also help formulate management plans.

Excess consumption of combination OTC products containing paracetamol or NSAIDs may have placed the patient at risk of hepatic, gastric or renal damage. Consider urgent assessment of FBC, UECs, LFTs and screening for blood borne viruses if there is a history of drug injection.

6.2 Non-opioid symptomatic approaches to pharmaceutical opioid cessation or reduction

For most patients, abrupt withdrawal from opioids is uncomplicated, but they may benefit from a range of symptomatic medications such as those outlined in Table 6.

Table 6: Recommended medications for opioid withdrawal symptoms.
Source: DASSA, (2018).[48]

Symptoms	Medication
Nausea and vomiting	Anti-emetics
Gut cramps	Hyoscine butybromide
Diarrhoea	Loperamide
Headaches, muscle aches and pains	Paracetemol and/or NSAIDs
General withdrawal symptoms	Clonidine/Lofexidine
Insomnia, anxiety/agitation	Benzodiazepines (short term only and caution is required when also prescribing another CNS depressant)

After cessation or reduction, patients may require support with pain management. Non-pharmacological approaches include:

- Planned daily walks or exercise(s) / Physiotherapy/hydrotherapy
- Heat or ice packs
- Transcutaneous Electrical Nerve Stimulation (TENS) machines
- Counselling (e.g., cognitive behavioural therapy) which may be available in person, online or via telephone
- Relaxation therapy / mindfulness / yoga
- Nutritional change with support from a dietitian
- Attending a group pain management program
- Enhancing social connection.

Non-opioid pharmacological strategies may include use of:

- Paracetamol, non-steroidal anti-inflammatory drugs (either non-selective or COX-2 inhibitors)
- Adjuvant drugs (e.g., antidepressants or antineuropathic agents [for neuropathic pain only]).

6.3 Using opioids for pharmaceutical opioid maintenance, reduction or cessation[xv]

6.3.1 Opioid maintenance

While non-pharmacological and non-opioid approaches will be sufficient for most patients there is a group for whom opioids, such as methadone or buprenorphine/naloxone, will be required. If opioids are used to treat pharmaceutical opioid dependence via maintenance, reduction or cessation, compliance with relevant regulatory requirements regarding the prescribing of these drugs for this patient group is essential.

For such patients, an opioid dose equivalence calculator is an important starting point to calculate equi-analgesic doses. Note that these calculators are not totally reliable for guiding dose transfers onto buprenorphine/naloxone or methadone, as the calculators:

- Generally, relate to short-term, not chronic, pharmaceutical opioid use
- Have usually been determined with relatively low levels of opioid use (e.g., 20 or 30 oMEDD).[147]

Opioid dose equivalence calculators can be particularly problematic in relation to codeine (see below).

The Opioid Dose Equivalence Table (Table 7) was developed by the Faculty of Pain Management, ANZCA and is available here, along with a list of practical considerations and references that provide guidance in establishing patients' opioid dose equivalence.

An Opioid Calculator App is available free of charge in both iPhone and Android versions. It is available from the App Store or Google Play by searching for ANZCA Opioid Calculator. Alternatively, the app can be downloaded using the QR code below.

[xv] More detail is provided below concerning responding to codeine-related problems in particular.

Table 7: Opioid dose equivalence.
Source: Faculty of Pain Management, Australian and New Zealand College of Anaesthetists.[149]

Opioid	Dosage	Conversion factor	Proprietary names
Oral (swallowed) preparations *Note: Modified release formulations are marked as MR*			
Morphine	mg/day	1	Anamorph, Kapanol (MR) MS Contin (MR) MS Mono (MR), Ordine, Sevredol
Oxycodone	mg/day	1.5	Endone, OxyContin (MR), OxyNorm, Targin (MR)
Hydromorphone	mg/day	5	Dilaudid, Jurnista (MR)
Codeine	mg/day	0.13	Aspalgin, Codalgin, Panadeine Forte, Mersyndol, Nurofen Plus, others
Dextropropoxyphene	mg/day	0.1	Di-Gesic, Doloxene
Tramadol	mg/day	0.2	Durotram-XR (MR), Tramal, Tramadol SR (MR), Zydol, Zydol SR (MR), others
Tapentadol	mg/day	0.4	Palexia-SR (MR)
Sublingual preparations			
Buprenorphine	mg/day	40	Suboxone, Subutex, Temgesic
Rectal preparations *Note: Absorption from rectal administration is highly variable*			
Oxycodone	mg/day	1.5	Proladone
Transdermal preparations			
Buprenorphine	mcg/hr	2	Norspan
Fentanyl	mcg/hr	3	Denpax, Durogesic, Dutran, Fenpatch, Fentanyl Sandoz
Parenteral preparations			
Morphine	mg/day	3	DBL morphine sulphate injection DBL morphine tartrate injection
Oxycodone	mg/day	3	OxyNorm FI
Hydromorphone	mg/day	15	Dilaudid FI, Dilaudid-HP FI
Codeine	mg/day	0.25	Codeine phosphate injection USP
Pethidine	mg/day	0.4	Pethidine injection BP
Fentanyl	mcg/day	0.2	DBL fentanyl injection, Sublimaze
Sufentanil	mcg/day	2	-

Buprenorphine / naloxone appears to be safe and well tolerated among pharmaceutical opioid dependent patients. Opioid substitution dosages should be titrated according to patient responses. Careful consideration should also be given to the aim of dose titration. Some clinicians aim to provide dosages that simply ensure that withdrawal does not occur. Others aim to titrate the dose to remove risk of cravings.[48]

For more details on approaches to opioid substitution and maintenance therapy please see: National Guidelines for Medication-Assisted Treatment of Opioid Dependence.[150]

6.3.2 Reducing / tapering opioids

Buprenorphine / naloxone is an excellent opioid for tapering/withdrawal, as buprenorphine is a partial agonist and can be administered with once daily dosing. Buprenorphine / naloxone can be used for a withdrawal regime for the treatment of opioid dependence once appropriate regulatory authorisation has been obtained. Buprenorphine/naloxone should only be commenced when objective signs of opioid withdrawal are present (e.g., pupils dilated >5mm, goose bumps, yawning, sniffling, tachycardia).[48]

Opioid dosage reductions can be fast (10-25% of daily dose per week), or slow (10-25% of daily dose per month). The latter would apply if a patient had been using opioids for some years. Discontinuing or tapering opioid therapy is often hindered by the presence of problems such as patients' psychiatric comorbidities, under-developed coping skills or an unsupportive home environment.

If previous attempts at opioid weaning have proven unsuccessful, then the rate of tapering can be slowed.

The goal of tapering is to improve or maintain patient wellbeing while opioids are being withdrawn. Schedule frequent consultations and at each appointment ask about, and emphasise the benefits of tapering (e.g., improved pain, mood, alertness).

Referral for counselling or other support during the tapering process is recommended, especially if there are other significant issues. If a patient is not successfully reducing their dose, or there is an escalation in use beyond prescription, involve other practitioners such as pain or addiction specialists.[147]

7 Screening for codeine-related problems

The restrictions on codeine implemented in February 2018 may result in requests for prescribers to provide this medicine. It is estimated that approximately 20% of users of OTC codeine are codeine dependent.[151] See the TGA's Codeine Information Hub for tips on talking to patients about codeine and resources for patients.

Patients with codeine-related problems may not self-identify as 'people who use drugs'. They may be socially advantaged with high achievements in education and work roles, strong social supports and good incomes.

