A GUIDE TO

deprescribing

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OPIOIDS

KEY POINTS

- **Opioid therapy is not indicated for the long-term management of chronic non-cancer pain.**
- **Opioid treatment of chronic non-cancer pain does not seem to fulfil any of the key opioid treatment goals: pain relief, improved quality of life and improved functional capacity.**
- **Opioids are playing a diminishing role in the modern management of chronic pain.**
- **Multidisciplinary pain management programs utilising psychology, exercise and functional-based outcomes result in better quality of life and better pain management than use of opioids.**
- **Tolerance to the analgesic effects of opioids develops in almost all people with long term use.**
- **Long term opioid use is associated with serious adverse hormonal and psychological effects and increased mortality.**
- **Concurrent benzodiazepine use confers a higher risk of death from drug overdose with opioids.**
- **People with chronic non-cancer pain taking 120 oral morphine milligram equivalents or more should have their opioids decreased.**
- **An app to assist in opioid conversion prepared by the ANZCA – is available online: Opioid Calculator FPM ANZCA**
- **Patient education is essential to successfully taper opioids.**
- **Consumer resources are also available from the Hunter Integrated Pain Service www.hnehealth.nsw.gov.au/pain/**

CONTEXT

This guide considers the use of opioid medications in the treatment of chronic non-cancer pain.

RECOMMENDED DEPRESCRIBING STRATEGY

Deprescribing or tapering of opioids is more likely to be successful when the person is aware of the issues with long term opioid use.

A number of consumer resources are available to assist with management of chronic pain. A good quality Australian resource is available through the Hunter Integrated Pain Service at www.hnehealth.nsw.gov.au/pain/.

There are multiple sections written for consumers on understanding chronic pain, and understanding five key treatment areas: Biomedical, Mindbody, Connection, Activity and Nutrition.

People with chronic non-cancer pain taking long term oral morphine milligram equivalent of:

- 120mg or more daily should be considered for opioid deprescribing. This will usually include dose reduction with or without opioid rotation accompanied by appropriate education and information.
- 50mg or more daily should also be considered for opioid tapering, depending on individual circumstances (adverse effects, efficacy, risk of falls, etc).

People with chronic non cancer pain taking any dose of opioids should be closely monitored and those whose pain control is stable may be considered for dose reduction or cessation of opioids.

BACKGROUND

Opioids are commonly used to treat acute and malignant pain and can be used in palliative care and in the treatment of opioid addiction. This deprescribing guide applies to the use of opioids in chronic non-cancer pain.

Over the last couple of decades, opioids have increasingly been used in the management of persistent pain. **Opioid therapy is not indicated for the long-term management of chronic non-cancer pain based on current evidence**. The limited evidence supporting long term efficacy is weak and based on non-blinded, industry-sponsored trials with significant potential for reporting bias. This is outweighed by a consistent body of evidence demonstrating lack of long term analgesic efficacy, lack of improvement in function or quality of life and greater risk of harm to both individuals and society than previously recognised.[1]

Significant increases in the use of opioid medications for persistent pain have been accompanied by increases in opioid overdoses, abuse, addiction and diversion, as well as uncertainty about long-term efficacy.[2,3,4,5]

Opioids are playing a diminishing role in the management of chronic pain. Multidisciplinary pain management programs utilising psychology, exercise and functional-based outcomes result in better quality of life and better pain management than use of opioids.

Between 1992 and 2012, there was a 15 fold increase in opioid prescriptions from ~0.5M to 7.5M (see **Figure 1**).[6]

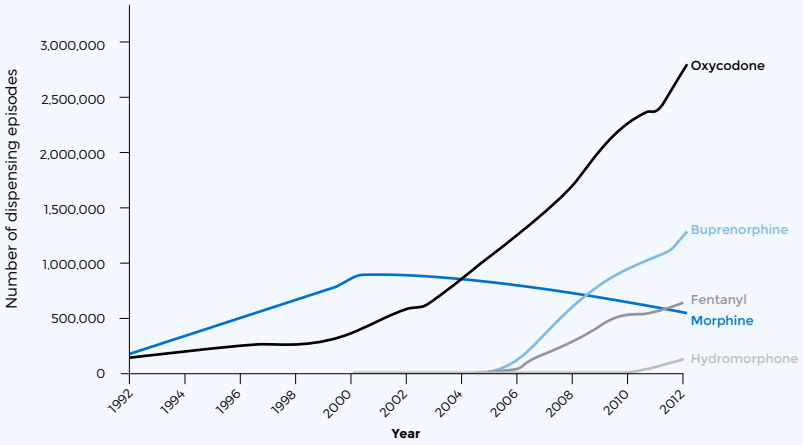


Figure 1: Opioid use in Australia 1992-2012[6]

