

Analgesic use in acute abdominal pain

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Abstract

Background: Traditional practice has been to avoid the use of analgesics in cases of acute abdominal pain until a definitive diagnosis has been established, for example after surgical consultation. However the Australian guideline 'Acute Pain Management: Scientific Evidence' (2005) states that "Pain relief does not interfere with the diagnostic process in acute abdominal pain in adults or in children". The purpose of this review is to provide an update on the current evidence regarding the effect of analgesics on the diagnostic process in acute abdominal pain published since the Acute Pain Management guideline in 2005.

Clinical Questions: In patients with acute abdominal pain, does administration of analgesics

1. alter the history given by the patient?
2. alter the physical examination?
3. result in more diagnostic errors than in patients not receiving analgesics?

Methods: Searches were undertaken in guideline websites, websites of centres for evidence-based practice and relevant health databases for evidence-based guidelines, health technology assessments, systematic reviews or randomised controlled trials (RCT) published since 2005.

Articles were selected and appraised by one reviewer in consultation with colleagues, using inclusion, exclusion and appraisal criteria established *a priori*.

Results: One systematic review and three RCTs were found which addressed the above questions. Two of the RCTs were appraised in the systematic review and were therefore not included in this review. The studies identified only assessed opiate analgesics; no studies on other types of analgesics were identified. The systematic review included studies with both adults and children. The RCT enrolled only adult subjects. Both the systematic review and RCT appeared to be well conducted studies without major methodological problems.

1. No studies were identified that explicitly evaluated the effect of analgesics on the history given by the patient.
2. The systematic review found that there was a non-significant trend toward changes in the physical examination with opiate administration, with a summary Relative Risk (RR) for adults of 1.51 (95%CI 0.85, 2.69) and RR for children of 2.11 (95%CI 0.60, 7.35). When combined, the summary RR for both adults and children became statistically significant 1.55 (95%CI 1.02, 2.36). The clinical significance of this finding is unclear since studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful change (such as changes in peritoneal signs).
3. The systematic review found that there was no significant change in the rate of incorrect management decisions among patients who received opiates, risk difference in adults 0.3% (95%CI -4.1%, 4.7%) and children -0.8% (95%CI -8.6%, 6.9%). This remained non-significant when adult and paediatric studies were combined (risk difference 0.1%, 95%CI -3.6%, 3.8%).

The RCT found no significant difference in clinically important diagnostic accuracy between the opiate and placebo groups. This was 86% (67/78) in the morphine group versus 85% (64/75) in the control group, a risk difference of 1% (95%CI -11%, 12%).

Conclusions: The results indicate that opiate analgesics provide analgesia without increasing the number of diagnostic errors. These findings are consistent in both adults and children.

A number of studies report that opiate administration altered the physical examination findings but the clinical implications of this are unclear. Even when changes in physical examination are noted, there is no increase in management errors.

Background

Traditional practice has been to avoid the use of analgesics in cases of acute abdominal pain until a definitive diagnosis has been established, for example after surgical consultation. This withholding of analgesics was for fear of masking symptoms and signs that lead to diagnosis, potentially resulting in delayed surgical intervention and adverse outcomes. This can be traced back to a recommendation made by Dr Zachary Cope in 1921¹. Dr Cope's caution may have been appropriate for his time, but given that this was over 70 years ago, his recommendation may not be so relevant today. Ironically the latest editions of Cope's original text now tentatively recommend judicious use of analgesics^{2,3}.

The Australian guideline 'Acute Pain Management: Scientific Evidence' (2005) states that⁴:

"A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief does not interfere with the diagnostic process in acute abdominal pain in adults (McHale & Lovecchio 2001, Level I; Thomas et al 2003, Level II) or in children (Kim et al 2002, Level II)."

The purpose of this review is to provide an update on the current evidence regarding the effect of analgesics on the diagnostic process in acute abdominal pain published since the Acute Pain Management guideline in 2005.

Clinical Questions

In patients with acute abdominal pain, does administration of analgesics

1. alter the history given by the patient?
2. alter the physical examination?
3. result in more diagnostic errors than in patients not receiving analgesics?

Methods

The Centre for Clinical Effectiveness undertook a systematic approach to identify and appraise the evidence related to this question. NICS staff and clinicians from the NICS Emergency Care Community of Practice (ECCoP) assisted in development of search terms and inclusion and exclusion criteria.