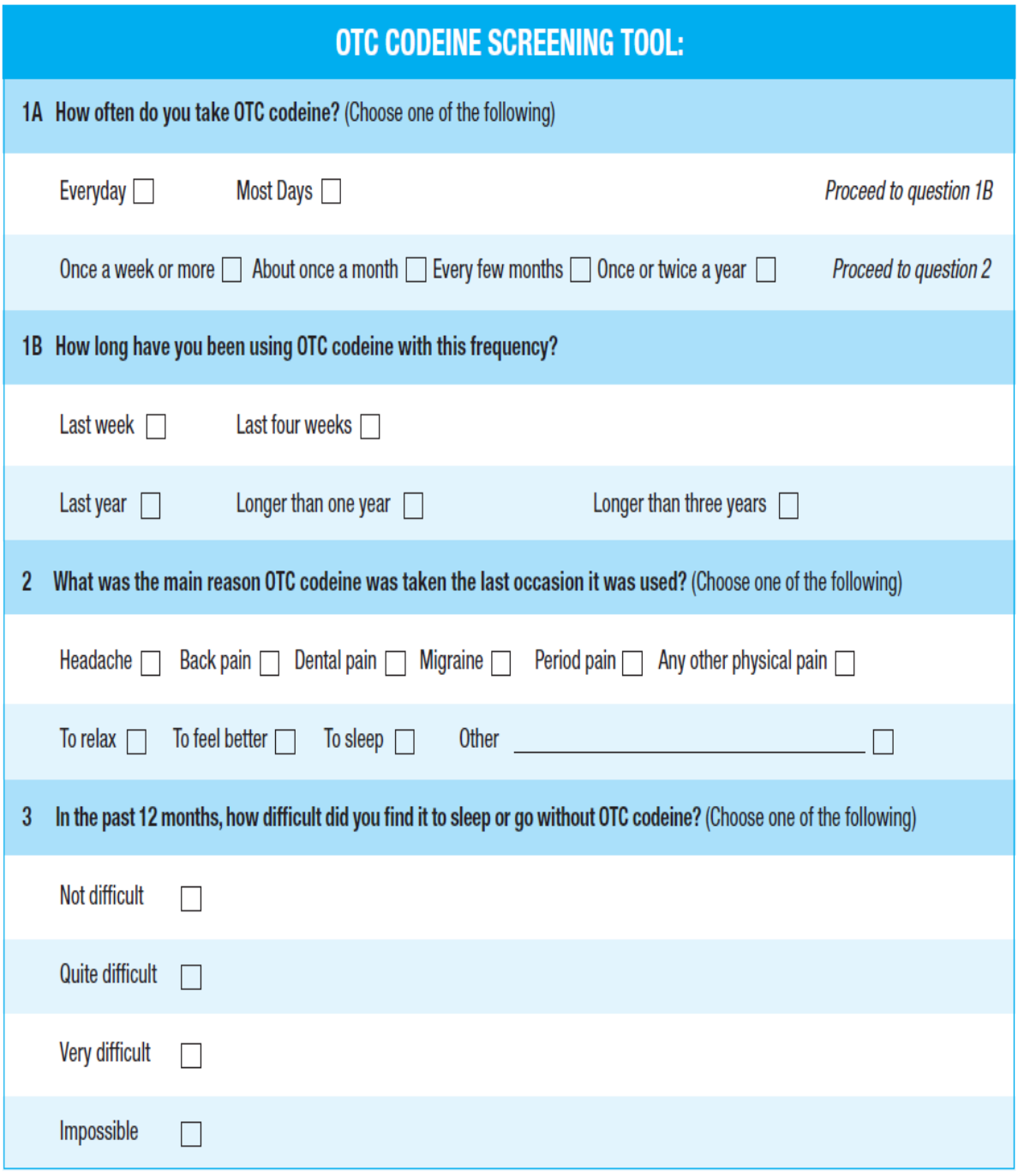
To determine if a patient is having difficulties with their use of codeine (or are likely to experience codeine withdrawal) first establish:

1. Quantity, frequency and duration of codeine use (unless using OTC codeine every or most days, for at least 1 month, patients are unlikely to have developed a major tolerance or dependence)
2. If the dose has increased over time
3. A past history of prescription opioid dependence/injecting drug use/other substance use problems
4. Mental health problems (such as anxiety and depression) or physical complications are present (e.g., from excessive exposure to paracetamol or NSAIDs)
5. Issues with other substances (such as alcohol, benzodiazepines, cannabis, stimulants)
6. If codeine has been used for conditions for which there is no indication
7. If the patient experiences symptoms if a dose is missed.[48]

Relevant investigations could include:

- FBC
- MBA 20
- Urine drug screen for drugs of dependence (e.g., methadone, buprenorphine, oxycodone and fentanyl)
- Serum paracetamol if relevant
- Urine pregnancy test.[48, 142]

The assessment tool in Figure 13 can help establish whether patients are likely to be dependent on codeine and require more intensive treatment.



OTC CODEINE SCREENING TOOL:

1A How often do you take OTC codeine? (Choose one of the following)

Everyday ☐ Most Days ☐ *Proceed to question 1B*

Once a week or more ☐ About once a month ☐ Every few months ☐ Once or twice a year ☐ *Proceed to question 2*

1B How long have you been using OTC codeine with this frequency?

Last week ☐ Last four weeks ☐

Last year ☐ Longer than one year ☐ Longer than three years ☐

2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)

Headache ☐ Back pain ☐ Dental pain ☐ Migraine ☐ Period pain ☐ Any other physical pain ☐

To relax ☐ To feel better ☐ To sleep ☐ Other _____ ☐

3 In the past 12 months, how difficult did you find it to sleep or go without OTC codeine? (Choose one of the following)

Not difficult ☐

Quite difficult ☐

Very difficult ☐

Impossible ☐

Figure 13: Codeine assessment screening tool. Patient's version.
Source McCoy, Nielsen & Bruno (2015).[152]

The Screening Tool is scored using the version of the Screening Tool at Figure 14. A score of 2 or more indicates a high likelihood that the patient will likely fall into either Group 1, 2 of 3 (below).

OTC CODEINE SCREENING TOOL:

1A How often do you take OTC codeine? (Choose one of the following)

Everyday ☐	Most Days ☐				*Proceed to question 1B*
Once a week or more ☐	About once a month ☐	Every few months ☐	Once or twice a year ☐		*Proceed to question 2*

1B How long have you been using OTC codeine with this frequency?

Last week ☐	Last four weeks ☐		1 Point
Last year ☐	Longer than one year ☐	Longer than three years ☐	2 Points

2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)

Headache ☐	Back pain ☐	Dental pain ☐	Migraine ☐	Period pain ☐	Any other physical pain ☐	0 Points
To relax ☐	To feel better ☐	To sleep ☐	Other _____ ☐			1 Point

3 In the past 12 months, how difficult did you find it to sleep or go without OTC codeine? (Choose one of the following)

Not difficult ☐	0 Points
Quite difficult ☐	1 Point
Very difficult ☐	1 Point
Impossible ☐	1 Point

Figure 14: Codeine assessment screening tool. Clinician's scoring version.
Source McCoy, Nielsen & Bruno 2015.[152]

8 Responding to codeine-related problems

The following recommendations for responding to codeine-related problems are adapted from DASSA (2018).[48]

There are likely to be three groups of patients who require assistance from prescribers for problems related to their codeine use. See the flow chart on page 49.

Group 1: Those who are not codeine dependent but are at risk of mild opioid withdrawal symptoms
Group 2: Those with mild to moderate dependence
Group 3: Those with moderate/severe codeine dependence.

Most patients experiencing difficulties with their codeine use will be in Group 1, with decreasing proportions in Groups 2 and 3 (see Figure 15).

