GUIDELINES

Prescribing strong opioids for pain in adult palliative care: summary of NICE guidance

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Pain is common in advanced cancer but also in the late stages of other incurable non-malignant diseases, such as heart failure and neurological conditions.1 2 Almost half of patients with advanced cancer are undertreated for their pain, largely because clinicians are reluctant to use strong opioids for effective analgesia.3 4 Strong opioids such as morphine are indicated for moderate to severe pain and should be prescribed only after a full assessment of the analgesic needs of the patient.

This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the care of people with advanced and progressive disease who require strong opioids for pain control.1 These patients are defined as those in moderate to severe pain who may never have used strong opioids, or those whose pain has been inadequately controlled by weak opioids such as codeine or tramadol. The guideline does not cover all aspects of pain management (including second line approaches) or pain control during the last days of life (for example, for patients who are being managed by the Liverpool care pathway, a care pathway that integrates the best aspects of care for dying patients that can be used in any clinical setting).

**Recommendations**

NICE recommendations are based on systematic reviews of the best available evidence. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

**Communication and provision of information**

When offering strong opioids as pain treatment to a patient with advanced and progressive disease:

- Ask about concerns such as addiction, tolerance, side effects, or fears that treatment implies the final stages of life. Reassure patients that addiction is very rare and that tolerance does not significantly affect pain management or result in the need for escalating doses. It is often helpful to explain to patients that strong opioids are indicated solely because of the level of pain that the patient experiences and not because they are near to the end of life
- Provide verbal and written information on the indications for strong opioids, effectiveness, speed of onset of pain relief, side effects and safe storage of the drugs
- Give information on out of hours contact, follow-up, and further prescribing
- Offer access to frequent review of pain control and side effects.

When barriers to treatment are identified and managed, patients are more likely to take analgesia as prescribed. This is best done with face to face advice plus information that the patient and carer can take away (such as a leaflet or DVD). This approach can result in measureable improvements in pain control and reduce adverse effects.6

**Starting strong opioids—titrating the dose**

If the patient is able to take oral medication, titrate the starting dose, taking account of pain control and side effects:

- Offer regular, oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain
- Use a typical daily starting dose of 20-30 mg oral sustained-release morphine given as 10-15 mg twice daily with 5 mg oral immediate-release morphine for breakthrough pain (if the patient has no hepatic or renal impairment)
- Adjust the dose to balance pain control and side effects, with frequent review
- Seek specialist advice if this balance is not reached after a few dose adjustments or if the patient has moderate to severe hepatic or renal impairment.

**Starting strong opioids—maintenance phase**

If the patient can take oral medication and if the optimal balance of pain control and side effects has been achieved:

- Offer oral sustained-release morphine as first line maintenance treatment
- Do not routinely offer transdermal patch formulations as first line maintenance treatment to patients in whom oral opioids are suitable
- Offer oral immediate-release morphine for the first line rescue medication of breakthrough pain in patients receiving maintenance oral morphine treatment
- Do not offer fast-acting fentanyl as first line rescue medication
- Seek specialist advice if pain remains inadequately controlled.

**Starting strong opioids if oral opioids are not suitable**

Oral opioids may be unsuitable for people with swallowing problems, when oral absorption is impaired or when pain is unstable. In such cases:

- Consider using transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed

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This is one of a series of BMJ summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guideline, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.
How effective are non-drug, non-surgical treatments for primary dysmenorrhoea?

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Primary dysmenorrhoea is a common, idiopathic, chronic pelvic pain syndrome, but its unknown aetiology prevents targeted treatment. Systematic reviews and randomised controlled trials have shown that non-steroidal anti-inflammatory drugs1-5 and hormonal regulation through oral contraception6 are significantly more effective for pain relief than placebo and are often used for symptom control.7 However, some women may not always find them effective or acceptable—for example, owing to side effects in the case of non-steroidal anti-inflammatory drugs.1 Non-drug treatments, including alternative and physical therapies, are increasingly being used for dysmenorrhoea. However, their effectiveness is still being debated.