1. Inclusion and exclusion criteria

Patients	Inclusion: Patients with acute abdominal pain (as defined by study authors), adults or children older than 12 months Exclusion: Pregnant women, infants under 12 months
Intervention	Inclusion: Any analgesia (from list of medications confirmed by NICS ECCoP Reference Group), any route Exclusion: Other medications
Comparison	Inclusion: No analgesic or placebo Exclusion: Other analgesics
Outcomes	Inclusion: Change in diagnostic parameters – patient history and clinical examination, accuracy of diagnosis as compared to a reference standard (diagnosis confirmed by surgical findings, imaging, other tests) Exclusion: Nil
Setting	Inclusion: Emergency Department or General Practice Exclusion: Other settings
Study design	Inclusion: Evidence-based guidelines, HTAs, systematic reviews, RCTs, controlled trials Exclusion: All other study designs, commentaries, editorials, draft documents
Evidence-based Guidelines	Inclusion: systematic approach to identify, select and critically appraise relevant research and/or explicit links between recommendations and the evidence. Exclusion: expert opinion only
Publication details	Inclusion: Studies in English and conducted on humans, published from Jan 2005 Exclusion: Studies in languages other than English, published prior to 2005

2. Search strategy

Searches were undertaken in guideline websites, websites of centres for evidence-based practice, Australian government health websites and relevant health databases. Full details of the sources of evidence searched are outlined in appendices.

2.1 Website identification

The review team were aware of a number of generic guideline clearinghouses and websites of guideline developers. Additional sources of guidelines specific to this research question were identified using the Google search engine. Initial searches for websites of relevant professional associations and peak bodies were undertaken but the huge number of sites identified (>2 million) prevented systematic searching within them. Websites of centres of evidence-based practice in the relevant professional groups were identified and assessed if they contained guidelines. Many of these sites are focused on education about evidence-based practice and do not contain publications or similar resources; these sites were excluded. Details of the search strategy and websites included are outlined in Appendix 1.

2.2 Website searches

Guideline websites were searched using the internal search engine. Centres of evidence-based practice and government websites were searched using an internal search engine where available. In addition, guideline or publication lists within the sites were scanned for items relevant to the research question.

2.3 Internet search

An internet search using the Google search engine was undertaken to identify relevant guidelines.

Google Advanced Search

With all of the words	analgesi* pain
With the exact phrase	
With at least one of the words	guideline evidence
Without the words	

A summary of all guidelines identified, their source/s and reasons for exclusion are detailed in Appendix 2.

2.4 Database searches

Database	Date of Search
All EBM Reviews (Ovid)*	April 23 rd 2007
Medline (Ovid) from 1966	April 23 rd 2007
CINAHL (Ovid) from 1982	April 23 rd 2007
The Cochrane Library**	April 30 th 2007

*(including The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, The Database of Abstracts of Reviews of Effects (DARE), ACP Journal Club)

** for HTAs

Search undertaken in Medline*

1. exp Abdominal Pain/	21. ergotamine.mp.	41. phenacetin.mp.
2. abdom\$.mp.	22. fentanyl.mp.	42. piroxicam.mp.
3. pain.mp.	23. heroin.mp.	43. salicylate\$.mp.
4. 2 and 3	24. diamorphine.mp.	44. sufentanil.mp.
5. 1 or 4	25. hydrocodone.mp.	45. sulindac.mp.
6. exp Analgesics/	26. hydromorphone.mp.	46. tramadol.mp.
7. analgesi\$.mp.	27. ibuprofen.mp.	47. hyoscine.mp.
8. Analgesia/	28. indomethacin.mp.	48. scopolamine.mp.
9. pain relief.mp.	29. indometacin.mp.	49. celecoxib.mp.
10. acetaminophen.mp.	30. ketamine.mp.	50. lumiracoxib.mp.
11. paracetamol.mp.	31. ketoprofen.mp.	51. parecoxib.mp.
12. alfentanil.mp.	32. ketorolac.mp.	52. rofecoxib.mp.
13. aspirin.mp.	33. morphine.mp.	53. valdecoxib.mp.
14. acetylsalicylic acid.mp.	34. naproxen.mp.	54. etoricoxib.mp.
15. codeine.mp.	35. nitrous oxide.mp.	55. or/6-54
16. dextromethorphan.mp.	36. nitrogen oxide.mp.	56. 5 and 55
17. diclofenac.mp.	37. opium.mp.	57. limit 56 to yr="2005 - 2007"
18. diflunisal.mp.	38. oxycodone.mp.	58. limit 56 to (humans and english language)
19. dihydroergotamine.mp.	39. oxymorphone.mp.	
20. dihydromorphone.mp.	40. pentazocine.mp.	

* search terms modified as required for use in other electronic databases

Due to technical limitations the search terms were restricted to generic names of analgesic drugs.

- Identification of Australian and US brand names could be achieved in a systematic way due to availability of drug dictionaries, however this could not be replicated with UK and European brands as the drug listings were only available to subscribers.

- Some of the commonly used drugs had thousands of brand names (eg paracetamol >3000). Copying available lists and pasting them into Medline was not possible due to the limit on number of characters per search string, and dealing with each brand name individually was beyond the agreed scope and time frame of the project.
- Precedent was sought within the Cochrane Library and reviews containing both generic and brand names as well as reviews with generic names only were found.

After consultation with NICS and the ECCoP Reference Group, a decision was taken to restrict to generic names.

3. Data Collection & Analysis

Studies were selected and appraised by one reviewer in consultation with colleagues in the project team, using inclusion, exclusion and appraisal criteria established *a priori*.

