Reconsidering Opioid Therapy

A Hunter New England Perspective

Existing evidence does not support the long term efficacy and safety of opioid therapy for chronic non-cancer pain

1. **Indications:** Current evidence based indications for opioid therapy are:
    i. Acute pain
    ii. Cancer pain
    iii. Palliative or "comfort" care
    iv. Opioid dependency / addiction

    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.

    It is possible that future research may define specific conditions or population cohorts that show sustained opioid responsiveness. In the meantime, if opioid therapy is to be used experimentally in conditions where evidence is lacking (eg. refractory neuropathic pain states such as trigeminal neuralgia or brachial plexopathy) it is recommended that a pain medicine specialist is involved.

2. **Efficacy:** The efficacy of opioids is supported by strong evidence from randomised controlled trials (RCTs) in acute pain[1] and from systematic reviews in cancer pain[2,3], palliative care[4] and dependency/addiction[5]. In chronic non-cancer pain systematic reviews of RCTs demonstrate modest, short-term analgesic benefit[6,7]. The degree of benefit is similar in neuropathic pain to other types of chronic non-cancer pain[6,8]. 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[6]). Tolerance and opioid-induced hyperalgesia are major limiting factors in regard to longer term use[9,10]. 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[11]. Population studies show that patients on long term opioid therapy describe relatively more troublesome pain and functional interference[12]. A recent dose response study shows a complete lack of correlation between marked increases or decreases in opioid dose and change in chronic non-cancer pain intensity[13].

3. **Harm:** There is growing evidence of harm from long term opioid use. The problems of constipation, biliary dyskinesia and cognitive impairment are well known. Additional adverse effects include increased risk of death[14,15], sleep apnoea[16,17,18], sexual and other endocrine dysfunction[19,20], immunosuppression[21], opioid induced hyperalgesia[22,23], driving impairment[24-27], opioid use to manage psychological distress (the "chemical coper")[28], misuse, addiction and diversion[29]. Patients with mental health and substance abuse problems are more likely to receive chronic opioid therapy (adverse selection) and at higher doses than people without those risk factors[30]. Opioid dependence makes it hard to wean and cease established opioids despite lack of

analgesic benefit[31]. The use of over-the-counter opioids such as codeine also has questionable benefit and significant risk of harm[32]. A focus on opioid therapy can distract both patient and prescriber from the evidence based active management strategies which demonstrate sustained long term pain reduction.

4. **Pain Assessment:**
    i. **General:** Multidimensional assessment is recommended for all types of pain. This leads to a broad, whole person management approach[33].
    ii. **Opioid risk:** The Opioid Risk Tool can be used to quantify the likelihood of opioid misuse. Contact with the Australian Prescription Shopping Information Service (1800 631181) is recommended and a real time "Electronic Recording and Reporting of Controlled Drugs" system is awaited.

5. **Opioid therapy for acute pain:** When opioids are used for acute pain (eg. post operative or post trauma pain) the time limited nature of treatment needs to be clearly stated.
    i. Case discussion and co-ordination between hospital and primary care is recommended if early treatment occurs in hospital.
    ii. Opioid therapy can usually be ceased within 1 week of surgery or injury. In more complex cases opioids should be weaned and ceased within **90 days** at most.
    iii. A daily oral morphine equivalent dose of **100mg** should not be exceeded in primary care (Table1).
    iv. A treatment agreement (verbal or written) can be used to explain potential benefits, adverse effects and therapeutic boundaries. Such therapeutic boundaries include; no early prescriptions; no replacement of lost prescriptions or medications; single prescriber with deputy; regular pharmacy; possible random urine drug testing. The evidence for treatment agreements preventing misuse is relatively weak[34].
    v. Review of therapy incorporates the 4 A's: **A**nalgesia, **A**ctivity, **A**dverse effects, **A**berrant behaviour. A focus on graded functional improvement is recommended.
    vi. Standardised measurement of pain and functional outcomes can be used (eg. Brief Pain Inventory or the ultra-brief PEG[35]).
    vii. The opioid should be weaned and ceased at completion of the agreed treatment period or earlier if there are insufficient gains or excessive adverse effects.
    viii. Any proposed variation of these recommendations should be discussed with a pain medicine or addiction specialist.

6. **Opioid therapy for cancer pain:** Opioid therapy has an established place in the treatment of pain associated with active cancer. A daily oral morphine equivalent dose of **300mg** should not be exceeded unless discussed with a palliative care, pain medicine or cancer specialist. If cancer therapy is successful and remission occurs then reduction in opioid dose and limitation of duration of therapy is recommended. A cancer diagnosis does not preclude direct or indirect opioid-related harms and appropriate opioid prescribing boundaries are still required.