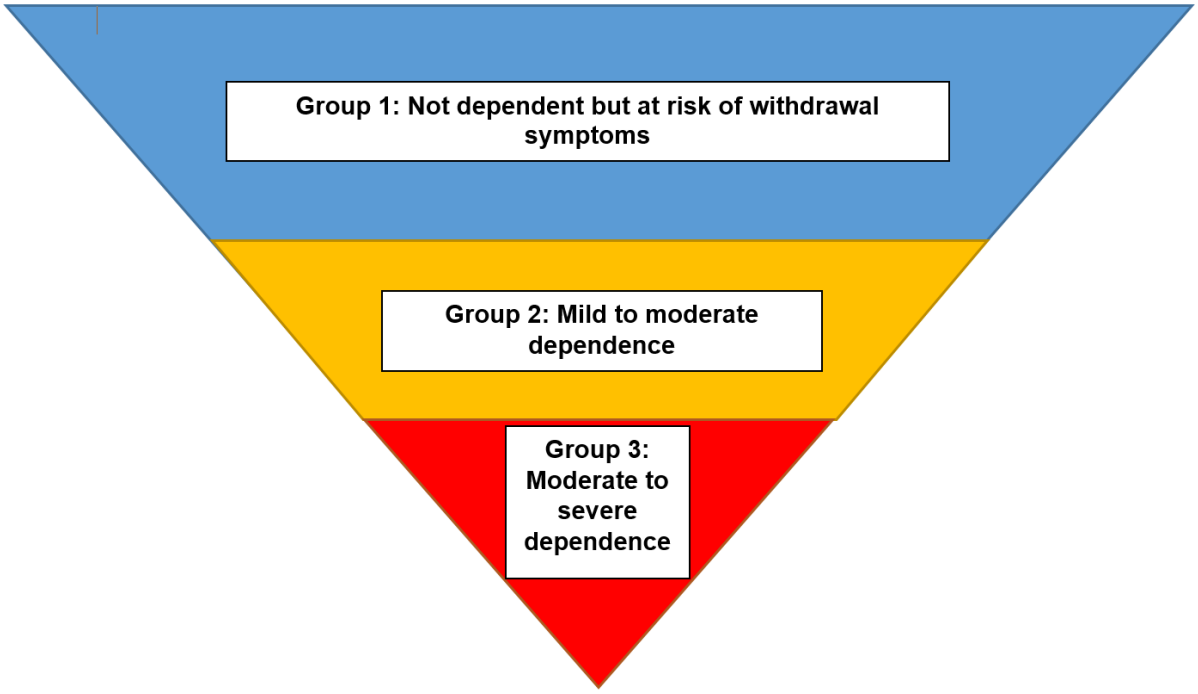


Figure 15: Typology of patients experiencing difficulties with their codeine use.

Approaches for each of the three groups are displayed in the flow chart on Page 49. The clinical management of each group is discussed below.

Group 1: Those who are not codeine dependent but at risk of mild opioid withdrawal symptoms

These are patients who have been using codeine daily or almost daily for more than a month:

- Using up to the recommended doses
- Without characteristics of dependence
- Without having tried to stop their codeine use.

A trial of symptomatic treatment for opioid withdrawal (see page 39) is indicated for this group. These patients would also benefit from education about opioid withdrawal and the importance of not confusing opioid withdrawal with worsening pain or other symptoms.

If a patient cannot cope with this approach, then it is likely that at least mild/moderate opioid dependence is present and that a short course of buprenorphine/naloxone is indicated.

Group 2: Those with mild to moderate dependence

These are patients who have been using codeine daily or almost daily for more than a month:

- At doses higher than recommended
- Without features of severe dependence/withdrawal
- With previous unsuccessful attempts at stopping or reducing their use.

These patients are most likely to benefit from:

- A supported withdrawal regime using a short course of buprenorphine/naloxone (see below)
- Use of other non-opioid analgesics such as paracetamol or NSAIDs
- Non-pharmacological treatments such as psychological approaches including cognitive behaviour therapy, guided imagery, meditation, and aerobic exercise.

When considering buprenorphine dosage, it is important to note that equi-analgesic opioid dosage calculators can underestimate the dose of buprenorphine required to replace codeine. This can result in buprenorphine doses that are too low, which has potential to contribute to poor clinical outcomes.

There is also considerable individual variability in the doses of buprenorphine required to replace codeine, which highlights the importance of individual dose titration.

A sample buprenorphine/naloxone withdrawal protocol is shown in Table 7. If the dosing levels in this protocol are insufficient, a period of maintenance with buprenorphine/naloxone may be required.

Withdrawal symptoms from long-term codeine use can persist for longer than the duration of the 5-6 day buprenorphine/naloxone regime. These symptoms can usually be managed with non-opioid medications. Inpatient withdrawal may be required:

- If the patient has been using multiple substances
- The codeine intake has been very high
- The withdrawal is severe despite buprenorphine/naloxone treatment.

Table 7: Supported withdrawal protocol.
(Source DASSA, 2018)

Supported Withdrawal Protocol	
	Treatment
Day 1	2 mg at onset of withdrawal as a supervised dose. Assess tolerance 2 hours later. Give an additional 2 to 4mg as a supervised dose 2 to 4 hours later prn if in severe withdrawal.
Day 2	4-8 mg mane supervised.
Day 3	4-6 mg mane supervised.
Day 4	2-4 mg mane supervised.
Days 5 and 6	2 mg mane then cease.

Group 3: Those with moderate/severe codeine dependence

This group have used codeine multiple times daily for more than a month (and probably much longer), exceeded recommended dosages, are probably unable to stop doing so despite being concerned about and experiencing harm from their use of the drug. They are also likely to be highly tolerant to the effects of codeine, experience withdrawal symptoms on cessation and have made unsuccessful attempts to stop in the past. They may also have:

- A history of other harmful substance use (such as prescription opioid use or injecting drug use)
- End organ damage
- Disabling mental health problems.

These patients are at significant risk of relapse. They are unlikely to respond to non-opioid withdrawal management and are not likely to cope with sudden cessation of opioids. They may also try to obtain prescribed or illicit opioids in lieu of OTC codeine, thereby exposing them to significant risks. They will probably require ongoing medication assisted treatment for opioid dependence (MATOD) with buprenorphine/naloxone or methadone (see National Guidelines for Medication-Assisted Treatment of Opioid Dependence).[150]

Some of these patients may not wish to enter a MATOD program due to its restrictive nature. These restrictions include the need for daily or almost daily

dispensing of their opioids from pharmacies or other settings. As a result, they may elect to undertake a Supported Withdrawal Protocol (see above) or an inpatient detoxification.

Figure 16 is a flow chart of approaches for each of the three groups.

Quick Guide to Managing Patients with OTC Codeine Use Problems

- Assess recent and past substance use history including codeine and other opioids, alcohol, benzodiazepines and any other substance use, and mental health problems
- Assess for gastrointestinal bleeding or ulcers with ibuprofen use
- Full blood count, liver and kidney function, urine drug screen, pregnancy test (+serum paracetamol if relevant).