Evidence-based guidelines are appraised using the Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument (www.agreecollaboration.org). The AGREE criteria cover 6 domains: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence. Reviewers are not blind to author, institution or affiliation as this information is required to address the AGREE criteria related to editorial independence in the guideline process.

All other studies are appraised for quality using standard evaluation criteria outlined in the appraisal tables in Appendix 3.

Results

There were a total of 571 journal articles and three guidelines found using the above search terms. No HTAs were identified. After reviewing the title, abstract or full text, one systematic review⁵ and three RCTs^{6,7,8} were found which met the inclusion criteria. No guidelines met the inclusion criteria. Reasons for exclusion of the guidelines can be seen in Appendix 2. Two of the RCTs were appraised in the systematic review^{6,7}, therefore these have not been included in our review. We also found a protocol for a Cochrane systematic review⁹ which is expected to be published sometime this year (issue 3). An additional review¹⁰ was found, however this was excluded as it was not a systematic review.

The studies identified only assessed opiate analgesics; no studies on other types of analgesics were found.

The systematic review⁵ included studies with both adults and children. The RCT⁸ enrolled only adult subjects.

Results of the two included studies are summarised here. Full details of appraisals can be found in Appendix 3.

The systematic review by Ranji et al⁵ included 12 randomised or quasi-randomised controlled trials (15 comparisons, 1353 participants) published prior to May 2006. The setting appeared to be emergency departments, but this was not specifically detailed. In all the studies opiate analgesics were compared with placebo. Intravenous (IV) morphine was used in seven studies; IV fentanyl, IV tramadol, IV papaveretum, buccal oxycodone and sublingual buprenorphine were each used in five separate studies. The outcomes were 1) alteration in the history given by the patient; 2) alteration in the physical examination findings of the patient; and 3) diagnostic errors defined as decisions resulting in 'management errors' such as performance of unnecessary surgery or failure to perform necessary surgery in a timely fashion.

The systematic review appeared to be well conducted with no serious methodological issues. The studies were not appraised individually; only a summary of methodological limitations was provided.

The authors indicated that the majority of studies had important methodological problems. Only one study indicated adequate concealment of allocation. In only four comparisons (three studies) were the outcome assessors blinded to treatment assignment. In addition, in all but two studies, the same physician examined the patient before and after the medication was administered. This would reduce the likelihood of a significant difference between opiates and placebo for any aspect of the physical examination. Pain relief did not differ significantly between opiate and placebo groups in five comparisons (from three studies). This could further reduce the likelihood of finding a difference between the two groups.

A RCT by Gallagher et al⁸ included 160 adults older than 21 years of age recruited from an academic medical centre emergency department (ED) in the United States. Patients were included if they had atraumatic abdominal pain of less than 48 hours' duration and were judged by the ED attending physician to warrant opiate analgesics for pain control. Patients were excluded who had isolated flank pain, pregnancy, an allergy to morphine, self-medicated with analgesic before coming to the ED, analgesic medication in the ED before screening for study entry, concurrent painful sickle cell crisis, systolic blood pressure less than 100 mmHg, refused participation, or were unable to provide informed consent.

The intervention used was morphine 0.1 mg/kg IV up to a maximum of 10 mg. The comparator was an equal volume of normal saline as a single IV bolus. The outcomes measured included: 1) Pain reduction: pain measured using a standard 0- to 100-mm visual analog scale before the study drug was administered and then 15 minutes after administration of the study drug. 2) Clinically important diagnostic accuracy: the proportion of patients whose provisional diagnosis was classified as accurate, that is, either identical to the final diagnosis or not different from it in a clinically important way. The provisional diagnosis was provided by an ED physician, who examined the patient only once, 15 minutes after administration of the study agent. The final diagnosis was determined at six weeks after the ED visit from all available sources: medical records, diagnostic test results, surgical findings and pathology reports. In instances in which the final diagnosis could not be determined by the research associate at six weeks, follow-up was transferred to the investigators, who contacted patients with periodic phone calls until either a definitive diagnosis was obtained or the presenting problem resolved. In the latter instance, patients with

no apparent cause for abdominal pain that had resolved and not recurred at follow-up were assigned the diagnosis of nonspecific abdominal pain. Patients were followed up for 18 months.

This study appeared to be a well conducted RCT with no obvious major methodological problems. Although groups were similar at baseline, the final diagnoses were unevenly spread between the two groups – the morphine group had more patients with biliary tract disease (17/78 vs 3/74) and fewer patients with non-specific pain (11/78 vs 24/75). It is difficult to know how this may have affected the results.

1. In patients with acute abdominal pain, does administration of analgesics alter the history given by the patient?

Ranji et al⁵ found that none of the studies included in their systematic review explicitly evaluated the effect of opiate administration on the history given by the patient.