EFFICACY

In chronic non-cancer pain, systematic reviews of RCTs demonstrate modest, **short-term** analgesic benefit.[7,8] However these research findings cannot be extrapolated into clinical practice given the short duration of therapy (average trial duration 5 weeks, range 1-16 weeks). Tolerance and opioid-induced hyperalgesia are major limiting factors in regard to longer term use.

SYSTEMATIC REVIEW

A systematic review of opioid response after 6 months of therapy in 25 non-randomised case series shows weak evidence of modest analgesic benefit and inconclusive data in regard to improvement in physical function and quality of life.[9] A Cochrane review in 2014 examined the evidence relating to opioids for osteoarthritis pain. Opioids were more beneficial in pain reduction than control interventions (the difference in pain scores was only 0.7 cm on a 10-cm visual analogue scale). Improvement of function with opioids was also only minimal (a difference in function scores of only 0.6 units on a disability scale from 0 to 10). Against these modest benefits, side effects for opioids were more common (22% vs 15%; NNH=14).[9]

OTHER ANALYSES

Other analyses of long-term opioid studies have confirmed the limited efficacy, high rate of side-effects and frequent withdrawal from studies. A review of 26 studies of long term opioid use in chronic non-cancer pain found only weak evidence that pain scores were lowered (change in pain scores of 1.55; 95% CI 0.85-2.25) and a high level of withdrawal due to adverse effects (22.9%) or lack of efficacy (10.3%)[10,11,12]

Chou et al recently reviewed all literature available 4209 papers in order to evaluate evidence for effectiveness and harms of long term (greater than 3 months) opioid therapy for chronic pain in adults.[13] Despite this extensive search, they were unable to find any studies that evaluated long-term outcomes of opioid use in relation to pain, function or quality of life.[13] These authors support the view of a previous update of a Cochrane review of the use of opioids for chronic low back pain, which concluded, **"We have no information from randomized trials supporting the efficacy and safety of opioids used for more than 4 months."**[14]

A position paper from the American Academy of Neurology further supports the limited evidence in long-term settings and states that the risks of chronic opioid therapy for some chronic conditions such as low back pain,[15] headache and fibromyalgia are likely to outweigh the benefit.[16]

REAL WORLD OUTCOMES

Long-term opioids are often associated with loss of efficacy and overall worse outcomes, often due to the development of tolerance.[17] A Danish "real world" population study compared 228 patients with chronic pain that were using opioids to 1678 patients with chronic pain using non-opioid therapy.[17] They found that opioid use was significantly associated with:

- higher level of reports of moderate, severe or very severe pain (~8 fold higher)
- more self-rated reports of poor health (~5 fold higher)
- a higher likelihood of not being engaged in employment (68% unemployed vs 45%)
- a higher use of the health care system (~2.5 fold more use)
- lower quality of life scores in all 8 domains of the Short Form 36 quality of life survey (more bodily pain, less general health, worse mental health, lower physical function, lower emotional, physical and social function and lower vitality)

While a causative relationship could not be ascertained, they concluded, "however, it is remarkable that opioid treatment of long term/chronic non-cancer pain does not seem to fulfil any of the key opioid treatment goals: pain relief, improved quality of life and improved functional capacity."[17]

DOSE OF OPIOID AND EFFICACY

The impact of increasing or decreasing dose of opioids as part of overall management within a tertiary pain service was evaluated by noting the impact of change in opioid dose on pain scores in 109 patients with chronic non-cancer pain over an average of 704 days.[18] Thirty-six subjects (33%) experienced an overall dose decrease in their opioid which ranged from –6.3% to –100% (tapered off). Of these, 18 (50%) subjects reported a decrease in their pain score, 10 (27.8%) subjects reported an increase in their pain score and 8 (22%) reported no change in their pain score. Similarly, of patients who had a dose increase, 49% reported a decrease in their pain score, 30% reported an increase in their pain score and 20% no change (see **Figure 2**).

This study suggests that patients are as likely to have improved pain scores with a dose decrease as with a dose increase of opioids.

