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Editorial

Codeine in mothers and children: where are we now?

The death of a child is always a tragedy, so when it was reported that a toddler had died at home in North America following ingestion of codeine prescribed for postoperative analgesia [1], clinicians were understandably alarmed. This child was subsequently found to be what is described as an ultra-rapid metaboliser of codeine. A study in children demonstrated hypercarbia and a depressed ventilatory response to carbon dioxide at plasma morphine concentrations above 20 $ng.l^{-1}$ [2], and his post-mortem plasma concentration of morphine was 32 $ng.l^{-1}$. It was presumed that excessively high morphine levels, together with airway obstruction, caused fatal respiratory depression. There followed a further report of two deaths and a 'near miss' related to the use of postoperative codeine in children [3].

In the ensuing months, the Food and Drug Administration (FDA) in the USA [4], the European Medicines Agency (EMA) [5] and the Medicines and Healthcare products Regulatory Agency (MHRA) [6] all issued warning notices related to the use of codeine in children. The MHRA recommended that "*codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen*". In addition, the MHRA stated that "*codeine is contraindicated in all children (i.e. younger than 18 years) who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea*", and that it *"is not recommended for children whose breathing might be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures"* [6]. The MHRA provided no advice regarding children without obstructive sleep apnoea having intermediate-sized surgery such as tonsillectomy/adenoidectomy.

In November 2013, a joint statement by the Royal College of Anaesthetists (RCoA), the Association of Paediatric Anaesthetists (APA) and the Royal College of Paediatrics and Child Health (RCPCH) was released [7]. Their conclusions were non-committal; "*Within the UK different solutions are being employed. These include continuing to use codeine with increased caution or adopting alternative opioid medication regimens: oral morphine, dihydrocodeine, oxycodone or tramadol are potential alternatives.*"

So what is the problem with codeine; after all, it has been in use for many years and prescribed, without apparent problems, for millions of patients worldwide?

One issue is that codeine's precise mechanism of action is unclear. Seventy to eighty percent of codeine is metabolised by glucuronyltransferase enzymes in the liver to codeine-6-glucuronide, the analgesic activity of which is unknown in humans, and 10% to norcodeine, a metabolite with no analgesic properties. A small proportion (5–10%) is metabolised by the cytochrome P450 2D6 enzyme system to morphine. Because codeine has only 0.5% of the affinity for mu-opioid receptors compared with morphine, it is widely believed that the major analgesic effect of codeine is as a result of its conversion to morphine [8, 9]. Codeine therefore behaves like a pro-drug, requiring metabolism to become clinically active. The bigger problem, however, is that there are a substantial number of different alleles coding for activity of the cytochrome 2D6 enzyme system and, indeed, gene duplication in a number of important ethnic groups. This results in a wide spectrum of enzyme activity (phenotype) across the range of different genotypes (genetic polymorphism). At one extreme, two abnormal genes lead to individuals with no 2D6 enzyme activity and no ability to convert codeine to morphine, so-called poor metabolisers. At the other extreme, duplication of active alleles results in individuals with

unusually high 2D6 enzyme activity and extensive conversion of codeine to morphine (ultra-rapid metabolisers). A typical North European population in the UK consists of 5-10% poor metabolisers and 0.03% ultra-rapid metabolisers [10]. Ultra-rapid metabolisers are particularly prevalent in Africa/Ethiopia (29%) and Saudi Arabia (21%) and this is thought to be an evolutionary development in relation to diet [11]. In addition to the wide genetic variability in enzyme activity, 2D6 is also inhibited or induced by the use of concomitant medications, which may also alter codeine's efficacy or side-effect profile.

Use of codeine in pregnancy

Codeine remains an immensely popular analgesic during the peripartum period, with two recent studies indicating that the incidence of exposure to codeine during pregnancy is 5-6%, increasing to almost 30% in the postpartum period [12–14]. To enable a comprehensive evaluation of codeine usage in pregnancy and the postpartum period, it is essential to determine its safety during the first trimester, its efficacy, and its impact on breastfeeding and the neonate.

Evidence for the teratogenic effects of codeine in animal studies is inconclusive and seems to depend on the animal species tested [15, 16]. Of more concern is the association between use of codeine and birth defects in human epidemiological studies. In a recent population based case-control study [17], peri-conceptual treatment with opioid analgesics, in particular codeine, was associated with a higher incidence of birth defects, in particular a twofold increased risk of cardiac defects (atrioventricular septal defect, hypoplastic left heart syndrome, aortic stenosis) and spina bifida. Other studies have reported associations between peri-conceptual use of codeine and the incidence of neural tube defects [18] and neuroblastoma [19]. Co-administration of codeine with paracetamol is unlikely to explain the higher rate of congenital abnormalities, because paracetamol per se is not associated with an increase in birth abnormalities [20, 21]. The worrying associations between use of codeine and birth defects are, however, tempered by a recent Norwegian cohort study that failed to identify an association between use of codeine in pregnancy and an increased rate of congenital malformations [22]. Despite inconsistent evidence, there are sufficient red flags to question the safety of codeine during pregnancy.