2. In patients with acute abdominal pain, does administration of analgesics alter the physical examination?

Ranji et al⁵ found that:

- 14 of the 15 comparisons reported on changes in the physical examination; 11 comparisons (from nine studies, n=861) provided data that was in a format amenable to quantitative synthesis. Only two trials distinguished clinically significant changes such as loss of peritoneal signs from all other changes. These findings are detailed below.
- The nine comparisons (from seven studies, n=690) conducted in adult patients showed a non-significant trend toward changes in the physical examination with opiate administration, with a summary RR of 1.51 (95%CI 0.85, 2.69).
- The two comparisons (from two studies, n=171) conducted in paediatric patients showed a similar non-significant trend toward changes in physical examination with administration of opiates (RR 2.11, 95%CI 0.60, 7.35).
- Combining both adult and paediatric studies the summary RR was 1.55 (95%CI 1.02, 2.36). These results exhibited significant heterogeneity ($I^2=62.1\%$, $p=0.003$), indicating that the variation in individual study's estimates of the effect of opiates on the examination was greater than would be expected by chance alone. One source of non-random variation, suggested by the review authors, may have been the lack of adequate of analgesia for patients in the opiate group. In three comparisons (from two studies, n=336) pain relief did not differ significantly from that reported by the placebo group. Restricting the analysis to the studies with adequate analgesia (eight comparisons, seven studies, n=525) resulted in the risk for examination changes with opiate administration becoming statistically significant (RR 2.13, 95%CI 1.14, 3.98), but significant heterogeneity remained ($I^2=68.6\%$, $p=0.002$).
- Another potential source of heterogeneity may be that studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful changes (such as changes in peritoneal signs). Only two studies (n=74 and 63)^{7,11} specified changes in peritoneal signs as an outcome. Loss of peritoneal signs after drug administration was reported in the review. As the calculations in the review appeared to be inconsistent with the data presented from the included studies, the review authors were contacted and confirmed there was an error. Therefore we have reported directly from the original papers and calculated statistical significance (using STATA 8, www.stata.com) where appropriate data was available.

In a study by Thomas et al¹¹ (n=74) signs of peritoneal irritation were present on initial examination in 41.5% and 27.5% of the treatment and control groups, respectively. Actual numbers of participants were not provided. Loss of peritoneal signs were noted in two participants in the treatment group and one participant in the control group. Development of peritoneal signs occurred in one participant in the treatment group and one participant in the control group. The authors did not document if these differences were statistically significant.

Kokki et al⁷ reported 16 of 32 and 13 of 31 participants had abdominal guarding pre-dose in the treatment and control groups, respectively. Post-dose, three participants in the treatment group and one participant in the control normalized their guarding ($p=0.39$). In addition, three participants in the treatment group and none in the control group developed guarding post-dose ($p=0.054$).

3. In patients with acute abdominal pain does administration of analgesics result in more diagnostic errors than in patients not receiving analgesics?

Ranji et al⁵ found that:

- Twelve comparisons (from nine studies) supplied quantitative data on diagnostic accuracy, though definitions of diagnostic errors varied across the studies. The systematic review focused its analysis on the subset of studies that supplied sufficient information to apply their definition of potential management errors. Possible cases of delayed or unnecessary surgeries could be identified in seven studies (n=890), four adult (n=599) and three paediatric (n=291).
- In adult studies, meta-analysis indicated no significant change in the rate of incorrect management decisions among patients who received opiates (risk difference 0.3%, 95%CI -4.1%, 4.7%). Analgesia was adequate in all these studies and no significant heterogeneity was present ($I^2=8.7\%$, $p=0.35$). These results were calculated with the conservative assumption that the two patients with missing data in one study would have contributed to management errors in the opiates group. Excluding these two patients from the analysis

resulted in a pooled risk difference of 0% (95%CI -4.2%, 4.2%).

- Meta-analysis of the three paediatric studies found no significant difference between groups in incorrect management decisions (risk difference -0.8%, 95%CI -8.6%, 6.9%; $I^2=0.0%$, $p=0.71$).
- Across all studies (adult and paediatric), there was no change in the management error rate for those who received opiates (risk difference 0.1%, 95%CI -3.6%, 3.8%; $I^2=0.0%$, $p=0.67$).

Gallagher et al⁸ found that there was no difference in clinically important diagnostic accuracy. This was 86% (67/78) in the morphine group and 85% (64/75) in the control group, a risk difference of 1% (95%CI -11%, 12%).

Discussion

No research into the effect of analgesics on the history given by the patient, published since 2005 has been identified. Therefore we are unable to report any recent findings in this area.

The administration of analgesics may alter the physical examination in patients with acute abdominal pain. The results from adult only and children only studies both indicate non-statistically significant differences between patients given analgesics and the control group. However when the results of adult and child studies are combined the risk difference does become statistically significant. The clinical significance of this finding is unclear since studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful changes (such as changes in peritoneal signs). Given the concerns that opiates may mask clinical signs, it is interesting to note that in one of the studies which reported changes in peritoneal signs⁷, three patients developed guarding following administration of oxycodone.

Studying the effect of analgesics on change in physical examination is important. However, ultimately what is of more concern is the effect of analgesics on diagnostic errors. It is important that analgesics do not increase the number of diagnostic or management errors. The administration of analgesics did not result in an increase in the number of management errors or a difference in clinically important diagnostic accuracy of patients with acute abdominal pain.

