ED analgesia

Queen Mary University London MSc in Emergency and Resuscitation Medicine

Module 3: Lecture 8

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"Pain is, with very few, if indeed any exceptions, morally and physically a mighty and unqualified evil. And, surely, any means by which its abolition could possibly be accomplished, with security and safety, deserves to be joyfully and gratefully welcomed by medical science."
James Young Simpson, administrator of first obstetrical anesthesia

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General philosophy regarding acute pain management

Section references[1-20]

In striving to consider the importance of safe and effective pain relief in the ED setting, the following principles may be useful:

1. Pain is often (up to 52% of cases) the primary complaint and impetus for ED (or EMS) presentation.
2. Many things we do to patients, even "routine" interventions (*e.g.* IV or Foley catheter placement), can be painful.
3. Available evidence suggests that in children, procedure-related pain reduces tolerance for future medical procedures.
4. Acute care research suggests that patients in pain believe 20-30 minutes to be a reasonable interval for ED analgesia provision; within this interval MDs should either provide pain medication or explain why analgesia delay is necessary.
5. Pain treatment is not only intrinsically "useful" (*i.e.* humane), it also effects myriad medical benefits that are both general (*e.g.* improved history/exam) and disease-specific (*e.g.* improved tidal volumes in sickle cell patients with acute chest syndrome).
6. The historian should identify any pain medications tried prior to patients' ED presentation. If there has been failure of oral agents prior to ED presentation – and one study found that 44% of ED presenters had tried home meds ranging from NSAIDS to opioids – then oral agents are likely an unwise initial therapy in the ED.
7. Despite the well-characterized utility of "broad-spectrum" analgesics (*e.g.* NSAIDs, opioids), MDs should always consider whether the clinical scenario warrants disease-specific therapy (*e.g.* triptans for headache).
8. Pain therapy can be effective via many administration routes (*e.g.* PO, PR, IN, IV, IM, SQ, inhaled, oral transmucosal), but for adults in the ED with severe pain, the IV route is usually optimal. IV analgesia (including patient-controlled analgesia, reported useful in ED patients with vaso-occlusive sickle cell crisis) offers rapid effect, ease of titration, reliable pharmacokinetics, and maintenance of *NPO* status. Other notes on IV administration include:
    - The PO route has often been tried at home, and is time-consuming.
    - Despite its frequent employment, the IM route is – according to consensus EM opinion – suboptimal in the ED. Problems with IM injection are largely related to less reliable pharmacokinetics than those characterizing IV drug therapy. As compared with IV administration, IM analgesia tends to be more difficult to titrate, more uncomfortable (especially with multiple injections), and less predictable (post-IM drug levels may be affected by injection site, disease, and time of day).
    - In cases where needles are best avoided (*e.g.* pediatric patients), MDs may consider alternative administration routes (*e.g.* PO, transmucosal) and/or nonpharmacologic means of pain management (distraction, suggestion). Other routes of administration which are *investigational* at this time include: subdermal therapy through an indwelling subdermal catheter, function of which is facilitated by administration of recombinant hyaluronidase (FDA-approved), and use of a functional microarray to facilitate transdermal absorption of "topically" administered analgesia (FDA review in process). *Disclosure: Lecturer is an investigator (no financial ties to manufacturers) in these fields.*
9. Pain therapy is an ongoing process, even in a single ED visit. Clinicians should address pain often, rather than order an analgesic and forget the patient.
    - It is much easier to prevent than treat pain; give analgesics regularly when clinical circumstances dictate.
    - Frequent dosing provides optimal therapy with lower total dose.
    - Ignorance of the principle of ongoing pain treatment risks "windup," a phenomenon of recruitment and increased analgesia requirements (see definitions section below).
10. Though there are exceptions (*e.g.* cases in which NSAIDs are used for opioid-sparing effects), the best approach to analgesia tends to be one that is simple; polypharmacy is best avoided. A single agent, titrated appropriately, will usually work.
    - Clinicians should avoid premature switching to a second analgesic. Rather, the best approach is to choose an appropriate medication and optimize its dosing, before switching/adding agents.
    - Antiemetics are frequently "prophylactically" combined with opioids, but this practice lacks evidence basis – at least one prospective study of patients receiving IV morphine has demonstrated lack of need for prophylactic antiemetics. Many prophylactic agents are sedative, some have antianalgesic properties (*e.g.* promethazine [Phenergan]), and others (*e.g.* hydroxyzine [Vistaril]) have the disadvantage of requiring IM injection.
11. Physicians should document what is being administered, and whether it's working (*e.g.* in progress notes, pain scales).
12. Appropriate outpatient analgesics should be prescribed – patients requiring opioids in the ED tend to require outpatient opioids.
    - Study of pediatric fracture patients reveals that significant pain persists for about 3 days after ED discharge for most patients; about ¾ of patients needed pain medication <4 days and 95% of children required <7 days' analgesia.

- It is noteworthy that evidence demonstrates that short (appropriate) opioid courses are extremely unlikely to cause addiction.

13. To patients, pain is a major issue. Its overall priority should be correspondingly high for care providers for this reason alone.
14. Evolving data paint a picture of substantial importance of analgesia, for physiologic and psychological reasons.