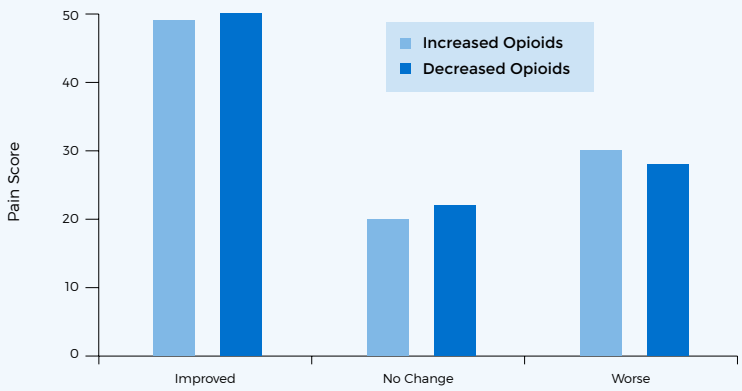


Figure 2: Impact of increased or decreased opioid dose on pain scores (percentage of patients)[18] (Adapted)

TOLERANCE

Opioid tolerance – a need for increased doses to achieve the desired effect – has been demonstrated in animal models and is seen in humans in both short term and long-term studies of opioids in humans.[19,20,21,22] In a prescription database study of six years of data from Norway, dose increases of 50% or more were reported in 35% of opioid users.[23] A similar insurance database study in the USA found that over 50% of patients who took opioids for 90 days were still taking them 3-5 years later.[24] Factors strongly associated with continuation of opioids were intermittent prior opioid exposure, daily opioid dose over 120 oral morphine milligram equivalents and possible opioid misuse.

There is only limited cross-tolerance between opioids as a result of differing characteristics and responses of opioid receptors.[25] As a result, rotation of opioids, to a net lower dose, can be a useful strategy for improving analgesia.[26]

OPIOID-INDUCED HYPERALGESIA

Excessive opioid exposure may also produce a paradoxical increase in pain sensitivity manifested as hyperalgesia (exacerbated painful response to noxious stimulation) and/or allodynia (painful response to non-noxious stimulation).[27] This opioid-induced hyperalgesia has been demonstrated in both short term and long-term use of opioids.[28,29] The mechanism of this effect is still being elucidated, but central pain sensitisation, NMDA receptor activity and spinal dynorphin release have all been implicated as factors.[30]

Opioid-induced hyperalgesia should be suspected when the treatment effect wanes in the absence of disease progression, particularly in the context of unexplained or increased pain. Opioid dose reduction, opioid rotation and NMDA receptor modulators are suggested treatments.[28,31]

ADVERSE EFFECTS

PRESCRIPTION OPIOID USE AND MORTALITY

An overall trend of increasing deaths from prescription opioid use and a decrease in deaths from illicit drug use has been noted in the past several years.[5] Opioid overdose deaths in the United States from 2000-2014 were reviewed recently.[32] They found an alarming increase in deaths due to opioids with illicit heroin use and licit prescription opioid use being the biggest drivers of drug overdose. There were ~ 4000 opioid related deaths per month in 2014 in the USA. [32]

In the 11 years from 2001 to 2011 there were 806 oxycodone-related deaths in Australia, of which 40% were people taking legitimate prescriptions for oxycodone as directed. It is interesting to note that there was a greater than a five fold increase in defined daily dose of oxycodone in the 11 year period. There is a close correlation between the average daily dose of oxycodone used and oxycodone-related deaths (see **Figure 3**).[4]

CAUTION WITH BENZODIAZEPINES

Most often, the deaths were caused by combinations of agents (often other centrally acting agents involved) and the deaths were not intentional.[4] The most commonly co-administered drugs were benzodiazepines, alcohol and other opioids. Coadministration of benzodiazepines, in particular, increases the risk of overdose mortality.[33] A history of benzodiazepine use more than doubled risk of mortality and current benzodiazepine use increased death from drug overdose almost four fold (see **Figure 4**).[33]

OPIOID DEPENDENCE, MISUSE AND ADDICTION

Prolonged use of opioids leads to many patients developing dependence, whereupon cessation causes an unpleasant withdrawal syndrome, which may include both physical and psychological features.

Physical features include agitation, insomnia, diarrhoea, rhinorrhoea, piloerection and hyperalgesia while psychological features may include anhedonia, dysphoria and craving.[34] Opioid dependence may emerge at different times for different patients and withdrawal symptoms may occur if cessation is sudden.