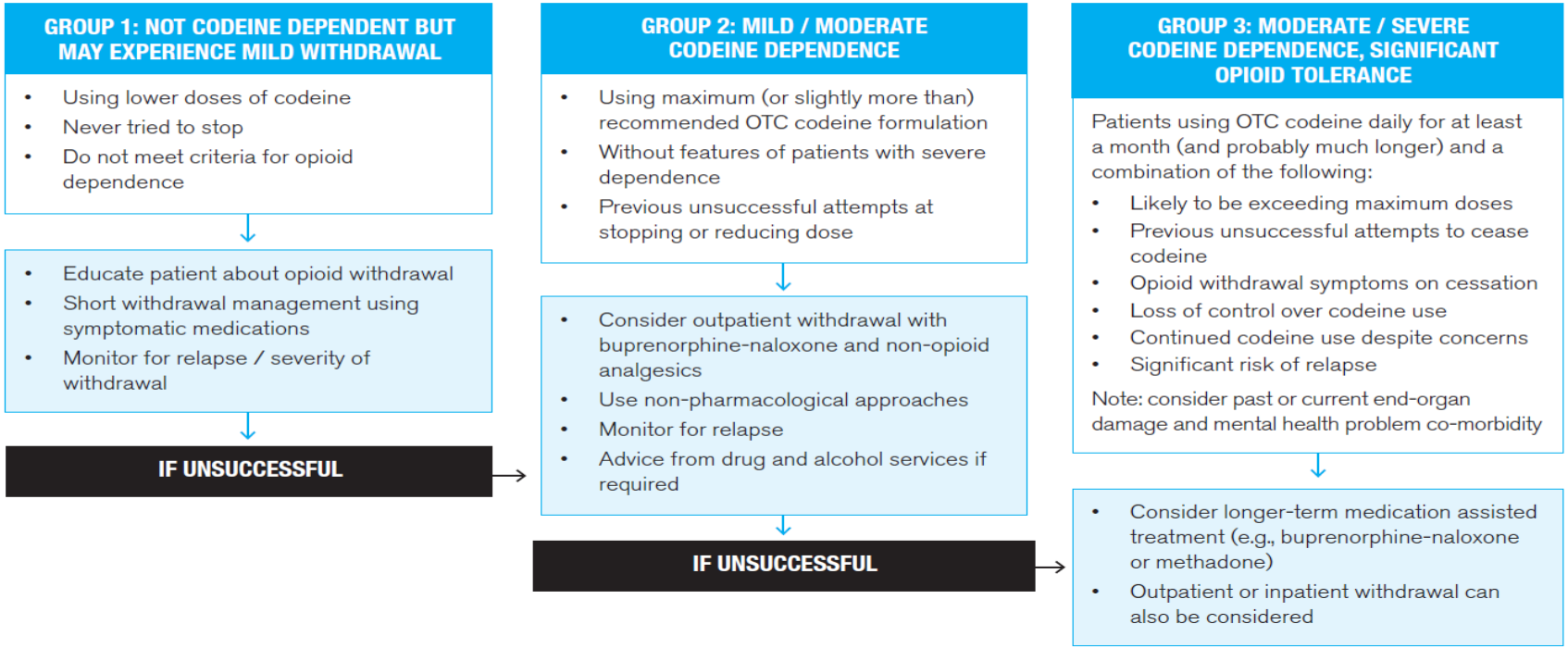


Figure 16: Quick Guide to Managing Patients with Regular OTC Codeine Use Problems.
Source: Dr Suzanne Nielsen personal communication .

9 Conclusion

Current trends towards more cautious use of pharmaceutical opioids represent a further ‘swing of the pendulum’ in the pattern of use of these medicines. Arguably, up until the early 1980s opioids were under-prescribed in Australia. As a result, many sufferers of acute and malignant pain were inadequately treated. The 1980s saw a revolution in the treatment of acute and malignant pain in Australia in which opioids played a major part. These successes led to the mistaken belief that opioids also had a prominent role to play in the treatment of PNCP.

From the mid-1980s the use of opioids grew exponentially. Many of these medicines were used for the treatment of PNCP, despite a lack of evidence of efficacy. Growing awareness of the harms associated with pharmaceutical opioids use, coupled with a clearer recognition of their lack of effectiveness for PNCP has led to a reversal of this trend.

Australia is now entering a phase of more judicious use of pharmaceutical opioids and is shifting away from the more liberal use that has occurred over the past two and a half decades.

A further factor likely to influence future patterns of pharmaceutical opioid prescribing and use is the implementation of the Electronic Recording and Reporting of Controlled Drugs (ERRCD) system. The establishment of an on-line, real time system will provide prescribers and dispensers with information regarding their patients’ use of these medicines. This important clinical tool aims to support clinical decision-making but it is also likely to bring to light a number of patients who have been obtaining opioids from different prescribers without informing them about their other consultations.

The ability to obtain prescriptions from multiple doctors coupled with the historically high levels of prescribing of these medicines has also resulted in a number of Australians using very high dosages of opioids. These ‘legacy patients’ may find it difficult to reduce or cease their use.

As Australia moves towards more cautious use of pharmaceutical opioids, it is important that those who have encountered difficulties as a result of previous approaches to the use of these medicines receive appropriate support. This may involve their pain treatment transitioning to:

- Non-pharmaceutical or non-opioid treatments
- Lower dose opioid therapy
- Opioid maintenance therapy approaches that are more strongly evidence-based.

Moving towards a more nuanced and evidence-based approach to the use of pharmaceutical opioids may, in the short term, cause some community disruption. This could range from an inability to obtain OTC codeine, through to reduced capacity to obtain stronger opioids as a result more cautious prescribing and enhanced monitoring.

The ultimate benefit of improving the quality of use of pharmaceutical opioids to the Australian community will come in the form of:

- Enhanced pain relief treatment practices
- Reduced harms from the opioids themselves (e.g., iatrogenic dependence, overdoses, opioid endocrinopathies)
- Reduced harms from the medicines contained in compound analgesics (paracetamol and NSAIDs)
- Reduced pharmaceutical costs.

The current problems associated with the overuse and inappropriate use of pharmaceutical opioids in Australia should also be seen in the context of the shortage of these drugs experienced in many developing countries. There a number of reasons for this shortage including:

- Accessibility and cost
- Barriers related to medical training
- Healthcare system restrictions
- Prescriber and patient perceptions
- Cultural bias.[153]

The lack of global access to these valuable medicines is also an issue that warrants close attention.

References

1. McDonald J., Lambert D. Opioid receptors. (2014). *Continuing Education in Anaesthesia Critical Care & Pain. 15*(5):219-24.
2. Macintyre P. (2007). Acute pain and opioids: Through the ages. *Australasian Anaesthesia.* 59-64.
3. Butler S. (1944). *The Odyssey of Homer.* New York: Walter J. Black, Inc.
4. Brownstein M. (1993). *A brief history of opiates, opioid peptides, and opioid receptors. Proceedings of the National Academy of Sciences. 90*(12):5391-3.
5. The Royal Australasian College of Physicians RACP (2009). *Prescription opioid policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use.* Sydney: RACP.
6. Roxburgh A., Bruno, R., Larance, B., Burns, L. (2011). Prescription of opioid analgesics and related harms in Australia. *Medical Journal of Australia. 195*(5):280-4.
7. Boudreau, D., Von Korff, M., Rutter, C., Saunders, K., Ray, G., Sullivan, M., et al. (2009). Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiology and Drug Safety. 18*(12):1166-75.
8. Chou, R., Turner, J., Devine, E., Hansen, R., Sullivan, S., Blazina, I., et al., (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine. 162*(4):276-86.
9. Blanch, B., Pearson, S., Haber, P. (2014). An overview of the patterns of prescription opioid use, costs and related harms in Australia. *British Journal of Clinical Pharmacology. 78*(5):1159-66.
10. Rintoul, A., Dobbin, M., Drummer, O. Ozanne-Smith, J. (2011). Increasing deaths involving oxycodone, Victoria, Australia, 2000-09. *Injury Prevention 17,* 254- 259.
11. Fischer, B., Jones, W., Urbanoski, K., Skinner, R., Rehm, J. (2013). Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005–2011. *Drug and Alcohol Review. 33*(1):19-26.
12. Paulozzi, L.J., Kilbourne, E., Desai, H. (2011). Prescription drug monitoring programs and death rates from drug overdose. *Pain Medicine. 12*:747-54.
13. Fischer, B., Nakamura, N., Urbanoski, K., Rush, B., Rehm, J. (2001). Correlations between population levels of prescription opioid use and prescription-opioid-related substance use treatment admissions in the USA and Canada since 2001. *Public Health.* 126(9):749-51.
14. Boscarino, J., Hoffman, S., Han, J. (2015). Opioid-use disorder among patients on long-term opioid therapy: Impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Substance Abuse and Rehabilitation. 6*:83.
15. Baldini, A., Von Korff, M., Lin, E. (2012). A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. *The Primary Care Companion to CNS Disorders. 14*(3).
16. Ballantyne, J. (2012). Safe and effective when used as directed: The case of chronic use of opioid analgesics. *Journal of Medical Toxicology. 8*(4):417-23.