Terminology

- *Hyperalgesia* – the state where a painful stimulus causes more pain than normally expected
- *Allodynia* – a cause of hyperalgesia; with increased irritation, nerve fibers normally not associated with pain sensation are recruited, such that nonpainful stimuli begin to induce pain
- *Recruitment* – stimulation of increasing numbers of nerve fibers as a result of spinal neurotransmitter release; recruitment can cause permanent changes in pain sensation
- *Inflammatory pain* – is caused by tissue injury related to heat, hypoxia, inflammation, or trauma; this injury leads to peripheral stimulation of nociceptors (pain receptors) of nonmyelinated C fibers
- *Neuropathic pain* – occurs when there is direct activation of either sensory nerves or sensory ganglia by nerve injury or disease
- *Neuralgic pain* – is similar to neuropathic pain, but does not involve nerve damage
- *Opium* – is derived from Greek name for juice, and refers to the juice of the poppy, *Papaver somniferum*
- *Opiates* – are opium-derived drugs and their semisynthetic congeners
    - morphine (after Morpheus, the Greek god of dreams) is one many of many alkaloids isolated from opium
    - codeine is another opium-derived alkaloid
- *Opioid* – is a more inclusive term and is generally preferred to "opiate"
    - applies to all agonists and antagonists with morphine-like activity
    - also applies to naturally occurring and synthetic opioid peptides
    - fentanyl (for example) could technically be said to be an opioid, but not an opiate (see above definition)
- *Endorphin* – refers to the three families (enkephalin, dynorphin, β-endorphin) of endogenous opioid peptides
- *Narcotic* – (derived from Greek word for stupor) has mostly legal context and is no longer useful as a medical term

Inadequate analgesia in modern medicine

Section references[2,3,6,7,13,16,21-46]

There is abundant documentation of inadequate analgesia in ED and other acute care settings

Despite ongoing attention paid to the "oligoanalgesia" problem, timely provision of pain medicine continues to be problematic

Part of the problem: Busy EM physicians are worried about inappropriate prescription of analgesics, and thus risk oligoanalgesia

ED overcrowding is having a particular impact on ability to rapidly assess and treat severe pain[21]

Intervals between assessment and analgesia are unacceptably long:

First, the study notes national consensus guidelines of British Association of Accident & Emergency Medicine

Guidelines call for pain med administration within time frames depending on pain severity (10-point scale)

"severe pain" (7-10) should receive pain medication within 20 minutes of triage/arrival

"moderate pain" (4-6) should be offered pain medication at triage

Guidelines also call for ongoing action after initial evaluation

90% severe pain pts should have documented reassessment within 30 min. Post-analgesia

75% of moderate pain pts should have documented reassessment within 60 min. Post-analgesia

Despite consensus on (very reasonable) goals, performance was poor by multiple analyses

In assessment of time intervals between arrival and analgesia administration, only a third met guidelines:

For A&E patients with moderate pain: mean 3 hrs 46 mins

For A&E patients with severe pain: mean 1 hr 12 mins

Documentation of effect/reassessment was rare

Detailed analysis of the study reveals where time delays occur

For moderate pain patients, significant delay was evidence at many steps

From arrival to MD assessment, mean interval was 142 minutes

An additional 26 minutes was required for prescription of analgesia

After analgesia prescription, medication administration occurred after over an hour (68 minutes)

For patients in severe pain, delays were lesser, but still concerning for multiple steps needing improvement

From arrival to MD assessment, mean interval was 42 minutes

An additional 16 minutes' delay occurred between MD assessment and pain medication order

14 minutes elapsed between MD order and medication administration

The British study results are probably quite similar to – if not better than – those that would be found in the U.S.

One 2012 US study of pediatric patients with long-bone fractures requiring admission[22]

10% received adequate analgesia within an hour of ED arrival

31% received inadequate (underdosed) analgesia within an hour of ED arrival

59% received no analgesia within first hour of ED arrival

Only 10% of those transported by EMS, received prehospital analgesia

Bottom line: after years of discussion (and many papers), ED pain medication remains slow to come

The problem is not limited to the ED: in some procedural situations, patient populations are allowed to endure pain

- Circumcision (*NEJM* editorial: "Infants have all the anatomical and functional components required for nociception")
- Parturition (ACOG/ASA): "There is no other circumstance where it is considered acceptable for a person to experience severe pain amenable to safe intervention, while under a physician's care.")

Physicians generally underestimate pain regardless of patient demographics

Controversy remains, but studies have identified particular risk factors related to undermedication in the E.D. population:

- Gender and gender-specific disease processes (*e.g.*, females with pelvic inflammatory disease)
- Extremes of age
  - In pediatrics, particularly those younger than 5-6 years old
  - In geriatrics: "The most apparent underuse of medication in emergency medicine is the need to more effectively treat acute pain in older patients." (Terrell et al, *AJEM* July 2006)
- Race and/or socioeconomic status (racial and ethnic disparity in analgesia is controversial; most recent data[23,24] suggest there is diminishing or even no such disparity in analgesia care in the ED)
- Chronic medical conditions (*e.g.*, sickle cell disease)
- MD-related factors (community, as opposed to university, hospital practice; lack of formal EM training; low-volume eds)

Inadequate analgesia has also been identified as a problem in foreign countries

Patients perceived as "drug-seeking" are at particular risk for undermedication

True frequency of drug-seeking behavior unknown but usually vastly overestimated

Patients with true pain syndromes may have "pseudoaddiction" related to incomplete pain control

These patients have suspicious behaviors: drug hoarding, clock watching, specific drug requests, etc.

Symptoms of pseudoaddiction disappear when adequate analgesic regimen is prescribed

Difficulty of distinguishing pseudo-addiction from real addiction is a reason to give patients "benefit of the doubt"

In chronic nonterminal conditions, opioids are used for long periods (up to 6 yrs in studies) without addiction problems

The situation of opioid-induced alterations in pain perception is becoming increasingly well-understood

Basically, these situations occur when opioid therapy results in propensity towards hyperalgesia and allodynia

Additionally, repeated doses of opioids may lead to pro-nociceptive effects (through unclear mechanisms)

The confounding effect of this is manifest by patients on chronic opioids, requiring increased doses of meds

Known drug-seekers should be offered alternative therapy, and when there is doubt err towards analgesic treatment

Agonist/antagonists can be prescribed to potential drug-seekers

It's may be better to "lose" to many drug-seekers than to deny appropriate analgesia once

The EM physician is, at the end of the day, the "tip of the spear" for medical care of patients in pain

EM doctors are necessarily less likely to know patients, and therefore must make decisions with imperfect data

It's easy to criticize either over- or undermedication with analgesia without having to actually be in the ED

