



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Chronic pain: patient outcomes with dose reduction or discontinuation of long-term opioid therapy

A systematic review investigated the effect on patient outcomes of strategies to reduce or discontinue long-term opioid therapy in people with chronic pain. While the studies included in the review were generally low quality there was some evidence that several types of intervention may be effective at reducing or discontinuing long-term opioid therapy and that pain, function and quality of life may actually improve with opioid dose reduction. The findings are consistent with the [Opioids Aware](#) resource and the NICE key therapeutic topic: [medicines optimisation in long-term pain](#), advising that there is only limited evidence that opioids are helpful in chronic pain and that individualisation of treatment is key.

Overview and current advice

Chronic pain is defined as pain lasting for more than 3 months. Chronic pain can affect people of all ages, but is more common in older people and is estimated to affect around 13% of adults in the UK, although this varies depending on the criteria and definitions used (British Medical Association [BMA]: [Chronic pain: supporting safer prescribing of analgesics](#)).

The management of patients with chronic pain can present significant challenges. The potential harms associated with prescription analgesics has prompted renewed efforts to assess the role of medicines, and opioids in particular, in pain management. It is important that people receive appropriate treatment for their pain with careful consideration of the benefits and risks of their treatment options.

Opioids can be effective analgesics for acute pain and for pain at the end of life but there is limited evidence at a population level that they are helpful for chronic pain. The [Opioids Aware](#) resource published by the Faculty of Pain Medicine states that opioids are generally less effective for chronic pain than for other types of pain and that they should be prescribed as a therapeutic trial, with outcomes of treatment agreed with the patient and reviewed regularly.

The NICE key therapeutic topic on [medicines optimisation in long-term pain](#) brings together the evidence base, resources and safety alerts relating to long-term opioid use. The NICE pathways on [controlled drugs](#), [neuropathic pain](#) and [low back pain and sciatica](#) bring together all related NICE guidelines and associated products on pain in a set of interactive topic based diagrams.

New evidence

A [systematic review](#) of 11 [randomised control trials](#) (RCTs) and 56 [observational studies](#), investigated the effectiveness of strategies to reduce or discontinue long-term opioid therapy and the effect on patient-oriented outcomes ([Frank et al. 2017](#)).

The analysis presented data on 12,546 adult participants (18 years or older) who were prescribed long-term opioid therapy for chronic pain (defined as pain lasting more than 3 months) from studies that reported on at least 1 of the questions of interest. Sample sizes ranged from 5 to 1,457. In the 61 studies that reported mean age of the participants, the mean age ranged from 23 to 67 years.

Database searches (MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane library) were conducted for studies published up to April 2017. Eligible studies for inclusion were RCTs, [cohort studies](#), [case-control studies](#) and [case series](#). Lower levels of evidence such as [case reports](#), [cross-sectional studies](#) as well as studies that did not describe the clinical intervention or report patient-level data, were excluded. The key questions for investigation were the effectiveness of strategies to reduce or discontinue long-term opioid therapy as well as the effect of dose reduction or discontinuation of opioid therapy on patient outcomes. In order to compare the studies, the authors converted opioid doses into oral morphine equivalent doses using a standardised [method](#). The mean daily dose ranged from 29 to 556 mg oral morphine equivalent doses. Patient outcomes included were: pain severity, pain related function, quality of life, opioid withdrawal symptoms, substance use, and adverse events.

The final sample of included studies published between 1980 and 2017, and were conducted across 9 countries, although 49 of the 67 studies were conducted in the USA. The authors assessed the quality of the evidence using the [GRADE](#) approach. This systematic review identified 67 studies of very low quality evidence assessing the effectiveness of strategies to reduce or discontinue long-term opioid therapy. Meta-analysis was not carried out due to heterogeneity between the studies.

All 67 studies explored the effectiveness of opioid reduction or discontinuation programmes and 40 studies explored the effect of dose reduction or discontinuation on patient outcomes. The studies were categorised into 8 different strategies which were used to reduce or discontinue long-term opioid therapy: interdisciplinary pain programmes, buprenorphine-assisted dose reduction, behavioural interventions, other outpatient programmes, other interventional programmes, detoxification, ketamine-assisted dose reduction and acupuncture.

From the studies reporting opioid discontinuation rates, the rates were calculated for the different discontinuation programmes. The mean rate was highest for the studies investigating buprenorphine-assisted dose reduction (91%, range: 33% to 100%, n=470) and detoxification (91%, range: 91% to 100%, n=200) and lowest for studies investigating ketamine-assisted dose reduction (18% and 27% in 2 studies, n=168). Most studies (31) looked at the effectiveness of interdisciplinary pain programmes, representing 9,915 participants - the mean opioid discontinuation rate amongst these studies was 87% (range: 29% to 100%).

