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# Do Opiates Affect the Clinical Evaluation of Patients With Acute Abdominal Pain?

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## CLINICAL SCENARIO

A 28-year-old woman with no significant past medical history presents to the emergency department with right-sided abdominal pain, progressive over the past 3 days. She reports several episodes of vomiting greenish fluid within the last 24 hours but had no vomiting preceding the pain. She denies hematemesis, chills, dysuria, diarrhea, or vaginal discharge. The patient's last menses ended 2 weeks prior without further menstrual cramping or vaginal bleeding.

The patient is febrile and appears uncomfortable, but other vital signs are normal. Her lungs are clear, and her cardiac examination findings are normal. She has lower right-sided abdominal tenderness with guarding but also has tenderness in the right upper quadrant without guarding. Examination for a psoas sign is positive. Pelvic and rectal examinations make her generally uncomfortable but without other specific findings. Laboratory tests show a white blood cell count of  $11\,000 \times 10^3$  cells/ $\mu\text{L}$ . Levels of serum electrolytes, urea, creatinine, transaminases, bilirubin, and alkaline phosphatase are all within reference range. A pregnancy test result is negative.

The combination of right upper quadrant and lower abdominal pain

See also Patient Page.

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**Context** Clinicians have traditionally withheld opiate analgesia from patients with acute abdominal pain until after evaluation by a surgeon, out of concern that analgesia may alter the physical findings and interfere with diagnosis.

**Objective** To determine the impact of opiate analgesics on the rational clinical examination and operative decision for patients with acute abdominal pain.

**Data Sources and Study Selection** MEDLINE (through May 2006), EMBASE, and hand searches of article bibliographies to identify placebo-controlled randomized trials of opiate analgesia reporting changes in the history, physical examination findings, or diagnostic errors (those resulting in "management errors," defined as the performance of unnecessary surgery or failure to perform necessary surgery in a timely fashion).

**Data Extraction** Two authors independently reviewed each study, abstracted data, and classified study quality. A third reviewer independently resolved discrepancies.

**Data Synthesis** Studies both in adults (9 trials) and in children (3 trials) showed trends toward increased risks of altered findings on the abdominal examination due to opiate administration, with risk ratios for changes in the examination of 1.51 (95% confidence interval [CI], 0.85 to 2.69) and 2.11 (95% CI, 0.60 to 7.35), respectively. When the analysis was restricted to the 8 adult and pediatric trials that reported significantly greater analgesia for patients who received opiates compared with those who received placebo, the risk of physical examination changes became significant (risk ratio, 2.13; 95% CI, 1.14 to 3.98). These trials exhibited significant heterogeneity ( $I^2=68.6\%$ ;  $P=.002$ ), and only 2 trials distinguished clinically significant changes such as loss of peritoneal signs from all other changes; consequently, we analyzed risk of management errors as a marker for important changes in the physical examination. Opiate administration had no significant association with management errors (+0.3% absolute increase; 95% CI, -4.1% to +4.7%). The 3 pediatric trials showed a nonsignificant absolute decrease in management errors (-0.8%; 95% CI, -8.6% to +6.9%). Across adult and pediatric trials with adequate analgesia, opiate administration was associated with a nonsignificant absolute decrease in the risk of management errors (-0.2%; 95% CI, -4.0% to +3.6%).

**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 labeled 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.

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raises the possibility of pelvic inflammatory disease with perihepatitis (Fitz-Hugh-Curtis syndrome), but the normal liver function test results and the lack of purulent endocervical discharge or cervical tenderness make this diagnosis less likely. You regard the combination of vomiting beginning after the onset of pain, fever, right lower quadrant pain, guarding, and a psoas sign as most suggestive of appendicitis. You request a consultation with the on-call general surgeon, who agrees that appendicitis is most likely. However, the surgeon would like to assess the presence of the right upper quadrant pain herself. She cannot come to the emergency department for approximately 1 hour and requests that you not administer opiates before she can examine the patient, since she does not want analgesia to mask important physical findings. When you return to the bedside, the patient is visibly uncomfortable, although her vital signs are unchanged. She requests "something for the pain." You wonder if providing pain relief with opiate analgesics will affect the physical examination findings and/or result in either delays or unnecessary surgery.