Problem use of prescription opioids ranges from overuse (occasionally using more than prescribed), to misuse (use that is potentially harmful or dangerous), to opioid use disorder (or addiction). Addiction is characterized by repeated compulsive drug seeking (psychological dependence) and continued use despite adverse social, psychological, or physical consequences. Physical dependence can occur in patients receiving long term opioids with or without an opioid use disorder.

Figure 3: Oxycodone related deaths in Australia[4]

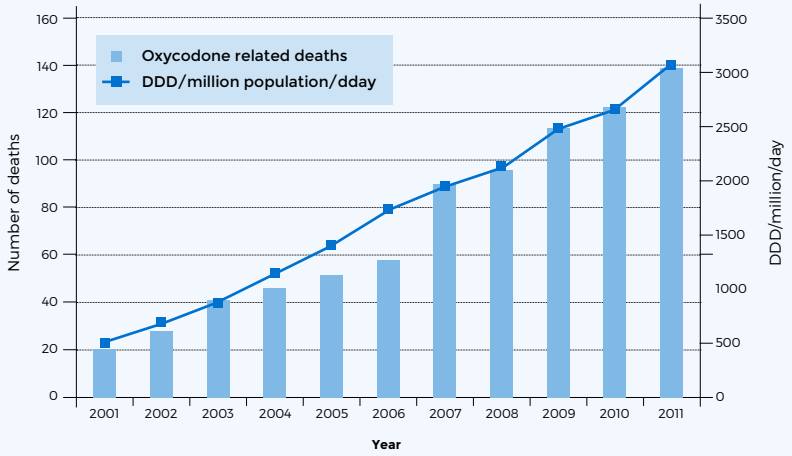


Figure 4: Death rates for drug overdose by benzodiazepine prescription history and daily opioid dose.

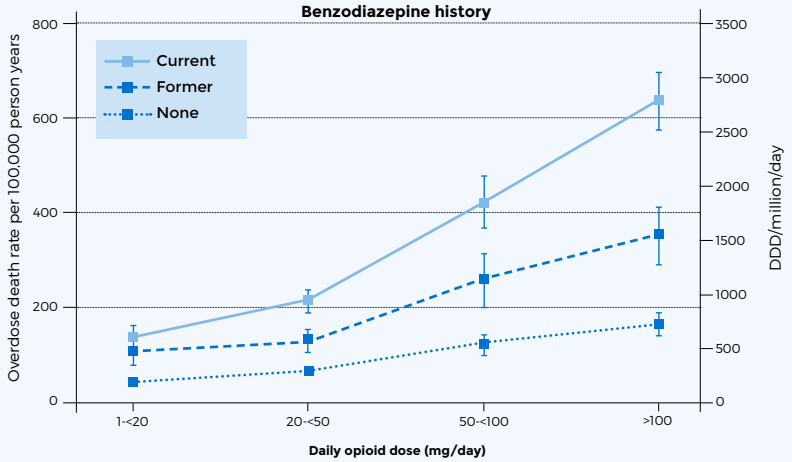
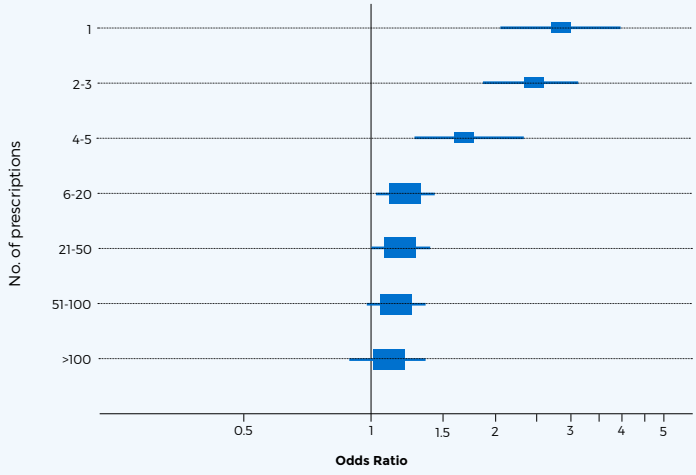


Figure 5: Hip fracture risk and number of opioid prescriptions [38]



In a primary care study of 801 patients in Canada who took opioids daily for the last 3 months, aberrant behaviour was common. The proportion of requests for early prescriptions was 47% overall, patients reporting lost or stolen medication was 33% overall and patients who increased the dose of medication without referral to their doctor was 39%.[35]

FALLS AND FRACTURE RISK

A number of adverse opioid effects, such as sedation and dizziness, can increase the propensity to falls due to central nervous system effects. Opioids may also decrease bone mineral density by impairing the production of endogenous sex steroids, and the effect on bone metabolism may directly weaken bone structure.[36] As elderly persons are at increased risk of developing osteoporosis and pain, the opioids used to treat pain in this population may increase the risk of subsequent fractures.