Initial pharmacologic approach

Despite plethora of new agents, general ED analgesia remains the province of a few classifications of drugs
- Important exception: diagnosis-specific therapies (examples below)
  - Sumatriptan for cephalalgia
  - Carbamazepine for neuralgia [*N.B.* use of "antiepileptics" for neuropathic pain is popular due to the infrequent or absent need for monitoring of laboratory tests, as well as improved safety margins]
  - Nasal salmon calcitonin for osteoporotic vertebral compression fractures
  - Dexamethasone for pharyngitis
  - Specific regional therapies (trigger-point injection, nerve block, intra-articular local anesthetic injection)
- New agents (*e.g.*, ketorolac, tramadol, COX-2 agents) only marginally complement existing pharmacopoeia

Physicians providing acute care should be familiar with an "increasing potency" stepwise approach to analgesia
- General philosophy: logical progression from nonopioids through potent opioids
- The general approach will be modified for different patient situations, but provides a useful framework

First step in a logical approach to acute pain therapy may in some cases consist of nonopioid analgesics
- These agents are quite effective in many conditions
- In general, nonopioids are associated with fewer nuisance side effects (*e.g.*, drowsiness, nausea) than opioids
- However, nonopioids are increasingly recognized as risking long-term sequelae (*e.g.* On hepatic, renal function)

Nonopioid analgesics used in the ED

Section references[3,7,25-59]

Acetaminophen (Tylenol)

General » *p*-aminophenol derivative providing analgesia comparable to aspirin; little anti-inflammatory activity
- Lack of anti-inflammatory properties relegates acetaminophen to 2nd-line use for many ED conditions (*e.g.*, sprains)
- Acetaminophen is only a weak inhibitor of cyclooxygenase in presence of peroxides found at inflammatory sites

Dosing » given orally or rectally

Advantages » reasonable first-step when:
- Pain isn't severe
- PO or PR route is appropriate
- NSAIDs are to be avoided (*e.g.*, pregnancy)

Disadvantages » few risks, especially with short-term therapy
- Administer with caution in patients with known or suspected (*e.g.*, alcoholic) liver disease
- Consider acetaminophen-containing OTC or prescription medications patient may have taken

Use in ED for analgesia
- Few studies have directly analyzed acetaminophen use in the ED; it was found useful in one analysis of dental pain
- Equianalgesic to NSAIDs in on randomized controlled trial (no additive or synergistic effect)[59]

Bottom line » little downside to use of acetaminophen in the unusual case in which it is appropriate for ED analgesia

NSAIDs

Provide analgesia through inhibition of cyclooxygenase in both its constitutive (COX-1) and inducible (COX-2) isoforms
- Aspirin irreversibly acetylates COX while other NSAIDs compete with arachidonic acid at COX active sites
- COX-1 is constitutively expressed; generates prostanoids involved in platelet aggregation, maintenance of GI integrity
- COX-2 generates prostaglandins that mediate inflammation and pain
- Based on above, COX-2 inhibition is thought to mediate analgesia, and COX-1 inhibition to mediate GI side effects
- Presence of renal COX-2 receptors means that nephropathy and salt retention can occur with COX-2 selective agents
- COX-2 selective agents have preferential activity for COX-2 sites

- At least two studies have demonstrated decrease in GI side effects compared to nonselective NSAIDs
- One prospective controlled trial suggested COX-2 provides analgesia as well as oxycodone
- These agents have indications for chronic therapy, but as of this time no clear indication for ED use

N.B. COX-1 and COX-2 selective agents do not appear to be cardioprotective

NSAIDs consist of different groups of agents depending on chemical structure

- Clinical relevance of this: if an agent doesn't work it may be reasonable to try another from a different class
- Some classes of NSAID which have been used for ED analgesia, with examples (incomplete listing):
  - Salicylic acid derivatives – aspirin
  - Indole/indene acetic acids – indomethacin (Indocin), sulindac (Clinoril)
  - Heteroaryl acetic acids – diclofenac (Voltaren), ketorolac (Toradol)
  - Arylpropionic acids – ibuprofen (Advil), other "-profens", naproxen (Naprosyn)
  - Agents with COX-2 selectivity – celexocib (Celebrex), rofecoxib, (Vioxx)
- In efforts to minimize GI toxicity, combination agents have been developed [*e.g.* Diclofenac/misoprostol (Arthrotec)]

Advantages

- Moderate to high efficacy in a variety of traumatic, inflammatory, and other conditions
- Especially useful for prostaglandin-mediated pain (*e.g.*, menstrual pain, ureteral colic)
- In short-term use, safe side effect profile with fewer nuisance side effects (*e.g.*, nausea, drowsiness) than opioids
- Opioid-avoiding or sparing effect in many cases

Disadvantages

- GI side effects related to ulcerative changes; estimates of GI toxicity based on the literature follow:
  - Gastric or duodenal ulcers develop in 15-30% of those taking NSAIDs regularly
  - 100,000 U.S. hospitalizations and 16,500 deaths occur annually as a result of NSAID-associated GI events
- Blockade of platelet aggregation
  - In one study of normal volunteers a single dose of IM ketorolac prolonged bleeding time by 50%
  - This may be particularly relevant in patients who may need operative intervention (*e.g.* Abdominal pain)
- Not used in pregnancy: inhibition of uterine motility and potential effects (*e.g.*, PDA, ICH, NEC) on neonates
- Inhibition of renal function
  - NSAIDs inhibit prostaglandin synthesis which has multiple potential effects, including hyponatremia
    - Renal prostaglandins are associated with maintaining water balance
    - Water retention disproportionate to sodium retention can cause hyponatremia
  - NSAIDs can cause nephrotic syndrome (especially in patients with other autoimmune disorders such as SLE)
  - NSAIDs can also cause interstitial nephritis
  - NSAID-related renal complications, less likely with short-course therapy, may appear after NSAID cessation
- COX-2 agents incur risks of cardiovascular side effects which tend to outweigh their benefits from ED prescription
- NSAIDs may be relatively ineffective for non-prostaglandin-mediated pain (*e.g.*, edema pressure, neuralgia)
- Some evidence suggests that NSAID therapy for fractures is associated with increased risk of non-union