Pregnancy outcomes such as mode of delivery and immediate complications are largely determined by the wellbeing of the maternal-fetal unit, and it is extremely unlikely that they would be affected by antenatal opioid therapy. However, Nezvalova-Henriksen et al. found a significant association between the use of codeine in pregnancy and adverse obstetric outcomes [22]. Specifically, the use of codeine at any time during pregnancy was associated with an increased risk of elective and emergency caesarean section and postpartum haemorrhage. Although the associations remain strong, patients who received codeine were also overweight, had multiple co-morbidities and were prescribed additional psychotropic agents, including antidepressants. Therefore, the causal role of codeine needs to be further evaluated, especially as recent research suggests that use of antidepressants during pregnancy per se is associated with an increased incidence of postpartum haemorrhage [23].

Postpartum analgesia

Because of genetic polymorphism, there is great variability in the relative contribution of morphine to analgesia. A pilot study tested the association between the 2D6 genotype and codeine analgesia in 45 women following elective caesarean section [24]. Although the study was underpowered to detect differences in analgesia between the four different genotypes, women at the genotypic extremes reported codeine effects consistent with their genotype: two poor metabolisers reported no analgesia as a result of taking codeine whereas two of the three utra-rapid metabolisers reported immediate pain relief from codeine but stopped taking it due to dizziness and constipation.

Unlike specific studies targeting the codeine-genotype interaction for adverse effects, studies comparing the analgesic efficacy of codeine are limited because of its almost universal co-administration with paracetamol. Despite this apparent confounder, the majority of studies have shown no differences in analgesia between paracetamol-codeine and non-steroidal anti-inflammatory drugs (NSAIDs). In fact, a recent meta-analysis concluded that NSA-

IDS are as effective as paracetamol-codeine in treating post-laparotomy pain, with fewer side-effects [25]. In addition, NSAIDs were superior to codeine for analgesia after second trimester abortion [26] and for the treatment of pain following vaginal delivery [27]. Pharmacogenetic testing (the AmpliChip CYP450 Test) [28] is a promising tool for customising codeine treatment, but the costs associated with testing (£365–790 (€437–946; $600–1300) and the availability of equally efficacious NSAID alternatives do not justify its routine use in clinical practice. With the availability of superior and more reliable alternatives such as NSAIDs, the continued use of the less efficacious, and more unpredictable, codeine for postpartum analgesia should be questioned.

Codeine and breastfeeding

Most opioids, including codeine, are readily secreted into breast milk. The actual effect of the drug on an infant is determined by a variety of factors: milk/plasma drug concentration ratio; volume of milk ingested; age of the infant; and the presence of active metabolites in the mother and infant [29]. Maternal administration of codeine results in infant plasma morphine concentrations that are only 2-4% of the toxic level in infants [30] and therefore it is probably safe to use in the immediate postpartum period in the majority of women. However, recent studies suggest that maternal codeine may cause depression of the infant central nervous system (CNS) in a dose-dependent manner; the reported dose ranges that caused symptomatic CNS depression in neonates were 1.4–1.6 $mg.kg^{-1}.day^{-1}$, with a 71% concordance between maternal and neonatal CNS depression [31]. Doses of less than 1 $mg.kg^{-1}.day^{-1}$ were not associated with adverse neonatal effects in these studies. However, patient-reported CNS depression is subjective, unreliable, and may not necessarily predict true complications. In fact, a large population-based retrospective cohort study confirmed that postpartum use of codeine was not associated with infant death or hospitalisation [32]. Currently, serious complications such as respiratory depression and apnoea are limited to isolated case reports, especially in breastfeeding mothers who are ultra-rapid metabolisers [33]. The probable cause of fatal respiratory depression in these cases is thought to be an acute increase in plasma levels of morphine and its subsequent transfer into breast milk, coupled with the inability of the neonate to handle the morphine overload [34]. Neonatal abstinence syndrome can occur following codeine therapy even in the absence of maternal addiction or dependence [35]. A prudent approach, therefore, would be to avoid codeine in high-risk ethnic groups such as Ethiopians, limit the dose to 1 $mg.kg^{-1}.day^{-1}$ in other mothers, move to NSAIDs as soon as possible, and closely monitor the mother-infant pair for evidence of CNS depression. A better option, perhaps, is to replace the routine use of codeine with NSAIDs in this population. This conclusion is fully supported by the Academy of Breastfeeding Medicine (ABM), which recommends non-opioid analgesics as first-choice therapy in breastfeeding mothers [36].