A recent meta analysis of eight studies found that opioids increase the risk of overall fractures by 88% and of hip fractures by 100%.[37]

The evidence indicates that an initial prescription for opioids increases the risk of fracture more so than longer term use. In a population study in the United Kingdom, patients with their first opioid prescription had a higher hip fracture risk than patients who had multiple prescriptions (see **Figure 5** page 4).[38]

ENDOCRINE/HORMONAL ADVERSE EFFECTS

Opioids may affect the hypothalamic-pituitary-adrenal axis, and lead to opioid induced androgen deficiency (OPIAD) with reduced testosterone production. This may lead to osteoporosis and immune suppression in men, with recent data suggesting that up to five million men have OPIAD in the USA.[39] Among men with back pain, on a daily dose of at least 120 oral morphine milligram equivalents long term, 19% used drugs for erectile dysfunction or testosterone replacement compared to only 7% of patients with pain but no opioids.[40]

Chronic opioid use can lead to amenorrhea or oligomenorrhea in premenopausal women due to a reduction in both testosterone and estradiol.[41]

LESS SERIOUS ADVERSE EFFECTS

Opioids are associated with a number of common, short-term, constitutional side effects, of which most cause no permanent harm and some improve with time (see **Table 1**).[15] An exception is constipation, which often requires management for the duration of opioid therapy.

ADVERSE EFFECT	FREQUENCY WITH OPIOID (%)	FREQUENCY WITH PLACEBO (%)	RELATIVE RISK
Constipation	41	11	3.6
Nausea	32	12	2.7
Sedation	29	10	3.3
Vomiting	15	3	6.1
Dizziness	20	7	2.8
Itching	15	7	2.2
Dry Mouth	13	9	1.5
Discontinuation of treatment (any reason)	24	15	1.4
Any adverse effect	80	56	1.4

Table 1: Common short term side effects of opioids[15]

FACTORS TO CONSIDER

A number of studies have shown that opioid tapering can result in improvements in pain management and a reduction in adverse effects.[24, 42, 43, 44, 45, 46] These studies suggest that many patients with persistent pain can achieve favourable pain and function outcomes after stopping or reducing opioids in multidisciplinary interventions.

The Center for Disease Control in the USA has released guidelines for prescribing opioids for chronic pain.[47, 48, 49, 50] One of their recommendations is that additional precautions should be implemented when dosage is increased to more than 50 oral morphine milligram equivalents (oMME), and that doses above 90 morphine milligram equivalents should be avoided.[47] The Hunter Integrated Pain Service in Australia recommends an opioid dose limit of 100 oMME.[1] The Faculty of Pain Medicine of the Australian New Zealand College of Anaesthetists has released recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain.[51] A phone or device-based application is also available to assist in opioid conversion that has been prepared by the ANZCA (Opioid Calculator FPM ANZCA).[52]

The tables below show the approximate morphine milligram equivalents of some common opioids and the doses that match the doses identified in the ANZCA opioid conversion application for caution (orange) and avoidance (red).[52]

CAUTION WITH OPIOID ROTATION

Opioid rotation (switching to a different opioid) can be used to limit the impact of tolerance and to manage adverse effects. However the main role of rotation is to lower the total opioid dose to facilitate tapering and cessation. A dose reduction of 25-50% of calculated equianalgesic dose is usually required. Opioid tolerance increases with duration of patient exposure to the opioid. Sustained high dose opioid use is usually associated with significant tolerance to the effects of that opioid. Conversion to an alternative opioid requires a greater level of dose reduction to account for this established tolerance.

IN FAVOUR OF DEPRESCRIBING

- Opioids are playing a diminishing role in the management of chronic pain. Multidisciplinary pain management programs utilising psychology, exercise and functional-based outcomes result in better quality of life than use of opioids. As such, many patients taking long term (greater than 6 months) opioid therapy for non-cancer chronic pain may be considered for dose reduction and/or cessation.