Conclusions

The results indicate that opiate analgesics provide analgesia without increasing the number of diagnostic errors. These findings are consistent in both adults and children.

A number of studies report that opiate administration altered the physical examination findings but the clinical implications of this are unclear. Even when changes in physical examination are noted, there is no increase in management errors.

References

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Disclaimer

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Appendix 1: Website identification

GOOGLE Advanced Search: (To identify Centres of Evidence Based Professional Practice)

With all of the words	
With the exact phrase	evidence based
With at least one of the words	
Without the words	
Don't return the results of the file format	Adobe Acrobat PDF(.pdf)
Return results where my terms occur	In the title of the page

RESULTS:

Web Results = 462,000			
Searched within results for:	Results returned:	Pages Searched:	Websites found:
Emergency	726 (Google cut this down to 58)	All	1
Primary Care	1030	Pages 1-20 (no results found after page 5)	1
Physician	194 (Google cut this down to 42)	All	0
"Family Physician"	103	All	0
"General Practitioner"	5	All	0
"General Practice"	516	Pages 1-15 (no results found after page 1)	1
Nurse	318 (Google cut this down to 94)	All	0
Nursing	21,800	Pages 1-15 (no results found after page 2)	5
Anaesthetics	35 (Google cut this down to 26)	All	0
Anesthesiology	690	Pages 1-15	0

WEBSITES SEARCHED:

Guideline Services	Centres of Evidence-Based Practice (containing GLs)	Australian Government Health Websites
Joanna Briggs Institute www.joannabriggs.edu.au	Evidence Based Emergency Medicine http://ebem.org/index.php	Australian Government Department of Health and Ageing http://www.health.gov.au
National Health and Medical Research Council (NHMRC) www.nhmrc.gov.au	Centre for Evidence Based Medicine http://www.cebm.utoronto.ca/	Australian Institute of Health and Welfare http://www.aihw.gov.au
New Zealand Guideline Group (NZGG) www.nzgg.org.nz	Centre for Evidence Based Nursing http://www.york.ac.uk/healthsciences/centres/evidence/cebn.htm	Health Insite http://www.healthinsite.gov.au
National Guideline Clearinghouse US (NGC) www.guidelines.gov	Western Australian Centre for Evidence Based Nursing and Midwifery http://wacebnm.curtin.edu.au/	ACT Health http://www.health.act.gov.au
TRIP Database www.tripdatabase.com	Academic Centre for Evidence Based Practice http://www.acestar.uthscsa.edu/	NSW Health http://www.health.nsw.gov.au
Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk	Centre for Evidence Based Nursing Aotearoa http://www.health.auckland.ac.nz/cebna/	NT Department of Health and Community Services http://www.nt.gov.au/health
National Institute for Health and Clinical Excellence UK (NICE) www.nice.org.uk		Queensland Health http://www.health.qld.gov.au
Guidelines International Network www.g-i-n.net		SA Department of Health http://www.health.sa.gov.au
		Tasmanian Department of Health and Human Services http://www.dhhs.tas.gov.au
		Victorian Department of Human Services http://www.dhs.vic.gov.au
		WA Department of Health http://www.health.wa.gov.au

Appendix 2: Guidelines Identified

Guidelines Identified	Located in:	Inclusion/exclusion:
<p>Children and Infants with Acute Abdominal Pain - Acute Management NSW Health 2005 http://www.health.nsw.gov.au/policies/PD/2005/pdf/PD2005_384.pdf</p>	NSW Health	Excluded – not evidence based
<p>Assessment and management of acute pain. Institute for Clinical Systems Improvement (ICSI) Bloomington (MN): 2006 Mar. 68 p. http://www.guidelines.gov/summary/summary.aspx?ss=15&doc_id=9009&nbr=4884</p>	NGC TRIP	Excluded – does not meet inclusion/exclusion criteria
<p>Clinical practice guideline for the management of postoperative pain. Version 1.2. Department of Defense, Veterans Health Administration Washington (DC): 2002 May. http://www.guidelines.gov/summary/summary.aspx?ss=15&doc_id=3284&nbr=2510</p>	NGC	Excluded – does not meet inclusion/exclusion criteria

Appendix 3: Critical Appraisal of Identified Research

Appraisal of included systematic review:

Study: Ranji et al⁵

Description of study

Patients	Adults and children
N	1353 (12 randomised or quasi-randomised controlled trials, 15 comparisons)
Setting	Emergency department
Intervention	Opiate analgesia: seven studies used intravenous morphine. The following drugs were each used in one study: IV fentanyl, IV tramadol, IV papaveretum, buccal oxycodone and sublingual buprenorphine.
Comparisons	Placebo
Outcomes	<p>1) Alteration in the history given by the patient</p> <p>2) Alteration in the physical examination findings of the patient</p> <p>3) Diagnostic errors: (those resulting in “management errors”, defined as the performance of unnecessary surgery or failure to perform necessary surgery in a timely fashion.)</p> <p>Data was extracted data on the incidence of all changes in the history and physical examination of the abdomen, including findings with the greatest relevance to diagnosing conditions requiring laparotomy, such as changes in the presence of peritoneal signs.</p> <p>Similarly, they extracted data on the incidence of all management errors. When they abstracted the data, they made no assumptions about the presence of examination changes or management errors and used only the information provided by the authors of the original studies.</p>
Inclusion Criteria	<p>Studies which addressed 1 of 3 key questions:</p> <ul style="list-style-type: none"> • Does administration of opiates alter the history given by patients with acute abdominal pain? • Does administration of opiates alter the physical examination of patients with acute abdominal pain? • Does administration of opiates result in errors in the clinical management of patients with acute abdominal pain? <p>Placebo-controlled trials of opiate analgesia in patients with acute abdominal pain that assigned treatment using a randomised or quasi-randomised design (ie alternating patients, as defined by the authors).</p> <p>Articles published until May 2006.</p>
Exclusion Criteria	Nil stated

Study Validity

Focused research question	Yes	
Specified inclusion/ exclusion criteria	Yes	

Explicit and comprehensive search strategy	Yes	Although the search may have missed some articles as it did not include all opiate drug names.
Reviewers blind to author, institution & affiliations	Not stated	
Validity of included trials appraised	Some	<p>The validity of included trials were appraised, however the authors did not report if the studies had specified inclusion/exclusion criteria, duration of follow-up, proportion lost to follow-up or intention-to-treat analysis. The authors indicated that the majority of studies had important methodological problems. Studies were not appraised individually; only a summary of methodological limitations was provided.</p> <ul style="list-style-type: none"> • Only one study indicated adequate concealment of allocation. • In only four comparisons (three studies) were the outcomes assessors blinded to treatment assignment. • In all but two studies, the same physician examined the patient before and after the medication was administered. This reduces the likelihood of a significant difference between opiates and placebo for any aspect of the physical examination. • Pain relief did not differ significantly between opiate and placebo groups in five comparisons (from three studies). This could further reduce the likelihood of finding a difference between the two groups.
Homogeneity between studies assessed	Yes	
Summary of main results presented	Yes	
Strengths and limitations of included studies discussed	Some	Not all criteria used. Refer to comments under 'validity of included trials appraised'.
Other comments		The baseline history was taken before the study medication was given. Similarly the examination and diagnosis were made before the study medication was given.

Results:

1. Effect of opiates on patient history

- None of the included studies explicitly evaluated the effect of opiate administration on the history given by the patient.
- All studies assessed patients' perceptions of changes in pain after receiving opiate or placebo. Analgesia was significantly greater in the opiate group compared to the placebo group in 10 of 15 comparisons (authors have stated this is 11 out of 15 comparisons but this appears incorrect and contradicts other information given in the article).

2. Effect of opiates on the physical examination

- 14 of the 15 comparisons reported on changes in the physical examination; 11 comparisons (from nine studies, n=861) provided data that was in a format amenable to quantitative synthesis. The only changes in physical examination specified by the authors of the systematic review were changes in peritoneal signs, detailed below.
- The nine comparisons (from seven studies, n=690) conducted in adult patients showed a non-significant trend toward changes in the physical examination with opiate administration, with a summary RR of 1.51 (95%CI 0.85, 2.69)
- The two comparisons (from two studies, n=171) conducted in paediatric patients that provided quantitative data showed a similar non-significant trend toward changes in physical examination with administration of opiates (RR 2.11, 95%CI 0.60, 7.35).
- Combining both adult and paediatric studies the summary RR was 1.55 (95%CI 1.02, 2.36). These results exhibited significant heterogeneity ($I^2=62.1\%$, $p=0.003$), indicating that the variation in individual studies' estimates of the effect of opiates on the examination was greater than would be expected by chance alone. One source of non-random variation, suggested by the review authors, may have been the adequacy of analgesia for patients in the opiate group. In three comparisons

(from two studies, n=336) pain relief did not differ significantly from that reported by the placebo group. Restricting the analysis to the studies with adequate analgesia (eight comparisons, seven studies, n=525) resulted in the risk for examination changes with opiate administration becoming statistically significant (RR 2.13, 95%CI 1.14, 3.98), but significant heterogeneity remained ($I^2=68.6\%$, $p=0.002$).

- Another potential source of heterogeneity may be that studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful changes (such as changes in peritoneal signs). Only two studies (n=74 and 63)^{7,11} specified changes in peritoneal signs as an outcome.

In a study by Thomas et al¹¹ (n=74) signs of peritoneal irritation were present in 41.5% and 27.5% of the treatment and control groups, respectively. Actual numbers of participants were not provided. Loss of peritoneal signs were noted in two participants in the treatment group and one participant in the control group. Development of peritoneal signs occurred in one participant in the treatment group and one participant in the control group.