Use of codeine in children

Tonsillectomy is the most common intermediate-sized operation undertaken in children that is associated with substantial postoperative pain lasting at least seven days, requiring 'step-up' analgesia (i.e. additional 'as required' analgesia when paracetamol and NSAIDs alone are insufficient). Tonsillectomy is decreasing in frequency in Western countries but an increasing proportion is being performed for obstructive sleep apnoea rather than recurrent tonsillitis; Erickson et al. [37] found that upper airway obstruction as an indication for tonsillectomy/adenoidectomy increased in the USA from 12% of patients in 1970 to 77% in 2005. A significant proportion of children with obstructive sleep apnoea are acutely sensitive to the respiratory depressant effects of opioids [38] and caution should be exercised if these patients require other intermediate-sized procedures aside from tonsillectomy/adenoidectomy. The tragic death described at the start of this editorial [1] can probably be attributed to a 'perfect storm' combination of obstructive sleep apnoea, a painful operation, prescription of regular codeine postoperatively and ultra-rapid metabolism.

In the face of the MHRA's pronouncement on the use of codeine in children, what are the alternatives? Dihydrocodeine is much less

potent than morphine and most preparations do not have a license in children under the age of 4 years; in addition, a small proportion undergoes metabolism to an active metabolite (dihydromorphone) and it is formulated in alcohol. Tramadol is an effective analgesic but it is metabolised by the 2D6 enzyme system to an active metabolite with a high affinity for the μ opioid receptors, thus increasing the likelihood of nausea and vomiting. In addition, there is an important pharmacodynamic interaction with ondansetron, since the analgesic effect of tramadol is partly due to increased release of serotonin, and ondansetron is a serotonin antagonist [39, 40]. Potential also exists for a pharmacokinetic interaction because ondansetron is, in part, also metabolised by the 2D6 enzyme system. The concurrent use of the two drugs results in a mutual reduction in effect; tramadol is a less potent analgesic and ondansetron is a less effective anti-emetic. Oral morphine is an attractive alternative in that it has reasonable bioavailability, is not a pro-drug and its metabolism does not involve the 2D6 enzyme system. However, it does have active metabolites that may accumulate with repeated dosage, and it is a controlled drug (Schedule 5 under the Misuse of Drugs Regulations 2001).

Possible strategies regarding postoperative analgesia for children having intermediate-sized operations are shown in Table 1. At one of our institutions, codeine is no longer available for children and has been replaced by dihydrocodeine in the formulary. It has also been abandoned at the Hospital for Sick Children in Toronto, where it has been replaced by oral morphine [44].

The future

On the one hand, codeine is not an ideal analgesic agent, it is ineffective in a number of patients and it may actually cause death in a very small number of patients. However, on the other hand, it does have a long track record of usage, it is safe and effective in the majority of patients, it is cheap and palatable, and there is no obviously superior alternative.

There have been some interesting developments, for example in the use of intranasal analgesics such as diamorphine [45] and oral tapentadol, a centrally acting analgesic with a dual mode of action (similar to levorphanol). Its potency is somewhere between tramadol and morphine but, although licensed in the UK for adults, it

Table 1 Possible strategies for postoperative analgesia for children having intermediate-sized operations.

1. Perform the AmpliChip CYP450 Test [28]. This is superficially attractive but expensive and practically unhelpful; it will not identify all children at risk of respiratory depression with codeine as there is overlap in 2D6 activity between extensive and ultra-rapid metabolisers, with at least one of the children reported as coming to harm with codeine being an extensive metaboliser rather than an ultra-rapid metaboliser [3]. Extensive metabolisers have an enzyme activity score of between 1 (normal) and 2, compared with intermediate metabolisers who have an activity score of 0.5 and poor metabolisers who have an activity score of 0.
2. Observe children closely, both intra- and postoperatively, for their response to opioid administration. This appears sensible in that an excessive response may indicate increased sensitivity, but there is no evidence that witnessed doses of codeine in hospital increase the safety of subsequent administration at home [41].
3. Do not prescribe fixed-dose combination analgesics such as paracetamol with codeine.
4. Prescribe regular paracetamol (in an effective dose [42]) as well as a NSAID, with no step-up analgesia. (The authors are aware of at least one hospital where this has occurred, leading to an increase in parental phone calls seeking advice and readmissions for poor oral intake due to inadequate pain relief, post-tonsillectomy).
5. Prescribe an individualised, dose-limited, opioid-based drug regimen whilst giving clear unambiguous written and verbal instructions to the family/carers. This should include a warning to return the child to hospital if any untoward response is noticed and provision of a 24-hour hotline number for telephone advice.
6. Consider abandoning adenoidectomy/tonsillectomy and other intermediate-sized operations as day-case procedures. There is, after all, significant pain in 50% of patients for up to one week postoperatively [43]; perhaps the child should remain in hospital and be monitored following morphine administration until pain is sufficiently well controlled with oral non-opioid analgesics.