- The following factors may be an indication for opioid dose tapering or cessation:
  - Patients with a lack of demonstrable clinical effectiveness
  - The existence of severe unmanageable adverse effects
  - Patients who are stable and have a decreased level of pain
  - Evidence of misuse, illegal or unsafe behaviours

If patients have a desire to discontinue their opioid therapy, then support and education will assist in achieving this goal.

AGAINST DEPRESCRIBING

- Patients who require analgesia for serious acute pain (e.g. fractures) may require short term opioid therapy for several weeks.

- Opioid therapy can usually be ceased within one week of surgery or injury. In more complex cases, opioids should be weaned and ceased within 90 days, at most.[1]

MEDICATION	EXAMPLE OF A TYPICAL DOSE	ORAL MORPHINE MILLIGRAM EQUIVALENTS
Codeine oral	30mg	4
Oxycodone oral	10mg	15
Morphine oral	10mg	10
Norspan transdermal	5mcg/hr	10/day
Fentanyl transdermal	12mcg/hr	36/day
Hydromorphone oral	8mg	40

Table 2: oral Morphine Milligram Equivalents of common opioids.[52]

MEDICATION	APPROXIMATE DOSE FOR CONCERN (50 OMME)	APPROXIMATE DOSE TO BE AVOIDED (120 OMME)
Codeine oral	320mg/day	Not applicable
Oxycodone oral	30mg/day	80mg/day
Morphine oral	50mg/day	120mg/day
Norspan transdermal	25mcg/hour	60mcg/hr
Fentanyl transdermal	25mcg/hour	37mcg/hr
Hydromorphone oral	10mg/day	24mg/day

Table 3: oral Morphine Milligram Equivalents of doses for caution and avoidance for common opioids.[52]

DISCONTINUATION SYNDROMES

Patient education is essential to successfully taper opioids. Clear written and verbal instructions should be provided to patients and families to educate them about the tapering protocol that will minimise withdrawal symptoms.

Opioid withdrawal can develop within hours of drug cessation. While the effects of withdrawal are unlikely to be life threatening in patients without significant comorbidities, it can be quite uncomfortable. Signs and symptoms of withdrawal may include:

- gastrointestinal symptoms (e.g., abdominal cramping, nausea, vomiting, diarrhoea)
- musculoskeletal symptoms (e.g., myalgias, arthralgias, muscle spasms)
- anorexia, yawning, lacrimation, salivation, rhinorrhea, piloerection, insomnia, anxiety, irritability, dysphoria
- manifestations of sympathetic hyperactivity such as diaphoresis, tachycardia, fever, mydriasis or mildly elevated blood pressures
- In people who have significant comorbidities, withdrawal should be medically managed.

TAPERING STRATEGIES

The rate of tapering is dependent on the clinical context, considering the duration of treatment and the reason for tapering. The aim is to limit withdrawal symptoms and avoid escalation of patient distress.

LONG TERM TREATMENT WITHOUT CLEAR BENEFIT

In situations where long term opioid therapy has been maintained (at times for many years) without meaningful improvement in function, the desired outcome is weaning to cessation if possible. One practical strategy is to reduce the daily opioid dose each month by 10-25% of the starting dose. This brings cessation in 3-9 months.

END OF AGREED TRIAL OR FAILURE OF TREATMENT

If weaning is required after a shorter period of opioid therapy, such as after failure to achieve the goals of an opioid trial, or after a negotiated treatment phase for acute pain, then a faster rate of weaning is generally appropriate. One option is a step-wise reduction of the daily opioid dose each week by 10-25% of the starting dose.

SIGNIFICANT ADVERSE EFFECTS

If weaning is required in response to significant adverse effects or opioid misuse, then daily step-wise reduction may be more appropriate. Alternatively, immediate opioid cessation and pharmacological treatment of withdrawal symptoms can be considered.

PREVIOUS FAILED ATTEMPTS AT TAPERING

If a previous attempt at opioid weaning has proven unsuccessful, then the rate may be slowed. This can be achieved by reducing the size of the dose reduction each month and/or by increasing the time spent at each dose level (e.g.. 2 or 3 months between reductions).

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RESOURCES

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- ANTIHYPERTENSIVES
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- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was prepared by Dr Peter Tenni and Dr Chris Orlikowski in consultation with the Deprescribing Clinical Reference Group. Some information has been adapted from the Hunter Integrated Pain Service, with permission of Dr Chris Hayes.

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