Choosing the NSAID to use – general guidelines

- Different agents (especially in different classes – see above) may have different efficacy for a given patient
  - There is little supporting literature for this principle but it makes some pharmacological sense
  - Changing classes may allow room for changing a patient's regimen without resorting to opioids
  - In general, difficult to predict which agent will be more potent in an individual patient
- Some agents (*e.g.*, indomethacin) seem to have more prominent side effects
- Many ED investigations comparing varying agents have failed to identify one NSAID as superior to another
- While detailed discussion of COX-2 agents is beyond coverage of this handout, some salient points include:
  - COX-2 agents have well-characterized risk with respect to cardiovascular side effects
  - COX-2 agents are not reliably safe in patients with asthma & aspirin intolerance
  - There are suggestions of increased warfarin levels due to cytochrome inhibition by COX-2 agents
  - Nephrotoxicity is risked as renal glomeruli, interstitium, and vasculature constitutively express COX-2

Outlining details of individual NSAIDs is outside this discussion's scope – an example agent (ketorolac) is described below

Ketorolac (Toradol)

General » NSAID (see above); particularly useful in pain with inflammation/trauma

Dosing » most experience is with 30-60mg IM or IV (OU use is useful for corneal abrasions/ulcers)

Advantages » easy (IM or IV) analgesia with no respiratory depression

Disadvantages » NSAID side effects (see above)

Use in ED » studies demonstrate ED utility of IV ketorolac, though it's unclear whether IV ketorolac is better than PO NSAIDs

- Studies assessing both IV and IM routes have found ketorolac superior to meperidine for renal colic analgesia
- Opioid-sparing effect of ketorolac: sickle cell crisis patients receiving IV ketorolac probably require less morphine
- Ketorolac *vs.* Oral non-steroidal agents: how much difference in efficacy?
  - At least 5 ED studies have failed to demonstrate superiority of ketorolac to oral NSAIDs
  - Similar pain score reduction, rescue medication rates, and side effect occurrence
  - One well-conducted trial questions extra "placebo" effect from IM *vs.* PO administration
- Interestingly, and with high import to EM, one study suggests NSAIDs increase non-union in fracture patients

Bottom line » example of useful NSAID which can be given by multiple routes, can attenuate or eliminate need for opioids

Ketamine (Ketalar)

General » phencyclidine-like agent causing dissociative anesthesia – sedation and analgesia with altered pain perception

- Effects: trance-like cataleptic state with open eyes (nystagmus may be seen)
- Random tonic extremity movements may occur and sympathomimetic effects are commonly noted

Dosing » in the ED, ketamine is usually given as a procedural sedative/analgesic rather than as a simple analgesic

- Ketamine has been reported useful in the acute care setting when given IV, IM, PO, IN, and PR
- Onset and duration vary by route of administration (very quick when used IV)
- Other medications (*i.e.*, atropine, benzodiazepine) are usually co-administered due to side effects of ketamine
- One 2013 study[58] demonstrates use of low-dose ketamine (15 mg) to allow for opioid-sparing for hydromorphone use in ED
- IN ketamine can be potentially useful as a non-dissociative analgesic (0.5 to 0.75 mg/kg)[60,61]

Advantages

- Excellent analgesia with preservation of airway reflexes and no hypotension (hypertension may be an issue)
- Demonstrated utility as an "opioid-sparing" agent in the prehospital setting[57]

Disadvantages

- Caution for increasing intracranial or intraocular pressure
- Risk of laryngospasm
- Emergence reactions
- Post-ketamine vomiting (usually occurs hours after drug administration)

Use in ED » analgesia/sedative for short painful procedures where local anesthesia not ideal (*e.g.*, incision/drainage)

Bottom line » useful primarily for procedural sedation, but may be appropriate for analgesia in some circumstances

- Emerging literature is suggesting utility to subdissociative dosing for effective analgesia[62]
- Data suggest small doses of ketamine (0.15 mg/kg or 0.30 mg/kg) can be adjuncts to opioid analgesia[63]
  - Higher doses: more likely to reduce pain
  - Higher doses: more likely to induce dysphoria and dizziness

Nitrous oxide (Nitronox)

General » inhaled rapid-onset, short-acting analgesic which is usually used in the ED during procedures

Dosing » generally self-administered (by patient) in 50:50 mix with oxygen; onset and offset within 3-5 minutes

Advantages » related to excellent safety/efficacy profile and ease of use

- Noninvasive means for easy provision of analgesia with accompanying light sedation
- Particularly useful for short painful procedures (*e.g.*, I & D, fracture reduction); obviates need for opioids
- Excreted unchanged by lungs – not affected by renal/hepatic function

Disadvantages » may accumulate in enclosed body cavities (*e.g.*, middle ear or bowel) or lungs (COPD patients)

Use in ED » like ketamine, useful primarily for procedural analgesia (*e.g.*, dental procedures, joint reduction)

Bottom line » like ketamine, primarily a procedural analgesic

Opioid analgesics used in the emergency department

Section references[1,2,33,64-94]

A brief review of opioid pharmacology is in order before consideration of specific agents:

- Opioids provide analgesia by receptor-mediated blockade of neurotransmitter release and pain transmission
- Clinical relevance of receptor types is found in tracking effects and side effects of agonists and antagonists
- There are 3 general classes of opioid receptors (μ, κ, δ) with multiple subtypes (not addressed here)
- Most clinically used opioids (with exception of agonist/antagonist agents) are relatively selective for μ receptors
    - μ receptor is associated with analgesia; this is main analgesia mechanism of clinical importance
    - μ receptor is also associated with euphoria, respiratory depression, miosis, constipation
- There is diversity of opioid receptors, resulting from different splice variants of the μ and κ receptors
    - Clinical relevance of this: cross-tolerance may be incomplete between various opioids
    - Bottom line: when one opioid is "maxed out" a switch to another opioid may well have salutary effects
    - When a switch is contemplated, the second opioid should be started at half the equivalent dose of the "failed" opioid
- Especially in elderly, constipation is common, persistent, and difficult to treat (early supportive measures can help deal with this)
- As opioid doses increase, μ-selectivity declines and effects from other receptors become increasingly relevant
    - κ receptor associated with some analgesia; also sedation, GI motility, and dysphoria side effects of opioids
    - δ receptor effects poorly elucidated; appear to be spinal analgesia and antinociception for thermal stimulus