Kokki et al⁷ reported 16 of 32 and 13 of 31 participants had abdominal guarding pre-dose in the treatment and control groups, respectively. Post-dose, three participants in the treatment group and one participant in the control normalized their guarding ($p=0.39$). In addition, three participants in the treatment group and none in the control group developed guarding post-dose ($p=0.054$).

3. Effect of opiates on potential management errors

- Twelve comparisons (from nine studies) supplied quantitative data on diagnostic accuracy, though definitions of diagnostic errors varied across the studies. The systematic review focused its analysis on the subset of studies that supplied sufficient information to apply their definition of potential management errors. Possible cases of delayed or unnecessary surgeries could be identified in seven studies (n=890), four adult (n=599) and three paediatric (n=291).
- In adult studies, meta-analysis indicated no significant change in the rate of incorrect management decisions among patients who received opiates (risk difference 0.3%, 95%CI -4.1% 4.7%). Analgesia was adequate in all these studies and no significant heterogeneity was present ($I^2=8.7\%$, $p=0.35$). These results were calculated with the conservative assumption that the two patients with missing data in one study would have contributed to management errors in the opiates group. Excluding these two patients from the analysis results in a pooled risk difference of 0% (95%CI -4.2% 4.2%).
- Meta-analysis of the three paediatric studies found no significant difference between groups in incorrect management decisions (risk difference -0.8%, 95%CI -8.6% 6.9%; $I^2=0.0\%$, $p=0.71$).
- Across all studies (adult and paediatric), there was no change in the management error rate for those who received opiates (risk difference 0.1%, 95%CI -3.6% 3.8%; $I^2=0.0\%$, $p=0.67$).

Authors' Conclusions

Opiate administration may alter the physical examination findings, but these changes result in no significant increase in management errors. The existing literature does not rule out a small increase in errors, but this error rate reflects a conservative definition in which surgeries labelled as either delayed or unnecessary may have met appropriate standards of care. In published research reports, no patient experienced major morbidity or mortality attributable to opiate administration.

Our comments

Appears to be a well conducted systematic review with no obvious serious methodological issues. Main concern is that the majority of the studies included did have important methodological problems. In addition there was significant heterogeneity in many of the meta-analyses indicating that the studies and results were not consistent.

Appraisal of included randomized control trial:

Study: Gallagher et al⁸

Description of study

Patients	Adults > 21 years.
N	160
Setting	Emergency Department
Intervention	Morphine 0.1 mg/kg IV up to a maximum of 10 mg.
Comparisons	Placebo: an equal volume of normal saline as a single IV bolus.
Outcomes	<ul style="list-style-type: none"> • Pain reduction: pain measured using a standard 0- to 100-mm visual analog scale before the study drug was administered and then 15 minutes after administration of the study drug. • Clinically important diagnostic accuracy: this was defined <i>a priori</i> by its complement, clinically important diagnostic error, using two independent, blinded investigators to identify any discordance between the provisional and final diagnoses that might adversely affect the patient's health status. The provisional diagnosis was provided by an ED physician, who examined the patient only once, 15 minutes after administration of the study agent. The final diagnosis was determined at six weeks after the ED visit from all available sources: medical records, diagnostic test results, surgical findings and pathology reports. In instances in which the final diagnosis could not be determined by the research associate at six weeks, follow-up was transferred to the investigators, who contacted patients with periodic phone calls until either a definitive diagnosis was obtained or the presenting problem resolved. The final diagnosis assigned to patients was determined by radiographic or tissue diagnosis, a clear response to medical or surgical intervention, or spontaneous resolution. In the latter instance, patients with no apparent cause for abdominal pain that had resolved and not recurred at follow-up were assigned the diagnosis of nonspecific abdominal pain. Patients were followed up for 18 months.
Inclusion Criteria	Patients with atraumatic abdominal pain of less than 48 hours' duration who were judged by the ED attending physician to warrant opiate analgesics for pain control.
Exclusion criteria	Isolated flank pain, pregnancy, an allergy to morphine, self-medicated with analgesic before coming to the ED, analgesic medication in the ED before screening for study entry, concurrent painful sickle cell crisis, systolic blood pressure less than 100 mmHg, refused participation, or were unable to provide informed consent.

Study Validity

Specified inclusion/ exclusion criteria	Yes	
Adequate method of randomisation	Yes	Block randomisation schedule was determined by an online randomisation plan generator.
Concealment of allocation	Yes	
Groups similar at baseline	Yes	Although groups were similar at baseline, the final diagnoses were unevenly spread between the two groups – the morphine group compared to the control group had a large number who had final diagnoses of biliary tract disease (17/78 vs 3/74); and had a smaller number with non-specific pain. (11/78 vs 24/75). It is difficult to know how this may have effected or biased the results.
Blinding - patients/ investigators/	Yes	To assess blinding, research associates asked study physicians to indicate whether they believed the patient they had just seen had received opiate or placebo. The attending physicians correctly identified the study

assessors		arm in 63% of the patients.
Sufficient duration of follow-up	Yes	Up to 18 months - until either a definitive diagnosis was obtained or the presenting problem resolved.
Proportion lost to follow up	<1%	Zero in morphine group, one in the placebo group lost to follow-up.
Objective & independent assessment of outcomes	Yes	
Inclusion of all subjects in analysis	No	As well as patients being lost to follow-up, an additional two patients in the morphine group and three in the placebo group were not included in the analysis because of missing or multiple provisional diagnoses. One patient in the placebo group withdrew early before receiving the study treatment.
Other comments:	Nil	