currently has no license for use in pregnancy, breastfeeding mothers or children.

Currently, there is uncertainty as to how best to fill the so-called 'analgesic vacuum'. All stakeholders have a duty to safeguard obstetric and paediatric patients and to provide effective analgesia postoperatively. We do not know the safest and most effective analgesic regimen to use after obstetric procedures such as caesarean section and in children following tonsillectomy. Research is urgently needed in this area. In the meantime, we require a region-based approach with specific regimens taken up by tertiary centres and adopted by their associated networks. In addition, aspects beyond a focus on pharmacology are required, including education of patients and parents and easier access to effective alternatives, especially for pain relief at home after intermediate surgery.

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References

1. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultra-rapid-metabolism genotype, and postoperative death. *New England Journal of Medicine* 2009; **361**: 827–8.
2. Lynn AM, Nespeca MK, Orpheim KE, et al. Respiratory effects of intravenous morphine infusions in neonates, infants and children after cardiac surgery. *Anesthesia and Analgesia* 1993; **77**: 695–701.
3. Kelly LE, Rieder M, van den Anker J. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 2012; **129**: e1343–7.
4. Food and Drug Administration. Safety review update of codeine use in children; new Boxed Warning and contraindication on use after tonsillectomy and/or adenoidectomy, 20th February 2013. http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm (accessed 14/03/2014).
5. European Medicines Agency. Restrictions on the use of codeine for pain relief in children – CMDh endorses PRAC recommendation, 28th June 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001829.jsp&mid=WC0b01ac058004d5c1 (accessed 14/03/2014).
6. Medicines and Healthcare products Regulatory Agency. Codeine for analgesia: restricted use in children because of reports of morphine toxicity. *Drug Safety* Update July 2013. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400 (accessed 14/03/2014).
7. Royal College of Anaesthetists, Association of Paediatric Anaesthetists and Royal College of Paediatrics and Child Health. Guidance for the administration of codeine and alternative opioid analgesics in children, November 2013. http://www.apagbi.org.uk/sites/default/files/images/Codeine_Nov2013.pdf (accessed 14/03/2014).
8. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of μ opioid receptor binding constants for for selected opioid drugs. *Regulatory Toxicology and Pharmacology* 2011; **59**: 385–90.
9. Thorn CF, Klein TE, Altman RB. Codeine and morphine pathway. *Pharmacogenetics and Genomics* 2009; **19**: 556–8.
10. Cascorbi I. Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. *European Journal of Clinical Investigation* 2003; **33** (Suppl 2): 17–22.
11. Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopean population carrying duplicated and multiduplicated functional CYP2D6 alleles. *Journal of Pharmacology and Experimental Therapeutics* 1996; **278**: 441–6.
12. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *European Journal of Clinical Pharmacology* 2011; **67**: 953–60.
13. Daw JR, Mintzes B, Law MR, Hanley GE, Morgan SG. Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). *Clinical Therapeutics* 2012; **34**: 239–49.
14. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology* 2014; **120**: 1216–24.
15. Williams J, Price CJ, Sleet RB, et al. Codeine: developmental toxicity in hamsters and mice. *Fundamental and Applied Toxicology* 1991; **16**: 401–13.
16. Zellers JE, Gautieri RF. Evaluation of teratogenic potential codeine sulfate in CF-1 mice. *Journal of Pharmaceutical Sciences* 1977; **66**: 1727–31.
17. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *American Journal of Obstetrics and Gynecology* 2011; **204**: 314–e1.
18. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstetrics and Gynecology* 2013; **122**: 838–44.
19. Cook MN, Olshan AF, Guess HA, et al. Maternal medication use and neuroblastoma in offspring. *American Journal of Epidemiology* 2004; **159**: 721–31.