Morphine

General » gold-standard opioid agonist with relative μ-selectivity

Dosing » is regularly used IV, IM, SQ, and PO (in outpatient setting)

- Onset 5-20 minutes IV, 10-15 mins IM/SQ, with effective analgesia for 3-4 hours
- Maximal respiratory depression occurs within 5-10 minutes after IV administration, 30 minutes of IM injection

Advantages » standard texts clearly note advantages over meperidine, which is actually used more commonly

- Longer half-life with metabolism little affected by hepatic or renal problems
- Much less CNS toxicity
- No myocardial depression
- Naloxone reverses untoward effects of morphine much easier than those of meperidine
- Morphine absorption after IM injection less variable, erratic, and incomplete

Disadvantages » primarily related to respiratory and, to a lesser degree, cardiovascular depression

- To minimize respiratory depression use smaller incremental doses in patients at age extremes
    - Beware hypoxia in patients with respiratory disease (*e.g.*, COPD)
    - Beware use of morphine with other agents (*e.g.*, benzodiazepines) with respiratory depressant effects
- Some patients may have histamine-mediated reactions, but true allergy is unusual
- Like other opioid agonists, morphine causes increased biliary pressure
    - Morphine is probably not much worse in this respect than most other opioid agonists
    - Best analgesia for pancreatic or biliary pain is meperidine, agonist/antagonist, or nonopioid

Use in ED » studied and proven effective in myriad conditions: orthopedics, renal colic, intra-abdominal conditions, etc.

- Rapidly effective and relatively easy to titrate when given IV
- Side effects in general practice (*e.g.*, nausea, respiratory depression) are reasonably easy to predict, detect, and treat
- Morphine and nausea
    - Nausea is uncommon (*Goodman and Gilman's*) when morphine given in acute setting
    - Though antiemetics are often co-administered, this is probably unnecessary and may compound side effects
- 2012 report[95] describes excellent efficacy of PCA morphine as used in the ED for acute abdominal pain
    - 0.1 mg/kg initial dose
    - 1 to 1.5 mg subsequent doses with 6-minute lockout

Bottom line » generally speaking, this is the first-choice agent (given IV) for acute analgesia in patients with severe pain

Hydromorphone (Dilaudid)

General » synthetic opioid

Dosing » given IV preferentially; timing characteristics similar to morphine

Advantages » similar to morphine

- Probably associated with same or slightly better analgesia as morphine (0.015 mg/kg hydromorphone with 0.1 mg/kg morphine)
- As compared to morphine, associated with lesser incidence of pruritis
- Allows for lower volume injection (this is uncommonly clinically relevant)
- Clearly demonstrated utility, when applied as a part of an "automatic" analgesia regimen in the ED[91]
  - 1mg hydromorphone given per protocol
  - 1mg repeat dose given if inadequate pain relief after 15 minutes
  - Regimen is associate with safe, more effective pain control than "standard" therapy

Disadvantages » less familiar to many practitioners but no major disadvantages

Meperidine (Demerol)

General » synthetic opioid; 10% potency of morphine; one of the most commonly used opioids in US

Dosing » given IM, IV, SQ; IV onset usually within 5-10 minutes with duration 2-4 hours

Advantages » only advantage over morphine is less biliary tract spasm and this is a borderline difference

Disadvantages » toxicologic, rather than efficacy, considerations relegate this agent to largely second-line use

- Occurrence of untoward effects may be increased due to frequency of usage of IM route (attendant delay in effects)
- Overdose dx may be difficult to because of absence of pinpoint pupils, due to antimuscarinic-mediated mydriasis
- As compared to morphine, pre-sedation treatment with meperidine is associated with longer recovery times (Losek, '06)[74]
  - Study of ketamine/midazolam pts receiving either morphine or meperidine within a few hours pre-sedation
  - Authors' conclusion: "We recommend meperidine not be used for initial ED pain treatment of children."
- Metabolite normeperidine causes CNS stimulation (*e.g.*, anxiety, disorientation, seizures, hallucinations)
  - Pts susceptible: those with poor renal function or frequent dosing (*e.g.*, sickle cell disease, PCA pumps)
  - Meperidine's depressant effects may protect against normeperidine, thus there can be toxicity after naloxone

Use in ED » studied and shown useful in many ED conditions, but less effective than nonopioids for renal colic and headache

Bottom line » a reasonable first-line agent for pain associated with biliary spasm, otherwise second-line

Fentanyl (Sublimaze, Actiq)

General » synthetic opioid 100 times more potent than morphine

Dosing » generally given IV, with rapid onset due to lipophilicity (7000x morphine) and rapid CNS uptake

- Should be given in multiple smaller doses for better titration and reduced side effects (*e.g.*, chest wall rigidity)
- When given IV, onset is within 1-2 minutes with duration 20-30 minutes
- Oral-transmucosal route (OTM) primarily used for procedural analgesia in children (onset/duration 15/60 minutes)
  - This route also used for cancer breakthrough pain (primarily for patients with opioid tolerance)
  - In the lower doses (200µg or 400µg) OTM fentanyl may prove useful in the acute pain setting[88]
  - Intranasal fentanyl may not be as efficacious as morphine but is useful due to ease of administration[89]
  - OTM fentanyl adds significant analgesia in NO-facilitated hematoma-block fracture reduction[93]
  - OTM safe and effective for tactical/battlefield analgesia
- Nasal delivery (1.7 mcg/kg of 150 mcg/ml) provided pediatric analgesia equal to 0.1 mg/kg morphine in one study
  - Another study finds IN fentanyl (1.5 mcg/kg) allows for much more rapid analgesia in children (than IV morphine)
  - A third study[90] demonstrates 2 mcg/kg (max 100 mcg) IN fentanyl highly effective in pediatric ortho trauma pain
    - Atomizer used in children aged 3-18
    - Max dosage based on 1 ml max volume (50 mcg/ml in each naris)
    - Dosage based on bioavailability of 71%
    - Analgesia checked at 10 minutes post-dosing
  - IN fentanyl (1-3 mcg/kg) appears to provide rapid, effective analgesia in pediatric patients (especially younger ones)[61]