7. **Opioids for palliation or comfort care:** This approach involves acceptance of the patient's limited prognosis in a situation where there is no curative treatment available and little prospect of functional recovery. The primary aim is simply to reduce suffering. When opioids are used in this context a priority is given to reducing distress rather than improvement in physical and cognitive function. In an elderly and/or frail cohort the increased risk of falls and cognitive impairment are of particular concern and the balance of benefit and harm needs careful consideration. In some cases opioid use may shorten life expectancy. A daily oral morphine equivalent dose of **100mg** for non-cancer pain or

300mg for cancer related pain should not be exceeded unless discussed with an appropriate specialist.

8. **Opioid therapy for dependency / addiction:** Opioid Substitution Therapy incorporates tight therapeutic boundaries including daily pickups, observed medication taking and urinary drug screening. These are appropriate where there are concerns about opioid misuse. Opioid dose and duration of therapy are guided by a doctor with training in addiction medicine. The general practitioner remains pivotal to whole person care in treating opioid dependency[36]. Although opioid cessation and abstinence is a desirable alternative to maintenance therapy[37] there is an inherent risk of destabilising the patient.

9. **Redirecting opioid therapy for chronic non-cancer pain:** Across the developed world it has been common practice to maintain patients with chronic non-cancer pain on long term opioids despite lack of supporting evidence. In part this was a consequence of overly optimistic or conflicted extrapolation of evidence from acute pain management or palliative care. The chronic pain evidence base has become clearer in recent years and a change in therapeutic direction is now required. The following steps are recommended to redirect the management of patients on long term opioids for chronic non-cancer pain:
    i. Patient education regarding the potential harms and limited benefits of long term opioid therapy.
    ii. The medical intention to work toward opioid cessation is declared along with a willingness to provide ongoing non-pharmacological supportive care.
    iii. A time frame to cessation is negotiated. Speed of opioid weaning depends on clinical context. The aim is to limit withdrawal symptoms and avoid escalation of patient distress whilst maintaining appropriate prescribing boundaries. With chronic opioid therapy a typical plan reduces the opioid by 10-25% of the starting dose each month. This achieves cessation in 3-9 months.
    iv. Shift the focus to evidence based active self-management management strategies (see www.hnehealth.nsw.gov.au/pain /Community resources).
    v. The involvement of a pain medicine specialist and multidisciplinary pain management team may be helpful.

    Additional steps that may be helpful in certain situations include the use of a treatment agreement (as discussed in the Acute Pain section above) and testing for opioid induced hypopituitarism (serum testosterone, TSH, serum prolactin and fasting morning serum cortisol). Any evidence of hypopituitarism strengthens the case for dose reduction.

10. **Opioid rotation:** Opioid rotation[38] 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 weaning and cessation. A typical rotation involves changing to a new opioid at approximately 50% of the equivalent dose.

11. **Driving:** The majority of studies of driving performance show no significant psychomotor or cognitive impairment in patients on stable long-term opioid therapy for non-cancer pain. However the combination of long term opioid use with benzodiazepines or other psychoactive medication can produce significant driving impairment[24-27]. In addition the use of any opioids by opioid naïve patients is likely to cause impairment. The following recommendations aim to reduce the risk of driving related harm:
    i. Opioid naïve patients should not drive if exposed to opioids.
    ii. Patients on stable long term opioids are unlikely to be significantly impaired in driving performance. However this cannot be medically guaranteed and assessment in a driving simulator and/or via on-road driving tests is recommended to exclude impairment.
    iii. Patients on long term opioids and benzodiazepines should not drive. If either agent is ceased the person is safe to drive after one week.

iv. Patients on both long and short acting opioids should not drive for 6 hours after a supplementary short acting dose.
v. Patients on long term opioids should not drive for one week after a dose increase.
vi. Patients on long term opioids should not drive if they feel sedated for any reason eg. sleep deprivation or the use of additional drugs including alcohol or cannabinoids.

Table 1. Recommended opioid dose limits for non-cancer pain

Drug	Maximum dose	Prescribing examples
Morphine	100mg oral daily	Kapanol or MS Contin 50mg twice daily
Oxycodone	60mg oral daily	Oxycontin 30mg twice daily
Methadone	30mg oral daily	Physeptone 15mg (1.5 tablets) twice daily or 10mg (1 tablet) three times daily
Hydromorphone	20mg oral daily	Jurnista 20mg (16+4mg tablets) daily
Buprenorprhine	40mcg/hr transdermal	Norspan 20mcg/hr patches x2
Fentanyl	37mcg/hr transdermal	Durogesic 25mcg/hr + 12 mcg/hr patch

Note Determination of equianalgesic doses is inexact. Doses listed are considered approximately equivalent in the context of limiting dose escalation.

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