17. Svendsen, K., Borchgrevink, P., Fredheim, O., Hamunen, K., Mellbye, A., Dale, O. (2011). Choosing the unit of measurement counts: The use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliative Medicine. 25*(7):725-32.
18. WHO Collaborating Centre for Drug Statistics Methodology. (2016). *Defined Daily Dose*. Oslo: WHOCCDSM.
19. Berterame, S., Erthal, J., Thomas, J., Fellner, S., Vosse, B., Clare, P., et al. (2016). Use of and barriers to access to opioid analgesics: A worldwide, regional, and national study. *The Lancet. 387*(10028):1644-56.
20. Nielsen, S., Degenhardt, L., Hoban, B., Gisev, N. (2014). *Comparing opioids: A guide to estimating oral morphine equivalents (OME) in research. Sydney*: National Drug and Alcohol Research Centre.
21. Pain and Policy Studies Group. (2018). *Opioid Consumption Data*: University of Wisconsin. Available from: http://www.painpolicy.wisc.edu/opioid-consumption-data.
22. Nielsen, S., Gisev, N., Bruno, R., Hall, W., Cohen, M., Larance, B., et al. (2017). Defined daily doses (DDD) do not accurately reflect opioid doses used in contemporary chronic pain treatment. *Pharmacoepidemiology and Drug Safety. 26*(5):587-91.
23. Degenhardt, L., Gisev, N., Cama, E., Nielsen, S., Larance, B., Bruno, R. (2016). The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. *Pharmacoepidemiology and Drug Safety. 25*: 521-538.
24. Degenhardt, L., Larance, B., Mathers, B., Azim, T., Kamarulzaman, A., Mattick, R., et al. (2007). *Benefits and risks of pharmaceutical opioids: Essential treatment and diverted medication.* Sydney: National Drug and Alcohol Research Centre.
25. Fischer, B., Jones, W., Rehm, J. (2014). Trends and changes in prescription opioid analgesic dispensing in Canada 2005–2012: An update with a focus on recent interventions. *BMC Health Services Research. 14*(1):90.
26. Fischer, B., Gooch, J., Goldman, B., Kurdyak, P., Rehm, J. (2014). Non-medical prescription opioid use, prescription opioid-related harms and public health in Canada: An update 5 years later. *Canadian Journal of Public Health. 105*(2):146-9.
27. Humphreys, K. (2017). Avoiding globalisation of the prescription opioid epidemic. *The Lancet. 390*(10093):437-9.
28. Sites, B., Beach, M., Davis, M. (2014). Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. *Regional Anesthesia and Pain Medicine.* 39(1):6.
29. Guy, G., Zhang, K., Bohm, M., Losby, J., Lewis, B., Young, R., et al. (2017). Vital signs: changes in opioid prescribing in the United States, 2006–2015. *Morbidity and Mortality Weekly Report. 66*(26): 697–704.
30. Center for Behavioral Health Statistics and Quality. (2015). *Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health.* Rockville (MD): Substance Abuse and Mental Health Services Administration. HHS Publication No. SMA 15- 4927, NSDUH Series H-50.
31. Rudd, R., Seth, P., David, F., Scholl, L. (2016). Increases in drug and opioid-involved overdose deaths-United States, 2010–2015. *Morbidity and Mortality Weekly Report. 65.*

32. Centers for Disease Control (2017*). Provisional counts of drug overdose deaths, as of 8/6/2017.* Atlanta GA: Centers for Disease Control, National Center for Health Statistics.
33. Drug Enforcement Administration. (2016). *National Drug Threat Assessment Summary.* Arlington, Virginia: Drug Enforcement Administration.
34. Office on Womens' Health. (2016). White Paper: *Opioid Use, Misuse, and Overdose in Women.* Washington Office on Womens' Health.
35. Centers for Disease Control and Prevention. (2013). *Prescription Painkiller Overdoses: A Growing Epidemic, Especially Among Women.* Centers for Disease Control, National Center for Health Statistics.
36. Case, A., & Deaton, A. (2015). Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proceedings of the National Academy of Sciences. 112*(49):15078-83.
37. Weiss, A., Elixhauser, A., Barrett, M., Steiner, C., Bailey, M., O'Malley L. (2017). *Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009–2014.* Rockville (MD): Agency for Healthcare Research and Quality.
38. Fischer B. (2015). Prescription opioid use, harms and interventions in Canada: A review update of new developments and findings since 2010. *Pain Physician.18*:605-14.
39. Government of Canada. (2016). *National report: Apparent opioid-related deaths (2016).* Ottawa: Government of Canada.
40. Leong, M., Murnion, B., & Haber, PS. (2009). Examination of opioid prescribing in Australia. *Internal Medicine Journal. 39*:676-81.
41. Roxburgh, A., Burns, L., Drummer, O., Pilgrim, J., Farrell, M., Degenhardt, L. (2013). Trends in fentanyl prescriptions and fentanyl-related mortality in Australia. *Drug and Alcohol Review. 32*(3):269-75.
42. Monheit, B., Pietrzak, D., Hocking, S. (2016). Prescription drug abuse – A timely update. *Australian Family Physician*. *45*:862-6.
43. Nicholas, R., Lee, N., Roche, A. (2011). *Pharmaceutical Drug Misuse Problems in Australia: Complex Issues, Balanced Responses.* Adelaide: Flinders University, 2011.
44. Derry, S., Moore, R., McQuay, H. (2010). Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Systematic Reviews.* (4): CD008099.
45. Moore, R., Wiffen, P., Derry, S., Maguire, T., Roy, Y., Tyrrell, L. (2013). Non-prescription (OTC) oral analgesics for acute pain-an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews.*
46. Toms, L., Derry, S., Moore, R., McQuay, H. (2009). Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database of Systematic Reviews.* doi: 10.1002/14651858.CD001547.pub2.
47. Daniels, S., Goulder, M., Aspley, S., Reader. S. (2011). A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. *Pain 152*(3):632-42.
48. Drug and Alcohol Services SA. *Managing patients with regular OTC codeine use.* Adelaide: DASSA, 2018.
49. Dutch, M. (2008). Nurofen Plus misuse: An emerging cause of perforated gastric ulcer. *Medical Journal of Australia. 188*(1):56-7.

50. Frei, M., Nielsen, S., Dobbin, M., & Tobin, C. (2010). Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: A series of 27 cases. *Medical Journal of Australia. 193*(5):294-6.
51. McDonough, M. (2011). Misuse of codeine-containing combination analgesics. *Medical Journal of Australia.194*(9):486.
52. Robinson, G., Robinson, S., McCarthy, P., & Cameron, C. (2010). Misuse of over-the-counter codeine-containing analgesics: Dependence and other adverse effects. *The New Zealand Medical Journal (Online). 123* (1317).
53. Nielsen, S., Tobin, C., & Dobbin, M. (2012). OTC codeine: Examining the evidence for and against. *Australian Pharmacist. 31*(3):236.
54. Roxburgh, A., Hall, W., Burns, L., Pilgrim, J., Saar, E., Nielsen, S, et al. (2015). Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *The MedicalJjournal of Australia. 203*(7):299.
55. Mill, D., Johnson, J., Cock, V., Monaghan, E., Hotham, E. (2018) Counting the cost of over-the-counter codeine containing analgesic misuse: A retrospective review of hospital admissions over a 5 year period. *Drug and Alcohol Review 37*, 247–256.
56. Harrison, C., Charles, J., Henderson, J., Britt, H. (2012). Opioid prescribing in Australian general practice. *Medical Journal of Australia. 196*(6):380-1.
57. Campbell, G., Nielsen, S., Larance, B., Bruno, R., Mattick, R., Hall, W., et al. (2015). Pharmaceutical opioid use and dependence among people living with chronic pain: Associations observed within the pain and opioids in treatment (POINT) cohort. *Pain Medicine. 16*(9):1745-58.
58. NSW Agency for Clinical Innovation. (ND).*Opioid recommendations in General Practice.* Sydney: NSW Agency for Clinical Innovation.
59. Campbell, G., Nielsen, S., Bruno, R., Lintzeris, N., Cohen, M., Hall, W., et al. (2015). The Pain and Opioids IN Treatment Study: Characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain. 156*(2):231–42.
60. Roxburgh, A., Hall, W., Dobbins, T., Gisev, N., Burns, L., Pearson, S, et al. (2017). Trends in heroin and pharmaceutical opioid overdose deaths in Australia. *Drug and Alcohol Dependence. 179(Supplement C)*:291-8.
61. Penington Institute. *Australia's Annual Overdose Report.* Melbourne: Penington Institute, 2016.
62. Penington Institute. *Australia's Annual Overdose Report.* Melbourne: Penington Institute, 2017.
63. Lam, K., Kunder, S., Wong, J., Doufas, A., Chung, F. (2016). Obstructive sleep apnea, pain, and opioids: Is the riddle solved? *Current Opinion in Anaesthesiology. 29*(1):134-40.
64. White, J., & Irvine, R. (1999). Mechanisms of fatal opioid overdose. *Addiction. 94*(7):961-72.
65. Nadpara, P., Joyce, A., Murrelle, E., Carroll, N., Barnard, M., et al. (2017). Risk factors for serious prescription opioid-induced respiratory depression or overdose: Comparison of commercially insured and Veterans Health Affairs populations. *Pain Medicine. 19*, 76-96.
66. Ramachandran, S., Haider, N., Saran, K., Mathis, M., Kim, J., Morris, M., et al. (2011). Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy. *Journal of Clinical Anesthesia. 23*(3):207-13.