Emerging randomized controlled trial data demonstrate safety and efficacy for nebulized fentanyl

- Most data in children, with dose of 3 mcg/kg

Breath-actuated delivery device not useful for ages under 3 years

Advantages » related to high efficacy, ease of titration, and relatively rapid offset

No histamine release and minimal cardiovascular effects when titrated properly

Ease of use by transmucosal route for pediatric patients (although arguably negated by high incidence of vomiting)

Disadvantages » respiratory depression and chest wall rigidity are major concerns

Co-administration of agents such as benzodiazepines compounds risk of hypoventilation or apnea

Rapid administration or doses >5-8 μg/kg may result in chest wall rigidity

Inspiratory motor neuron stimulation causes sustained inspiration

Chest wall rigidity extremely rare, if ever, at ED doses (<3-5 μg/kg)

Use in ED » established safety/efficacy for ED use (*e.g.*, lacerations, orthopedics, abscess incision/drainage, trauma)

May be particularly helpful in patients who need analgesia but who have borderline blood pressure

Broad range of studies now clearly demonstrate fentanyl utility in a variety of situations (*e.g.* Transmucosal analgesia)

Has demonstrated utility in the prehospital setting where its rapid onset/offset make this agent attractive

Bottom line » very useful analgesic in certain situations; sometimes the first-choice agent for acute pain management

Other opioid agents

Alfentanil (Alfenta)

Compared to fentanyl, alfentanil has: 20% potency, 33% duration, 38% half-life

Repeat dose accumulation less of a problem than with fentanyl

Advantages and pharmacology make alfentanil theoretically useful in the ED

Currently no data on ED utilization of this agent so it remains unrecommended

Sufentanil (Sufenta)[96]

Fentanyl analog with potency range to morphine estimated at 700-1000x

Preliminary work has been done in prehospital setting (with physicians present)

Sufentanil (0.15 mcg/kg initially then 0.075 mcg/kg as needed q3-minutes)

Morphine comparison (0.15 mg/kg initially then .075 mg/kg as needed q3-minutes)

No difference in efficacy or side effects between the two above regimens

Butorphanol (Stadol)

Agonist/antagonist (effects primarily at κ receptors)

May be used parenterally or intranasally

Useful when pure agonists are not appropriate (*e.g.*, biliary spasm, suspicion of drug-seeking behavior)

Like other agonist/antagonists, psychotomimetic side effects are relatively problematic (also with transnasal route)

For transnasal spray route, early ED studies indicate >90% patients with pain relief within 15 minutes

Codeine

Given PO; characterized, like oxycodone and methadone, by high oral-parenteral potency ratio

Codeine's analgesic effects are primarily due to metabolism of a small portion (10%) to morphine

Codeine's well-characterized anti-tussive effects are probably due to direct action of codeine

Relatively high rates of nausea relegate codeine to secondary role behind that of hydrocodone (see below)

Hydrocodone (Vicodin)

Oral agent, approx. Equipotent to generally-used doses of codeine, but with significantly lower incidence of nausea

Arguably, one of the most useful opioids for oral prescription from the ED (can be given in multiple strengths)

Head-to-head ED trial, 5mg hydrocodone/APAP had similar safety/efficacy as found with 5mg oxycodone/APAP

Oxycodone (Percocet)

Most potent opioid prescribed for outpatient oral therapy from the ED

Like other agents, comes with aspirin or acetaminophen; caution patients about additive toxicity from OTC meds

Propoxyphene (Darvon)

Goodman and Gilman's states popularity of this agent due to unrealistic fears of addictive potential of other opioids

Arguably provides little analgesia beyond that of the co-administered aspirin or acetaminophen

Compared to most other opioids, relatively high risk of toxicologic problems

Long half-life of norpropoxyphene (30 hours) translates into increased risk for accumulation

Delusions, hallucinations, seizures may be difficult to treat
Large doses of naloxone may be required to ameliorate toxicity, and can be incompletely effective

Pentazocine (Talwin)
Agonist-antagonist oral agent, used most often in patients with chronic severe pain or who are addiction risks
Some pills come with naloxone
The naloxone is destroyed rapidly by the liver
Inclusion of naloxone is for prevention of parenteral injection of PO drug
May be useful for oral prescription in the ED population in whom drug-seeking is suspected

Buprenorphine (Buprenex and others)
Preliminary study[92] suggests 0.4 mg sublingual buprenorphine is equally efficacious for fracture pain as 5 mg morphine
Trial above did not assess what's known to be an adequate dose of morphine, so uncertain what to make of results
When no IV access is available and sublingual buprenorphine is available this may be a useful option

Tramadol (Ultram)

General » centrally acting oral agent marketed for management of chronic pain; its mode of action is incompletely characterized
Parent and metabolite bind to μ-opioid receptors; despite μ-binding, naloxone incompletely reverses analgesia from tramadol
Complementary analgesic pathway likely related to inhibition of reuptake of norepinephrine and serotonin

Dosing » oral medication for long-term use – analgesia begins within an hour of dosing and peak effects occur in 2-3 hours

Advantages » intended to provide effective analgesia with less potential for abuse than that associated with other opioids

Disadvantages » primarily related to fact that tramadol is an opioid, even though a relatively weak one
Cannot be used in patients suspected of "drug-seeking" as it is associated with some risk of dependency
Opioid-like side effects (*e.g.*, dizziness, somnolence, nausea, constipation, pruritis) have been observed in trials

Use in ED » ED study showed tramadol fared poorly *vs.* Hydrocodone/acetaminophen

Bottom line » at this time, little ED role

Analgesia in specific clinical situations

Specific approach to analgesia should be individualized for the patient and clinical situation

A few selected diagnoses will be mentioned as examples of current areas of clinical pain research

This handout is not intended as a pain text – diagnoses considered in this section simply represent some areas of interest

Analgesia in the prehospital setting [57,73,79,82,83,89,96-111]

Despite prevalence of pain in EMS-transported patients, analgesia provision rates are poor (about 10%) even for isolated fractures