20. Rebordosa C, Kogevinas M, Horvath-Puho E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. *American Journal of Obstetrics and Gynecology* 2008; **198**: 178.
21. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth defects Prevention Study. *Obstetrics and Gynecology* 2010; **115**: 109–15.
22. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *European Journal of Clinical Pharmacology* 2011; **67**: 1253–61.
23. Palmsten K, Hernandez-Diaz S, Huybrechts KF, et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *British Medical Journal* 2013; **347**: f4877.
24. VanderVaart S, Berger H, Sistonen J, et al. CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: a pilot study. *Therapeutic Drug Monitoring* 2011; **33**: 425–32.
25. Nauta M, Landsmeer ML, Koren G. Codeine-acetaminophen versus nonsteroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: a systematic review of randomized trials. *American Journal of Surgery* 2009; **198**: 256–61.
26. Jackson E, Kapp N. Pain control in first-trimester and second-trimester medical termination of pregnancy: a systematic review. *Contraception* 2011; **83**: 116–26.
27. Deussen AR, Ashwood P, Martis R. Analgesia for relief of pain due to uterine cramping/involution after birth. *Cochrane Database of Systematic Reviews* 2011; **5**: CD004908.
28. de Leon J, Susce MT, Murray-Carmichael E. The AmpliChip CYP450 genotyping test: integrating a new clinical tool. *Molecular Diagnosis and Therapy* 2006; **10**: 135–51.
29. Spigset O, Hagg S. Analgesics and breast-feeding: safety considerations. *Paediatric Drugs* 2000; **2**: 223–38.
30. Sindrup SH, Brosen K. The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* 1995; **5**: 335–46.
31. Lam J, Kelly L, Ciszkowski C, et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *Journal of Pediatrics* 2012; **160**: 33–7.
32. Juurlink DN, Gomes T, Guttmann A, et al. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: a retrospective cohort study. *Clinical Toxicology* 2012; **50**: 390–5.
33. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatric Drugs* 2008; **10**: 399–404.
34. Koren G, Cairns J, Chitayat G, Leeder SJ. Pharmacogenetics of morphine poisoning in a breast fed neonate of a codeine-prescribed mother. *Lancet* 2006; **368**: 704.
35. Nair V, Soraisham AS, Akierman A. Neonatal withdrawal syndrome due to maternal codeine use. *Paediatrics and Child Health* 2012; **17**: e40–1.
36. Montgomery A, Hale TW, Academy of Breastfeeding. ABM clinical protocol #15: analgesia and anesthesia for the breastfeeding mother, revised 2012. *Breastfeeding Medicine* 2012; **7**: 547–53.
37. Erickson BK, Larson DR, St. Sauver JL, Meverden RA, Orvidas LJ. Changes in the incidence and indications of tonsillectomy and adenotonsillectomy, 1970-2005. *Otolaryngology, Head and Neck Surgery* 2009; **140**: 894–901.
38. Waters KA, McBrien F, Stewart P, Hinder M, Wharton S. Effects of OSA, inhalational anesthesia, and fentanyl on the airway and ventilation of children. *Journal of Applied Physiology* 2002; **92**: 1987–94.
39. Arcioni R, della Rocca M, Romano S, Romano R, Pietropaoli P, Gasparetto A. Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT_3 spinal receptor involvement in acute pain in humans. *Anesthesia and Analgesia* 2002; **94**: 1553–7.
40. De Witte JL, Schoenmaekers B, Sessler DI, Deloof T. The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesthesia and Analgesia* 2001; **92**: 1319–21.
41. Tremlett M. Whither codeine? *Pediatric Anesthesia* 2013; **23**: 677–83.
42. Medicines and Healthcare products Regulatory Agency. Paracetamol: updated dosing for children to be introduced. *Drug Safety* Update July 2011. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123113 (accessed 14/03/2014).
43. Stewart DW, Ragg PG, Sheppard S, Chalkiadis GA. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. *Pediatric Anesthesia* 2012; **22**: 136–43.
44. Wong C, Lau E, Palozzi L, Campbell F. Pain management in children: part 2 – a transition from codeine to morphine for moderate to severe pain in children. *Canadian Pharmacists Journal* 2012; **145**: 276–9.
45. Kendall J, Maconochie I, Wong ICK, Howard R. A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. *Emergency Medical Journal* 2014 Jan 21: doi: 10.1136/emermed-2013-203226.

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Editorial

Cognitive aids: time for a change?

Cognitive aids are documents, visual prompts or decision guides that, unlike guidelines or protocols, are used when tasks are being performed. In anaesthetics and emergency care, checklists and algorithms are the most common formats used.

Checklists contain actions or tasks that cannot be readily recalled due to their sheer number, or where the correct sequence of tasks is