67. Sigmarsdottir, B., Gudmundsdottir, T., Zoëga, S., Gunnarsson, P. (2017). Drugs that can cause respiratory depression with concomitant use of opioids. *Scandinavian Journal of Pain. 16*:186.
68. Hillman, D., & Lack, L. (2013). Public health implications of sleep loss: The community burden. *Medical Journal of Australia.199*(8):7-10.
69. Chiu, Y., Silman, A., Macfarlane, G., Ray, D., Gupta, A., Dickens, C., et al. (2005). Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain.* 115(3):316-21.
70. Harned, M., Sloan, P. (2016). Safety concerns with long-term opioid use. *Expert Opinion on Drug Safety. 15*(7):955-62.
71. Correa, D., Farney, R., Chung, F., Prasad, A., Lam, D., Wong., J. (2015). Chronic opioid use and central sleep apnea: A review of the prevalence, mechanisms, and perioperative considerations. *Anesthesia & Analgesia. 120*(6):1273-85.
72. Zeng, Z., Lu, J., Shu, C., Chen, Y., Guo, T., Wu, Q., et al. (2015). A comparison of nalbuphine with morphine for analgesic effects and safety: Meta-analysis of randomized controlled trials. *Scientific Reports. 5: 10927*
73. Aurora, R., Chowdhuri, S., Ramar. K., Bista, S., Casey, K., Lamm, C., et al. (2012). The treatment of central sleep apnea syndromes in adults: Practice parameters with an evidence-based literature review and meta-analyses. *Sleep. 35*(1):17-40.
74. Filiatrault, M., Chauny, J., Daoust, R., Roy, M., Denis, R., Lavigne, G. (2016). *Medium Increased Risk for Central Sleep Apnea but Not Obstructive Sleep Apnea in Long-Term Opioid Users: A Systematic Review and Meta-Analysis.* Darien ILL: American Academy of Sleep Medicine.
75. Mason, M., Cates, C., Smith, I. (2015). Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane Database of Systematic Reviews.*
76. Chaparro, L., Furlan, A., Deshpande, A., Mailis-Gagnon, A., Atlas, S., Turk, D. (2013). Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews.*
77. Saadatabadi, H., Ahmadkhani, H., Gonabadinejad, L., Moghadam, L. (2016). The relationship between Restless legs Syndrome and opioid abuse / relapse. *International Journal of Medical Research & Health Sciences. 5*(11):238-44.
78. Doleman, B., Read, D., Lund, J., Williams, J. (2015). Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: Systematic review and meta-analysis. *Regional Anesthesia and Pain Medicine. 40*(6):706-12.
79. Gaskell, H., Moore, R., Derry, S., Stannard C. (2016). Oxycodone for pain in fibromyalgia in adults. *Cochrane Database of Systematic Reviews.*
80. Meng, W., Yuan, J., Zhang, C., Bai, Z., Zhou, W., Yan, J., et al. Parenteral analgesics for pain relief in acute pancreatitis: A systematic review. *Pancreatology. 13*(3):201-6.
81. Wolff, R., Aune, D., Truyers, C., Hernandez, A., Misso, K., Riemsma, R., et al. (2012). Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. *Current Medical Research and Opinion. 28*(5):833-45.

82. Yancy, W., McCrory, D., Coeytaux, R., Schmit, K., Kemper, A., Goode, A., et al. (2016). Efficacy and Tolerability of Treatments for Chronic Cough. *Chest. 144*(6):1827-38.
83. Pergolizzi, J. (2012). Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. *Drugs & Aging. 29*(12):993-5.
84. Siemens, W., Gaertner, J., Becker, G. (2015). Advances in pharmacotherapy for opioid-induced constipation: A systematic review. *Expert Opinion on Pharmacotherapy.* 16(4):515-32.
85. Leonard, J., Baker, D. (2015). Naloxegol. *Annals of Pharmacotherapy.* 49(3):360-5.
86. Adbel-Shaheed, C., Maher, C., Williams, K., Day, R., McLachlan, A. (2016). Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: A systematic review and meta-analysis. *JAMA Internal Medicine. 176*(7):958-68.
87. van Ojik, A., Jansen, P., Brouwers, J., van Roon, E. (2012). Treatment of chronic pain in older people: Evidence-based choice of strong-acting opioids. *Drugs and Aging. 29*(8):615-25.
88. Chou, R., Turner, J., Devine, E,. Hansen, R., Sullivan, S., Blazina, I., et al. (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine. 162*(4):276-86.
89. Chen, A., Ashburn, M. (2015). Cardiac effects of opioid therapy. *Pain Medicine*. *16* (suppl1): S27-S31.
90. van Ojik, A., Jansen, P., Brouwers, J., van Roon, E. (2012). Treatment of chronic pain in older people. *Drugs & Aging. 29*(8):615-25.
91. Marks, J., van der Heijde, D., Colebatch, A., Buchbinder, R., Edwards, C. (2012). Pain pharmacotherapy in patients with inflammatory arthritis and concurrent cardiovascular or renal disease: A Cochrane systematic review. *The Journal of Rheumatology Supplement. 90*:81-4.
92. O'Rourke, T., Wosnitzer, M. (2016). Opioid-induced androgen deficiency (OPIAD): Diagnosis, management, and literature review. *Current Urology Reports. 17*(10):76.
93. Seyfried, O., Hester, J. (2012). Opioids and endocrine dysfunction. *British Journal of Pain. 6*(1):17-24.
94. Yee, A., Loh, H., Hisham, H., Ng, C. (2014). The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: A meta-analysis study. *The Journal of Sexual Medicine.11*(1):22-32.
95. Yee, A., Loh, H., Hisham, Ng C. (2014). Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: A meta-analysis study. *International Journal of Impotence Research. 26*(5):161-6.
96. Deyo, R., Smith, D., Johnson, E., Tillotson, C., Donovan, M., Yang, X., et al. (2013). Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine. 38*(11):909-15.
97. Teng, Z., Zhu, Y., Wu, F., Zhu, Y., Zhang, X., Zhang, C. (2015). Opioids contribute to fracture risk: A meta-analysis of 8 cohort studies. *PLoS One. 6*(10):6.