Results:

Pain reduction:

- Reduction in pain was strongly associated with group allocation: median change in pain among patients randomised to morphine was -33 mm (IQR -8mm to -73mm) vs -2 mm (IQR 1 to -16 mm) in the placebo group; using a standard 0- to 100-mm visual analog scale. Although this is a clinically significant difference, it has not been documented if it is statistically significant.

Clinically important diagnostic accuracy defined by its complement, clinically important diagnostic error: any discordance between the provisional and final diagnoses that might adversely affect the patient's health status:

- This was 86% (67/78) in the morphine group versus 85% (64/75) in the control group, a difference in diagnosis of 1% (95%CI -11%, 12%).

Complications:

- Complications were similar in both groups:
 - 13 patients had a systolic blood pressure less than 90 mmHg recorded, seven patients in the morphine group and six patients in the control group.
 - 16 patients who complained of nausea or vomiting were in the morphine group, 21 patients were in the control group. 27 patients received antiemetics, nine patients were in the morphine group and 18 patients were in the control group.

Authors' Conclusions

Although administration of intravenous morphine to adult ED patients could lead to as much as a 12% difference in diagnostic accuracy, equally favouring opiate or placebo, their data are most consistent with the inference that morphine safely provides analgesia without impairing clinically important diagnostic accuracy.

Our comments

Appears to be a well conducted RCT with no obvious major methodological problems. The only areas of concern seem to be their inappropriate definition of sensitivity and specificity; and the lack of explanation of what 'accuracy' means and how this was calculated. These two issues mean it is difficult to make any clinical sense of these terms.

Appendix 4: amendment made in August 2006.

Original text	Changes made after correspondence with Dr Sumant Ranji	Page
<ul style="list-style-type: none"> Another potential source of heterogeneity may be that studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful change (such as changes in peritoneal signs). Only two studies (n=74 and 63) specified changes in peritoneal signs as an outcome; loss of peritoneal signs after drug administration occurred in 5.6% and 18.7% of patients in the groups receiving opiates and in 2.6% and 7.7% of those in the respective control groups. The authors did not document if these differences were clinically or statistically significant. 	<ul style="list-style-type: none"> Another potential source of heterogeneity may be that studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful changes (such as changes in peritoneal signs). Only two studies (n=74 and 63)^{7,11} specified changes in peritoneal signs as an outcome. Loss of peritoneal signs after drug administration was reported in the review. As the calculations in the review appeared to be inconsistent with the data presented from the included studies, the review authors were contacted and confirmed there was an error. Therefore we have reported directly from the original papers and calculated statistical significance (using STATA 8, www.stata.com) where appropriate data was available. <p>In a study by Thomas et al¹¹ (n=74) signs of peritoneal irritation were present on initial examination in 41.5% and 27.5% of the treatment and control groups, respectively. Actual numbers of participants were not provided. Loss of peritoneal signs were noted in two participants in the treatment group and one participant in the control group. Development of peritoneal signs occurred in one participant in the treatment group and one participant in the control group. The authors did not document if these differences were statistically significant.</p> <p>Kokki et al⁷ reported 16 of 32 and 13 of 31 participants had abdominal guarding pre-dose in the treatment and control groups, respectively. Post-dose, three participants in the treatment group and one participant in the control normalized their guarding (p=0.39). In addition, three participants in the treatment group and none in the control group developed guarding post-dose (p=0.054).</p>	5
<p>The administration of analgesics may alter the physical examination in patients with acute abdominal pain. The results from adult only and children only studies both indicate non-statistically significant differences between patients given analgesics and the control group. However when the results of adult and child studies are combined the risk difference does become statistically significant. The clinical significance of this finding is unclear since studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful change (such as changes in peritoneal signs).</p>	<p>The administration of analgesics may alter the physical examination in patients with acute abdominal pain. The results from adult only and children only studies both indicate non-statistically significant differences between patients given analgesics and the control group. However when the results of adult and child studies are combined the risk difference does become statistically significant. The clinical significance of this finding is unclear since studies generally did not distinguish between potentially beneficial changes (such as improved localisation of tenderness) and potentially harmful changes (such as changes in peritoneal signs). Given the concerns that opiates may mask clinical signs, it is interesting to note that in one of the studies which reported changes in peritoneal signs⁷, three patients developed guarding following administration of oxycodon.</p>	6
-	11.Thomas, S.H., et al., <i>Effects of morphine analgesia on diagnostic accuracy in Emergency Department patients with abdominal pain: a prospective, randomized trial</i> . Journal of the American College of Surgeons, 2003. 196 (1): p. 18-31.	6