A2.2.1 A two-step approach versus the three-step ladder

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence for using a two-step analgesic ladder versus a three-step analgesic ladder for rapid effective and safe pain control? If the evidence supports the use of a three-step ladder, should codeine as compared to tramadol be used at step two?

Recommendation
1. It is recommended to use the analgesic treatment in two steps according to the child’s level of pain severity.
   *Strong recommendation, very low quality of evidence*

Domains and considerations

Quality of evidence
There are no formal comparisons between two-step and three-step treatment in children. The two potential medicines that might appear in the second step present challenges in children. Tramadol is generally not registered for use in children below the age of 12 years, as evidence of efficacy and safety is not available, and has not been submitted for evaluation by medicines regulatory agencies. Codeine presents well-known safety and efficacy difficulties related to genetic variability in biotransformation (CYP2D6), although it is registered for use and has been widely used in children. Uncertainty: yes, for the three-step pharmacological pain treatment approach.
Risks/benefits

Benefits
The potential benefit of having access to effective opioid analgesics outweighs the benefits of codeine in this age group.

Risks
The risks associated with strong opioids are recognized, but are acceptable in comparison to the uncertainty associated with codeine and tramadol.

Uncertainty: if there is new evidence for tramadol or an alternative intermediate potency opioid, then this benefit-risk assessment can be reconsidered.

Values and acceptability

In favour
The panel placed high value on effective treatment of pain.

Against
The panel acknowledged continuing barriers to access to strong opioids in many settings, but a strong recommendation in this regard could overcome this negative sentiment and promote wider access to opioids for pain relief.

Uncertainty: none.

Cost
Although tramadol is now off patent in many markets and generics have been launched, the problem of market authorization for children remains in several countries. Codeine is widely available and inexpensive, but presents potential lack of efficacy and/or safety problems in an unpredictable proportion of patients. Although access to strong opioids is variable, price is not generally a significant barrier.

Uncertainty: none.

Feasibility
Child-appropriate dosage forms for opioids are available with the exception of very young infants. Liquid preparations allow for easier dose titration, but concern about cost, stability, portability and storage remain.

The dosage forms reported in the 2010 EMLc are as follows:

- **granules**: modified release (to mix with water), 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
- **injection**: 10 mg (morphine hydrochloride or morphine sulfate) in 1 ml ampoule
- **oral liquid**: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml
- **tablet**: 10 mg (morphine sulfate)
- **tablet (prolonged release)**: 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).

Strong opioids are not available in all countries.

Uncertainty: none.

Research agenda
1. Research on potential alternatives to codeine as a second step in a three-step approach is needed.
2. Long-term safety data of non-steroidal anti-inflammatory drugs and paracetamol is needed.