98. Y. Wang, G., Wouldes, T., Russell, B. (2013). Methadone maintenance treatment and cognitive function: A systematic review. *Current Drug Abuse Reviews. 6*(3):220-30.
99. Gomes, T., Redelmeier, D., Juurlink, D., Dhalla, I., Camacho, X., Mamdani M. (2013). Opioid dose and risk of road trauma in Canada: A population-based study. *JAMA Internal Medicine. 173*(3):196-201.
100. Rudisill, T., Zhu, M., Kelley, G., Pilkerton, C., Rudisill, B. (2016). Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. *Accident Analysis & Prevention. 96 (Supplement C)*:255-70.
101. Strand, M., Fjeld, B., Arnestad, M., Mørland, J. (2013). Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. *Traffic Injury Prevention. 14*(1):26-38.
102. Swart, L., van der Zanden, V., Spies, P., de Rooij, S., van Munster B. (2017). The Comparative Risk of Delirium with Different Opioids: A Systematic Review. *Drugs & Aging. 34*(6):437-43.
103. Cavaliere, F. (2016). Postoperative Delirium. In: Chiumello D, editor. *Topical Issues in Anesthesia and Intensive Care.* Cham: Springer International Publishing. pp55-63.
104. Lee, M., Silverman, S., Hansen, H., Patel, V., Manchikanti, L. (2011). A comprehensive review of opioid-induced hyperalgesia. *Pain Physician. 14*:145-61.
105. Cohen, S., Christo, P., Wang, S., Chen, L., Stojanovic, M. (2008). The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. *Regional Anesthesia and Pain Medicine. 33*(3):199-206.
106. Scherrer, J., Svrakic, D., Freedland, K., Chrusciel, T., Balasubramanian, S., Bucholz, K., et al. (2014). Prescription opioid analgesics increase the risk of depression. *Journal of General Internal Medicine. 29*(3):491-9.
107. Fischer, B., Murphy, Y., Kurdyak, P., Goldner, E. (2016). Depression – A major but neglected consequence contributing to the health toll from prescription opioids? *Psychiatry Research. 243 (Supplement C)*:331-4.
108. Sullivan, M., Edlund, M., Zhang, L., Unützer, J., Wells, K. (2006). Association between mental health disorders, problem drug use, and regular prescription opioid use. *Archives of Internal Medicine. 166*(19):2087-93.
109. Goesling, J., Henry, M., Moser, S., Rastogi, M., Hassett, A., Clauw, D., et al. (2015). Symptoms of depression are associated with opioid use regardless of pain severity and physical functioning among treatment-seeking patients with chronic pain. *The Journal of Pain. 16*(9):844-51.
110. Braden, J., Sullivan, M., Ray, G., Saunders, K., Merrill, J., Silverberg, M., et al. (2009). Trends in long-term opioid therapy for non-cancer pain among persons with a history of depression. *General Hospital Psychiatry. 31*(6):564-70.
111. Blozik, E., Laptinskaya, D., Herrmann-Lingen, C., Schaefer, H., Kochen, M., Himmel, W., et al. (2009). Depression and anxiety as major determinants of neck pain: A cross-sectional study in general practice. *BMC Musculoskeletal Disorders. 10*(1):13.

112. Scherrer, J., Salas, J., Copeland, L., Stock, E., Ahmedani, B., Sullivan, M., et al. (2016). Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. *The Annals of Family Medicine.14*(1):54-62.
113. Scherrer, J., Salas, J., Copeland, L., Stock, E., Schneider, F., Sullivan, M., et al. (2016). Increased risk of depression recurrence after initiation of prescription opioids in noncancer pain patients. *The Journal of Pain. 17*(4):473-82.
114. Martins, S., Fenton, M., Keyes, K., Blanco, C., Zhu, H., Storr, C. (2012). Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. *Psychological Medicine. 42*(6):1261-72.
115. Wiese, A., Griffin, M., Stein, C., Mitchel, E., Grijalva, C. (2015). Opioid analgesics and the risk of serious infections among older adults. *Open Forum Infectious Diseases. 2(suppl_1)*:1222.
116. Sacerdote, P., Franchi, S., Panerai, A. (2012). Non-Analgesic Effects of Opioids: Mechanisms and Potential Clinical Relevance of Opioid-Induced Immunodepression. *Current Pharmaceutical Design. 18*(37):6034-42.
117. Sacerdote, P., Manfredi, B., Mantegazza, P., Panerai, A. (1997). Antinociceptive and immunosuppressive effects of opiate drugs: A structure-related activity study. *British Journal of Pharmacology. 121*(4):834-40.
118. Budd, K. (2006). Pain management: Is opioid immunosuppression a clinical problem? *Biomedicine & Pharmacotherapy. 60*(7):310-7.
119. Portenoy, R., & Foley, K. (1986). Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain. 25*(2):171-86.
120. Porter, J., Hick, H. (1980). Addiction rare in patients treated with narcotics. *New England Journal of Medicine. 302*(2):123.
121. Max, M. (1990). Improving outcomes of analgesic treatment: Is education enough. *Annals of Internal Medicine. 113*(11):885-9.
122. Gart, M. (2017). *Pain is not the fifth vital sign* [cited 2018 8 December]. Available from: http://medicaleconomics.modernmedicine.com/medical-economics/news/pain-not-fifth-vital-sign?page=0,1.
123. Tompkins, D., Hobelmann, J., Compton, P. (2017). Providing chronic pain management in the “Fifth Vital Sign” Era: Historical and treatment perspectives on a modern-day medical dilemma. *Drug and Alcohol Dependence. 173 (Supplement 1)*: S11-S21.
124. Joranson, D., Gilson, A., Dahl, J., Haddox, J. (2002). Pain management, controlled substances, and state medical board policy: A decade of change. *Journal of Pain and Symptom Management. 23*(2):138-47.
125. Manchikanti, L., Atluri, S., Hansen, H., Benyamin, R., Falco, F., Helm, S., et al. (2014). Opioids in chronic noncancer pain: Have we reached a boiling point yet? *Pain physician. 17*:E1-E10.
126. Morone, N., & Weiner, D. (2013). Pain as the 5th vital sign. Exposing the need for pain education. *Clinical Therapeutics. 35*(11):1728-32.
127. Edlund, M., Martin, B., Devries, A., Fan, M., Braden, J., Sullivan, M. (2010). Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP study. *The Clinical Journal of Pain. 26*(1):1.

128. Mularski, R., White-Chu, F., Overbay, D., Miller, L., Asch, S., Ganzini, L. (2006). Measuring pain as the 5th vital sign does not improve quality of pain management. *Journal of General Internal Medicine. 21*(6):607-12.
129. Van Zee, A. (2009). The promotion and marketing of OxyContin: Commercial triumph, public health tragedy. *American Journal of Public Health. 99*(2):221-7.
130. Gilson, A., Ryan, K., Joranson, D., Dahl, J. (2004). A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *Journal of Pain and Symptom Management. 28*(2):176-88.
131. Substance Abuse and Mental Health Services Administration. (2006). *Results from the 2005 National Survey on Drug Use and Health: National Findings.* Rockville, MD SAMHSA.
132. Paulozzi, L., Budnitz, D., Yongly, X. (2006). Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety. 15*:618-27.
133. Manchikanti, L., Helm, S., Janata, J. (2012). Opioid epidemic in the United States. *Pain Physician. 15*: ES9-ES38.
134. Jammal, W., & Gown, G. (2015). Opioid prescribing pitfalls: Medicolegal and regulatory issues. *Australian Prescriber. 38*(6):198.
135. Moulin, D., Amireh, R., Sharpe, W., Boyd, D., Merskey, H., Iezzi, A. (1996). Randomised trial of oral morphine for chronic non-cancer pain. *The Lancet. 347*: 143-146.
136. Ballantyne, J., & Shin, N. (2008). Efficacy of opioids for chronic pain: A review of the evidence. *The Clinical Journal of Pain. 24*(6):469-78.
137. Noble, M., Treadwell, J., Tregear, S., Coates, V., Wiffen, P., Akafomo, C., et al. (2010). Long-term opioid management for chronic noncancer pain (Review). Cochrane Database of Systematic Reviews. Art. No. CD006605.
138. Erikson, J., Sjogren, P., Bruera, E., Ekholm, O., Rasmussen, N. (2006). Critical issues on opioids in non-cancer pain: An epidemiological study. *Pain. 125*:172-9.
139. Häuser, W., Schug, S., Furlan, A. (2017). The opioid epidemic and national guidelines for opioid therapy for chronic noncancer pain: A perspective from different continents. *Pain Reports. 2*(3):e599.
140. Dowell, D., Haegerich, T., Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain-United States. *Journal of the American Medical Association. 315*(15):1624-45.
141. The Royal Australian College of General Practitioners. (2017). *Prescribing drugs of dependence in general practice, Part C2: The role of opioids in pain management.* Melbourne: The Royal Australian College of General Practitioners.
142. Faculty of Pain Medicine: Australian and New Zealand College of Anaesthetists. (2015). *Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain.* Melbourne: FPM, ANZCA.
143. Holliday, S., Hayes, C., Dunlop, A. (2013). Opioid use in chronic non-cancer pain: Part 1: Known knowns and known unknowns. *Australian Family Physician. 42*(3):98.