What is the evidence of the uncertainty?

This paper is based on our review in Clinical Evidence in which we examined a number of systematic reviews and trials that looked at the effects of many treatments for primary dysmenorrhoea, identified through literature searches (from database inception until January 2010) of the Cochrane Library, Medline, Embase, and bibliographic databases of the US Food and Drug Administration and the UK Medicines and Healthcare Products Regulatory Agency.

The quality of available evidence was moderate to poor, for both drug and non-drug treatments. In particular, well designed trials comparing interventions head to head or against placebo were scarce. The meta-analyses found...
that drug treatments (non-steroidal anti-inflammatory drugs and combined oral contraception) were effective. Evidence on surgical treatments found that laparoscopic uterine nerve ablation was ineffective.\(^{28,31}\) For non-drug treatments the review showed substantive uncertainty, which hampers the generation of clinical guidance. The table (on bmj.com) shows the results of our examination.

Transcutaneous electrical nerve stimulation (TENS)

A Cochrane review included seven very low quality randomised controlled trials (RCTs) of this physical treatment.\(^{19}\) Patients had greater pain relief with high frequency TENS than placebo (odds ratio 7.2, 95% confidence interval 3.1 to 16.5), but low frequency TENS was no more effective than placebo (1.48, 0.43 to 5.08). When high and low frequency TENS were compared, the results were conflicting. A subsequent RCT comparing high frequency TENS with sham TENS found that high frequency TENS significantly reduced pain (P=0.018).\(^{11}\) High frequency TENS seems to be the most effective form of TENS.

Behavioural therapy

A Cochrane review of five RCTs of behavioural interventions showed a potential benefit, but because of the inconsistency in reporting of data, small sample sizes, poor methodological quality, and age of the trials, this result should be viewed with caution.\(^{12}\)

Complementary and alternative therapies

Acupressure

We identified two acupressure trials, both deemed to be of very low/low quality, making definitive conclusions difficult.\(^{13,14}\) Seed pressure acupressure is based on the assumption that the ear is a microreflexology area, containing points correlating to every part of the body. Practitioners tape a seed over an acupoint in the ear and press it to create stimulation at that point.

Acupuncture

All trials involving this therapy were found to be of “very low” or “low” quality, making definitive conclusions difficult.

Spinal manipulation

A Cochrane review included two very low quality trials on high velocity, low amplitude manipulation and one very low quality trial on the Tofness technique (a light, non-force adjustment technique for the lower back). Owing to the small sample sizes and other methodological limitations in two of the three included RCTs, no definitive conclusions about benefit can be drawn about this form of therapy.\(^{19}\)

Topical heat

Two relevant RCTs were identified, both of low quality.\(^{20,21}\) The first compared four treatments: heated patch plus placebo; heated patch plus ibuprofen; unheated patch plus placebo; and unheated patch plus ibuprofen. Only heated patch plus placebo and unheated patch plus ibuprofen significantly reduced rates of pain and pain intensity, two days after treatment. Both results were comparable.\(^{20}\) The second RCT also compared four treatments: abdominal heat wrap (heated to 40°C for 8 hours from the first morning after the start of menses); unheated abdominal wrap (for same time period); high dose paracetamol (1000 mg four times a day); and placebo. The heated wrap significantly reduced pain after 8 hours of treatment compared with paracetamol (P=0.015). No data were reported for the placebo groups. Topical heat is likely to be just as effective as ibuprofen in alleviating pain but more effective than paracetamol.

**Vitamin E**

Low quality evidence from a systematic review and an RCT suggest that vitamin E offers some pain relief.

**Thiamine**

There is moderate quality evidence that, compared with placebo, 100 mg thiamine taken daily for 60 days can significantly increase the proportion of women experiencing “no pain.”