Undertreatment of pain occurs even when prehospital providers correct identify patients as having fractures
May be related to agents[109] selected for analgesia more than anything else
Fentanyl in combination with inhalational analgesia (methoxyflurane) has been found particularly effective for EMS[109]

Medical control is part of the problem, but even standing orders haven't been universally successful in improving analgesia rates
Studies that have reported on prehospital analgesia, have often found underdosing and suboptimal pain relief
Even physician-staffed EMS systems tend to achieve roughly 50% effective pain relief (as rated by patients)

There are multiple "right" answers and the most important goal should be to have EMS able to give something strong

Answer to better analgesia lies in tackling numerous barriers (*e.g.* Safety concerns), but interventions have been shown to be effective

Most important issue is proper use of selected analgesia (*eg.* Sufficient dosing), rather than specific analgesic selected

Interesting trends in prehospital analgesia
Use of intranasal fentanyl (which works as well as IV morphine)
Patient self-administration of inhaled anesthetic methoxyflurane (doesn't work as well as morphine but still efficacious)
Use of nitrous oxide (one 2013 study demonstrated excellent efficacy and few side effects in France[111]
Use of ketamine in one study demonstrated utility in combination with morphine[57]
Higher incidence of certain side effects (*e.g.* Disorientation) which may impact ability to get history at ED

Relatively high overall side effects incidence of morphine/ketamine: 39%
Since side effects were judged "minor" and ketamine allowed for lesser morphine, trial was judged a success
Study only assessed ketamine use in minor trauma

Analgesia in the multi-trauma patient [3,72,73,79,82,86,102,110,112-116]
Trauma patients are historically denied analgesia during their initial evaluation (and indeed, throughout their ED stays)
Some EMS services have tried nonpharmacologic approaches (*e.g.* TENS) with varying success
Recent data indicates trauma patients can receive analgesia without workup impairment
Trauma Combat Casualty Care (TCCC) courses for military are increasingly emphasizing early and effective analgesia[110]
"The prehospital practitioner has the first and perhaps only opportunity to break the pain cascade"
"Pain relief is a critical aspect of casualty care"
"Early, effective pain control is essential to successful outcomes after traumatic injury"
Untreated pain has multiple acute physiological effects which create severe casualty distress
Battlefield management is complicated
"Uncontrolled pain exacerbates injury and potentially increases mortality of otherwise survivable injuries"
Poorly treated pain also risks PTSD – early opioid administration reduces risk of PTSD development
TCCC courses' improved emphasis on pain management appears to be improving combat analgesia for trauma[110]
Protocols for early ED use of fentanyl suggest both safety and efficacy (better pain control, far sooner than non-protocol patients)
Titrated fentanyl is safe and effective in trauma, and obscuration of findings is a minimal problem (*caveat*: neuro exam in head-injured)
Fentanyl's short duration of action makes this agent an excellent choice
Opioid effects can be allowed to wear off, or be reversed with naloxone, in the rare case this is indicated
Concerns for overmedication have been voiced – problems occurred mostly in ICU/floor but reinforce importance of risk assessment

Analgesia in renal colic[117,118]
Standard therapy: opioids
Main problems in treating renal colic
Delayed administration of analgesia (perhaps due to concerns about diagnostic certainty – see next section)
Underdosing of analgesics in patients with severe pain, due to non-evidence-based safety concerns
Recent prospective controlled trial: morphine + ketorolac better than either agent alone
Morphine 5mg initial dose (*N.B.* a quite reasonable initial dose)
Ketorolac 15mg co-administered
No study has validated concerns about 1-2 doses of ketorolac with respect to renal function in setting of ureteral colic
Recent data suggests that in situations in which IV access is not practical IM NSAIDs provide reasonable pain relief

Analgesia in the acute abdomen [2,3,119-146]
Historic view: defer analgesia until definitive diagnosis (older editions of *Cope's*)
With time, many have realized that policy of deferred analgesia is not based on sound data
Earlier *Cope's* criticized by EM specialists and general surgeons for deferred analgesia policy
Many journal letters (written by both surgeons and emergency physicians) agree
Newer editions of *Cope's* » rapprochement with critics of deferred analgesia ("cruel practice" of deferred analgesia is condemned)
Fundamental question: What effects do opioids *really* have on the abdominal exam?
Little data (anecdotal or otherwise) to argue against some degree of pain relief
Early concerns of Cope were based on IM injection of up to 30mg of morphine
What data there is seems to support early analgesia in the acute abdomen
No evidence for exam impairment; diagnostic improvement suggested
Precedent for pre-exam sedation is well-documented in pediatric patients
Existing data do not support definitive conclusion either way
Significant theoretical advantages to early analgesia
In general, opioids block central rather than peripheral pain perception; tenderness still localizable
Removal of rectus spasm may improve exam quality

Calmer, less-suffering patients provide better history and exams

Early British surgical studies, first to address issue, suggested no problems with early analgesia, but serious methodological issues

U.S. ED study of IV morphine by emergency physicians for early abdominal pain relief also found no problems with analgesia

No difference in misdiagnosis found between MS and saline placebo group

"tendency" (p = 0.08) towards improved diagnosis in MS group (compared to placebo)

A preliminary U.S. study reported fentanyl did not obscure dx in abdominal pain (never reported in full-length paper, however)

A prospective randomized trial in Singapore specifically analyzed early tramadol analgesia in patients with RLQ pain

Analysis was done for all patients, as well as subset analysis for patients ultimately diagnosed with appendicitis

No masking of abdominal findings was found despite significant pain relief in the tramadol group

Recent randomized controlled trials, as well as retrospective reviews, strongly suggest analgesia safety in pediatric and adult patients

One study in pediatrics patients, and one study in adults, with very similar double-blind trial designs: opioids safe

A consecutive-patient review in pediatrics has found no opioid interference with diagnosis of appendicitis

Retrospective review of opioids' effect on sonographic Murphy's sign: no effect (trial at MGH)

2006 paper[141] provides both strong evidence (no danger from opioids in RCT design) and excellent review of literature