144. Holliday, S., Hayes, C., Dunlop, A. (2013). Opioid use in chronic non-cancer pain: Part 2: Prescribing issues and alternatives. *Australian Family Physician. 42*(3):104.
145. Machado, G., Maher, C., Ferreira, P., Pinheiro, M., Lin, C., Day, R., et al. (2015). Efficacy and safety of paracetamol for spinal pain and osteoarthritis: Systematic review and meta-analysis of randomised placebo controlled trials. *British Medical Journal. 350*:h1225.
146. Pharmaceutical Benefits Scheme. Opioid analgesics: Overview. (2014). Canberra: Australian Government Department of Health.
147. Royal Australian College of General Practitioners. (2015). *Prescribing drugs of dependence in general practice, Part A – Clinical governance framework. Melbourne*: RACGP.
148. Hunter Integrated Pain Service. (2013). *Opioid Treatment Agreement.* Newcastle: HIPS.
149. Faculty of Pain Management: Australian and New Zealand College of Anaesthetists (2014). *Opioid Dose Equivalence: Calculation of oral Morphine Equivalent Daily Dose (oMEDD).* Melbourne: FPM: ANZCAA.
150. Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. (2014). *National Guidelines for Medication-Assisted Treatment of Opioid Dependence.* Canberra: Australian Government Department of Health.
151. Nielsen, S., Cameron, J., Lee, N. (2011). Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: Implications for intervention and prevention. *Journal of Opioid Management. 7*(5):363-70.
152. McCoy, J., Nielsen, S., Bruno, R. (2015). *Detecting Codeine Dependence in Pharmacies: Development of a Screening Tool.* Hobart: University of Tasmania.
153. Manjiani, D., Paul, D., Kunnumpurath, S., Kaye, A., Vadivelu, N. (2014). Availability and utilization of opioids for pain management: Global issues. *The Ochsner Journal. 14*(2):208-15.
154. Pain management network: NSW Health. (ND). *5 As – Opioid therapy monitoring tool.* Sydney: PMN: NSW Health.

Appendix A: Example opioid treatment agreement (Hunter Integrated Pain Service)[148] available here.

OPIOID TREATMENT AGREEMENT

Oral or transdermal opioid use in non-cancer pain

This document provides information about opioid use as part of your pain management plan and seeks your written approval to proceed with the treatment.

Potential Benefits

1. Opioids (morphine-like substances) are more effective in the treatment of acute pain than chronic pain. While opioids can at times abolish acute pain, the expected reduction of chronic pain is only about 20% at the beginning of the treatment period.
2. Opioids can also at times improve other aspects of life including physical functioning and sleep.

Potential Problems

1. The benefits of opioids often become less over time. This is known as tolerance. Sometimes rotating to an alternative opioid can help to maintain pain reduction.
2. Side effects may include mental clouding, sedation, falls, driving impairment, constipation, nausea, itchiness, sweating, dry mouth, sleep and breathing problems and hormonal imbalance leading to weight gain, sexual dysfunction and/or osteoporosis. Sedative effects are more troublesome if opioids are combined with other drugs such as alcohol and benzodiazepines.
3. In some situations opioids can actually make pain worse. This is called opioid-induced hyperalgesia.
4. Dependence and addiction can be problems. Everyone on long-term opioids becomes physically dependent meaning that withdrawal symptoms occur if the treatment is stopped suddenly. Addictive behaviour occurs in a smaller proportion of people treated for ongoing pain.
5. Babies born to women on opioid therapy may require treatment for opioid withdrawal.

Practical Issues

1. Opioids are used as one part of a broad treatment package rather than as stand-alone therapy.
2. An initial opioid trial is undertaken to assess response before a decision is made on whether to begin a period of maintenance therapy. This decision will involve weighing up benefits and side effects.
3. One doctor only is responsible for prescribing your opioid medication. This is usually your general practitioner. Arrangements can be made for a deputy prescriber to cover medical absences. Using the same pharmacy on a regular basis is recommended.
4. If you are on maintenance treatment you will need to be reviewed by your doctor at least on a monthly basis.
5. Random urinary drug testing is commonly used as part of an opioid maintenance program.
6. When on maintenance treatment your doctor can in some situations get an authority from Medicare/ Pharmaceutical Benefits Scheme to prescribe up to one month's

medication at a time rather than the usual 14 day prescription. Additional authorisation from Pharmaceutical Services Branch in NSW (or similar authorities in other states) may be required in some cases.

7. The general policy in regard to opioid therapy is not to give early prescriptions and not to replace lost prescriptions or medication. Therefore, if you run out of medication early you may develop a withdrawal state. Although this is uncomfortable it is not life threatening.
8. If your behaviour suggests a problem with drug misuse or addiction then your doctor will consider tapering and ceasing the opioid medication or referral to a Drug and Alcohol service. Problem behaviours include giving your medication to others, use of your medication in a non-prescribed way, excessive use of other medications (including alcohol), repeated "loss" of medication, doctor shopping and worsening function at home or work.

My goals for opioid treatment are:

1. Reduction in my average pain score:

   i. At rest from __ / 10 to __ / 10
   ii. On exertion from __ /10 to __ / 10

2. Improvement in the following day-to-day activities

   i. _____
   ii. _____

3. Improved performance of the following exercises

   i. _____
   ii. _____

4. Other

   i. _____
   ii. _____

The planned duration of opioid treatment is _____

During the period of opioid treatment I would like to explore active management options through consultation with the following health professionals:

1. General Practitioner □
2. Physiotherapist □
3. Exercise physiologist □
4. Psychologist □
5. Other □

Agreement I have read the information provided and agree to a period of opioid treatment as part of my pain management plan.

Signature: _____

Witness: _____ Date: _____

Appendix B: The 5 As – Opioid therapy monitoring tool[154]

Once initiating opioid therapy, it should be monitored regularly by assessing what has been called the "5As" of Analgesia therapy. This monitoring tool, will assist you in adapting the treatment and management plan of your patient by evaluating whether the patient has a reduction in pain (Analgesia), has demonstrated an improvement in level of function (Activity), is experiencing significant Adverse effects, whether there is evidence of Aberrant substance-related behaviours, and mood of the individual (Affect).

1. Activity

What progress has been made in the patient's functional goals?

- Sitting tolerance
- Standing tolerance
- Walking ability
- Ability to perform activities of daily living

2. Analgesia

How does the patient rate the following over the last 24 hours? (e.g., on a scale from 0 to 10, where 0 = no pain, 10 = worst pain imaginable)

- Average pain?
- Worst pain?
- How much relief have pain medications provided? e.g. 10%, 20%, 30% or more?

3. Adverse effects

- Has the patient experienced any adverse effects from medication? (e.g. constipation, nausea, dizziness, drowsiness)

4. Aberrant behaviours

- Has the patient been taking medication/s as prescribed?
- Has the patient exhibited any signs of problematic behaviours or medication abuse/misuse?
- Signs of drug and alcohol use
- Unsanctioned dose escalations
- Has the patient reported lost prescriptions or requested early repeats?

5. Affect

- Have there been any changes to the way the patient has been feeling?
- Is pain impacting on the patient's mood?
- Is the patient depressed or anxious?

Contact Us
For more information about NCETA's research

visit or contact:

W: nceta.flinders.edu.au

E: nceta@flinders.edu.au

P: 08 8201 7535

NCETA
Australia's National Research Centre on AOD Workforce Development