**Fish oil**

An RCT of very low quality, with a population not restricted to primary dysmenorrhea, compared fish oil capsules taken twice daily for a month with placebo and showed that at three months menstrual symptoms were significantly lower in patients allocated to fish oil (P=0.04).\(^{24}\) Another RCT, also of very low quality, compared four interventions (fish oil, fish oil plus vitamin B-12, seal oil, and placebo) for at least three months and found no significant difference in pain scores between the groups (P=0.62).\(^{25}\) The benefit of fish oil for pain relief remains unclear.

**Herbal medicine**

There is very low evidence of benefit with toki-shakuyaku-san (a Japanese herbal remedy composed of several herbal plants, including angelica and peony root, that is taken three times daily) and ginger rhizome powder. Low to very low evidence of benefit exists with Iranian herbal medicine (highly purified saffron, celery seed, and anise). However, it is difficult to determine which of these is the most effective option. The effectiveness of Chinese herbal medicine when compared with placebo remains unclear; however, the limited available evidence suggests it gives better pain relief compared with conventional treatments, acupuncture, and topical heat. All of these findings should be interpreted with caution as all studies had serious methodological deficiencies.

**Is ongoing research likely to provide relevant evidence?**

We searched the ClinicalTrials.gov and Current Controlled Trials registers for relevant ongoing trials and found two that were still open to recruitment. The first, an Egyptian comparative randomised crossover study, compares the extracts of the roots of the South African uzara plant with ibuprofen. Primary outcomes of this study include pain intensity, rescue medication (percentage of women needing this and the time interval), and the participants’ overall evaluation of the study medication. The second randomised trial, from the United States, compares a three week administration of oral contraception with continuous administration. The primary outcome measure is the difference in subjective pain scores from baseline to six months post-treatment, as measured with the visual analogue scale.
RECOMMENDATIONS FOR FUTURE RESEARCH

Population: Women with diagnosis of primary dysmenorrhea established through a standard, sufficiently robust battery of tests for excluding disease

Interventions and comparisons: First line interventions compared with second line interventions after failure of first line treatments. (As individual responses to pain vary, stratification according to particular stratification markers is needed.)

These include behavioural, complementary, and alternative therapies and devices, either individually or in combination (including combination with drug treatment). Large, robust, high quality trials comparing these interventions against placebo and head to head comparisons are lacking in this field. Therefore multicentre trials are encouraged.

Outcomes: Pain (such as on visual analogue scale), disease specific quality of life (capturing sexual function), generic quality of life (such as EuroQol), and adverse effects of treatment—with repeat measurement of all outcomes over at least one year’s duration.

There is a dearth of good quality ongoing research for guiding practice in the near future. New research is needed, as well as a resynthesis of existing evidence in more imaginative ways. Research could include individual randomised controlled trials of various designs. Large simple trials can investigate effectiveness in a population. To facilitate patient selection for treatment, evaluation of the treatment effect in subgroups with particular stratification markers is needed. In addition, network and individual patient data meta-analyses of existing randomised data should be conducted. Moreover, “n of 1” trials may be used where large studies do not exist. This design would be particularly useful in randomly assigning women with chronic recurrent conditions like primary dysmenorrhea to second line alternatives, after standard treatment has failed. In this way, clinicians can provide care and answer clinical questions simultaneously.

What should we do in the light of the uncertainty?

The women with dysmenorrhea who do not respond to, do not wish to try, or do not tolerate hormonal manipulation and non-steroidal anti-inflammatory drugs may wish to try non-drug, non-surgical alternatives. Although interventions such as acupressure, behavioural therapies, herbal remedies, transcutaneous electrical nerve stimulation, thimine, topical heat, and vitamin E have some evidence of effectiveness, clinicians should advise patients that evidence for the effectiveness of these treatments is generally weak.

As the quality of evidence in these areas is poor, non-drug treatments are perhaps best offered as “n of 1” trials. By evaluating change in pain and quality of life over several treatment cycles, clinicians can monitor the effects of treatment and individualise care.

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