With these studies, preponderance of evidence clearly in favor of analgesia

2014 review and meta-analysis of six pediatric undifferentiated abdominal pain studies[146]

Analgesia is safe (no increased perforation or abscess) although side effects rate higher (*e.g.* pruritis, nausea)

No justification to withhold analgesia in pediatric abdominal pain patients with appy as major concern

2012 paper[95] reports use of PCA (morphine) for abdominal pain with significant efficacy (no diagnostic issues/problems reported)

Summary of data/information existing to this point:

1) there is very little or no data supporting opioid withholding in acute abdominal pain
2) what data exists seems to support early analgesia for acute abdominal pain
3) exam findings are very likely not masked, and may be enhanced/clarified/focused, by analgesia
4) in general, the more senior the physician, the less concern there is with masking of findings
5) any masking of abdominal exam findings is probably reversible with naloxone
6) long-term (*i.e.* Hours) opioid withholding in acute abdominal pain should be viewed as inappropriate

Caveats in provision of emergency department analgesia for patients with abdominal pain

Early E.D. analgesia policy should be instituted in a cooperative manner by specialists in EM and Surgery

Patients should not be given IM opioids and then discharged home

This has long ago been identified as a risk in treating undifferentiated abdominal pain

Recent study (Gallagher *et al*)[141] identified potential risk in assigning "abd pain unknown etiology" and discharging pt

In many cases, judicious dosing of opioid analgesia will achieve goal of pain relief and optimize patient evaluation

Smaller doses of opioids are preferable, and titration of analgesia is key – but inadequate analgesia doesn't help patients

One reasonable criticism of existing abdominal pain analgesia literature: low-dose analgesia doses are used

If inadequate analgesia is given, it's not likely to alter the exam, but also not likely to improve patient comfort

Thorough familiarity with relevant literature is suggested before it is simply quoted as "supporting analgesia"

These papers all have methodological flaws which have been (often correctly) noted by critics of analgesia

Two resources/reviews which may be useful: Thomas and Silen, *British Journal of Surgery*[139] and Gallagher *et al*[141]

Safety in emergency department analgesia

Advantage of opioid utilization in ED: availability of O_2 and resuscitation equipment

Opioid respiratory depression (mechanism: decreased brainstem sensitivity to blood CO_2) is the primary issue

Monitoring techniques which may be utilized during IV analgesia: cardiac, s_pO_2, and $ETCO_2$ monitoring

Initial therapy for opioid-induced hypoventilation: stimulation

Reversal agents may be useful: naloxone (half-life 1.1 hr) and nalmefene (half-life 10.8 hr; minimal experience)

The road to maximal patient safety: intelligent patient and drug selection, familiarity with agents, and close monitoring

Cases in acute pain management

Note: The following cases are intended to focus discussion on acute pain management. The accompanying handout can be consulted as a guide to the analgesia queries involved in the individual cases, but the reader should be cognizant that there are many reasonable approaches to therapy of acute pain and thus there may be many "right" answers to the cases.

Case #1

- 35 YO male long-haul truck driver with 3-4 hours of colicky left flank pain, radiating toward groin: "I have a kidney stone"
- patient reports urinary discoloration and urine dipstick reveals +++ blood
- hemodynamically stable with no positive findings except for left CVA tenderness
- analgesia issues to consider:
    1. At what point in clinical evaluation and management is analgesia indicated?
    2. What analgesics are most appropriate in this clinical setting?
    3. Can this patient safely leave the ED (*i.e.*, to go to Radiology) after analgesics are given?
    4. What other analgesia-related issues impact this patient's disposition plans?
    5. What about analgesia when the abdominal pain diagnosis isn't so apparent upon initial presentation?

Case #2

- 22 YO female presents late on a weekday night with 2 days of "severe sore throat" (her words)
- exam reveals significant exudative pharyngitis with no other issues
- analgesia issues to consider:
    1. Does this patient need an analgesic in the E.D.? As a prescription for outpatient management of pain?
    2. If so, what agents and routes of administration should be used in the ED?

Case #3

- 70 YO female sustained non-syncopal fall and has pain and exam suggestive of a hip fracture
- patient has no past medical history and is hemodynamically stable
- analgesia issues to consider:
    1. If one is to administer analgesia, what agents and routes of administration should be employed?
    2. What monitoring is indicated during her trip to X-ray?
    3. What about concerns surrounding analgesia and possible need for OR consent?

Case #4

- 50 YO male presents to ED Sunday evening, complaining of back pain with no other symptoms
- exam reveals no worrisome findings and patient is ambulatory with complaints of "severe pain"
- the patient is on disability since a motor vehicle collision; no history of operative intervention
- analgesia issues to consider:
    1. Does this patient require analgesia?
    2. What is the role of the patient's past medical history in managing his pain in the ED?
    3. What are issues surrounding provision of opioids to a patient such as this?

Case #5

- 20 YO male sustained fall while skateboarding 3 hours ago; c/o right shoulder pain
- patient cannot move his right arm but has no neurovascular complaints or findings
- X-rays confirm anterior shoulder dislocation, which is reduced in the ED with some difficulty
- analgesia issues to consider:
    1. What impact does procedural sedation/analgesia have on outpatient pain management?
    2. After this patient's shoulder is reduced, is outpatient analgesia required?

Case #6

- 50 YO male pedestrian involved in motor vehicle collision; entrapped legs at scene
- patient has apparent fractures in the right leg and complains of severe pain in the leg
- MedFlight arrives at the MVC scene and finds patient hemodynamically stable
- analgesia issues to consider:
    1. Should this patient receive analgesia if he remains entrapped? What if entrapment is relieved and he's 6 minutes away from trauma center by helicopter?
    2. What analgesia agents are used by prehospital providers?
    3. What are concerns about administration of opioid/nonopioid analgesics to this patient?

Case #7

- 50 YO male with history of migraine headaches, presents with cephalalgia
- patient has no differences between this headache and multiple previous episodes
- he reports that "Demerol has always worked well" in the past
- analgesia issues to consider:
    1. Which analgesia agents may be preferable in this situation?
    2. What are thoughts about use of meperidine in this patient?

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