Forty studies (5 RCTs, 6 controlled observational studies and 29 uncontrolled observational studies) examined the effect of dose reduction or discontinuation on patient outcomes. Thirty-six studies examined the effect of opioid dose reduction on pain severity, 12 on quality of life, 18 on opioid withdrawal symptoms and 11 on adverse events. The quality of evidence was graded as very low and the risk of bias was deemed serious for all outcomes assessed. The authors extracted outcomes from studies that were graded as 'fair' quality. Improvements were reported in pain severity (8 of 8 studies), function (5 of 5 studies) and quality of life (3 of 3 studies). The authors state that the reported incidence of opioid withdrawal symptoms during dose reduction varied widely but specific details are not included in the paper (3 'fair' quality studies, 15 'poor' quality). The paper does not report any data on adverse events other than the incidence of 1 opioid-related overdose death.

Commentary

Commentary provided by Dr Roger Knaggs, Associate Professor in Clinical Pharmacy Practice, University of Nottingham and Specialist Pharmacist in Pain Management, Primary Integrated Community Solutions Ltd, Nottingham

Opioids are often seen as some of the most potent analgesics available. Whilst they can be effective for acute pain following surgery or trauma at the end of life, there is much less evidence for their effectiveness for types of long-term pain, such as low back pain, neuropathic pain, osteoarthritis or fibromyalgia. Whilst there may be benefit in the short-term (no more than 3-4 months), and for certain individual people with chronic pain, there remains no study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy evaluating long-term (>1 year) outcomes related to pain, function, or quality of life. There has been a large increase in opioid prescribing in the UK and there is increasing evidence of harm above doses greater than the oral morphine equivalent dose (OMEQ) of 100 mg/day. There could be a substantial number of people who have been taking opioids for a long time but experience very limited pain relief and improved physical function. Hence there is a need to understand approaches to support them to reduce, and possibly discontinue, opioid treatment and to consider other treatments to manage their pain.

The authors of this systematic review concluded that several types of interventions may be effective to reduce or discontinue long-term opioid therapy and that pain, function and quality of life may improve with opioid dose reduction. The overall quality of evidence was very low due to methodological limitations across studies and an absence of adequately powered clinical trials. No data were reported on opioid withdrawal symptoms or adverse effects and therefore no conclusions can be drawn on how these affected patients.

In the three good quality trials of behavioural interventions and the 11 fair quality studies of interdisciplinary pain programs, participants received multimodal care that emphasised the development of self-management and non-pharmacological strategies. These findings are consistent with the NICE guideline on [medicines optimisation](#) which encourages the use of self-management plans to empower and involve people in the management of their condition and using the knowledge, skill and clinical expertise of several health and social care practitioners to create an individualised management plan for each person.

The overall quality of the evidence was also very low for the six pre-specified patient outcomes and, although fair quality studies reported improvements in pain severity, function and quality of life after opioid dose reduction, these findings could not be generalised across all studies and outcomes could not be quantified. The authors suggested several potential mechanisms for the reported improvements in outcomes after opioid dose reduction:

- Most interventions were designed to support patients to develop other strategies for managing their pain that may have provided more benefit than long-term opioid therapy.
- Opioid dose reduction may alleviate adverse effects of long-term opioid therapy that can negatively affect function and quality of life, such as constipation, fatigue, poor sleep and depressed mood.
- Resolution of opioid induced hyperalgesia^a, a paradoxical response in which people receiving opioid therapy become more sensitive to painful stimuli.
- Reverse causation - people successfully reduced opioids because pain severity decreased.

The observational design of the majority of the studies included in this review means they are susceptible to bias and confounding. Forty-nine of the 67 studies were conducted in the USA, which

means that the findings from these studies may not be generalisable to the UK population and UK prescribing practices. There is an [ongoing NIHR funded study \(i-WOTCH\)](#) assessing a support programme that aims to improve the everyday functioning for people living with long-term pain and reduce their opioid use.

This study highlights the importance of following the NICE guideline on [medicines optimisation](#). NICE recommends a regular, structured medicine review to determine how safe the person's medicines are, how well they are working for them (pain relief and improved physical activity), how appropriate they are for them, and whether their use is in line with national guidance.

^aThe British Medical Association (BMA) identify hyperalgesia as a potential harm associated with opioid use in [Chronic pain: supporting safer prescribing of analgesics](#) although the clinical significance in routine prescribing is not currently known.

Declaration of interests:

Dr Roger Knaggs has received research funding from Mundipharma Research Ltd and attended an Advisory Board for Actavis UK Ltd. He is currently Honorary Secretary for the British Pain Society, member of the Opioids Aware subcommittee, Faculty of Pain Medicine and a co-opted member of the Technical Committee for the Advisory Council on Misuse of Drugs.

Study sponsorship

Veterans Health Administration

References

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Medicines Evidence Commentaries form part of [NICE's Medicines Awareness Service](#) and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

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