### WHY IS THIS QUESTION IMPORTANT?

Abdominal pain is the most common reason for emergency department visits in the United States, accounting for 7.6 million visits in 2003.<sup>1</sup> Of these patients, 40% to 45% are eventually diagnosed with nonspecific abdominal pain, but 15% to 30% have conditions that require surgical treatment—principally appendicitis, intestinal obstruction, and cholecystitis.<sup>2,3</sup> Textbooks of surgery have historically discouraged the provision of opiate analgesia to patients with acute abdominal pain. The 1987 edition of *Cope's Early Diagnosis of the Acute Abdomen*<sup>4</sup> stated that "though it may appear crude, it is really prudent to withhold morphine until a reasonable diagnosis has been made and a plan of action formulated." The current edition condemns this practice<sup>5</sup> but adds that "it will

take many generations to eliminate [the practice of avoiding analgesia] because the rule has been so firmly ingrained in the minds of physicians." Other major textbooks take no stance,<sup>6</sup> explicitly endorse providing analgesia only after the decision to operate has been made,<sup>7</sup> or endorse use of parenteral analgesics at "moderate doses" prior to evaluation by a surgeon.<sup>8</sup>

Patients with acute abdominal pain may wait several hours before receiving analgesia, especially when surgical evaluation is required.<sup>9,10</sup> A 1999 survey showed that 67% of general surgeons preferred that pain medication not be administered before they could examine the patient,<sup>11</sup> in the belief that analgesia could impair the accuracy of diagnosis by obscuring physical examination findings. Most emergency medicine physicians still defer analgesia until after surgical evaluation,<sup>12</sup> although use of analgesia has increased in recent years.<sup>13,14</sup> Qualitative reviews of the literature have reached inconsistent conclusions about the evidence supporting the traditional practice of withholding analgesics,<sup>15,16</sup> and thus a quantitative assessment of the effects of opiate administration to patients with acute abdominal pain has the potential to improve patient care.

Articles in the Rational Clinical Examination series generally address the degree to which specific components of the clinical examination allow clinicians to rule in or rule out target diagnoses, including conditions that present as an "acute abdomen."<sup>17,18</sup> When the diagnosis is clear and the examining physician is the surgeon, a decision to perform surgery is made and the sensitivity and the specificity of the initial clinical findings for the diagnosis can be quantified. However, the diagnosis of the patient experiencing abdominal pain is rarely certain, and the initial examining physician is usually not the surgeon responsible for the operative decision. In this common scenario, the examining physician must make a decision to prescribe analgesics (usually opiates) while awaiting results from additional tests, surgical consultation, or both (FIGURE 1). In such cases,

the patient is reevaluated to confirm the original findings and make inferences about changes in symptoms and pain. The degree to which opiates alter the appropriate symptoms and signs therefore has the potential to alter the differential diagnosis and consequently the decision to operate or pursue other diagnostic tests or therapies.

Thus, we examined the effects of opiates on the clinical examination of patients with abdominal pain and also evaluated the effect of opiates on the operative decision, to determine the impact of changes in the examination. We evaluated the accuracy of the decision to operate rather than the diagnostic accuracy because, from a pragmatic point of view, the primary diagnostic goal of surgeons and nonsurgeons alike consists of the timely detection of conditions that require urgent surgery. Consequently, the most significant physical findings changed by opiates are those contributing to delayed necessary surgeries, or misleading findings leading to unnecessary surgeries.<sup>6,7</sup> For example, a patient with a preoperative diagnosis of appendicitis who proved to have a perforated ulcer would have needed surgery in either case. An error in diagnosis caused by an opiate effect on physical examination findings has fewer consequences for this patient than an erroneous decision to delay surgery (eg, perforated ulcer misdiagnosed as gastroenteritis). We thus investigated whether opiate administration was associated with either of 2 types of management errors: delayed surgery, ie, patients have conditions requiring urgent surgery but do not undergo surgery in a timely fashion; or unnecessary surgery, ie, patients undergo surgery but are found to have a condition for which surgery was not required.

### Pathophysiology of the Acute Abdomen

The diagnosis of an "acute abdomen" suggests symptoms and signs of an intra-abdominal disease that usually requires surgical treatment. Peritoneal signs, such as cough tenderness, ab-

dominal muscle rigidity with deep palpation (guarding), and increased pain on rapid retraction of palpation (rebound), are the classic descriptors of an acute abdomen.

An understanding of the innervation of the enteric visceral and somatic afferent nervous system helps explain the pathophysiology of these “peritoneal signs.” During embryogenesis, the afferent nerve roots travel with the arterial blood flow to the 3 visceral segments of the primitive embryo gut: the foregut, midgut, and hindgut. Pain from intra-abdominal organs originating from the foregut (eg, the stomach and proximal small intestine) causes epigastric pain; pain from midgut organs (eg, distal small intestine, ascend-

ing and proximal transverse colon) localizes to the periumbilical region; and pain originating in the hindgut (eg, distal transverse and descending colon) localizes to the suprapubic and left lower quadrant area.<sup>7</sup> Visceral pain is elicited primarily by inflammation or ischemia stimulating the receptor neurons. Pain transmission is initially mediated by unmyelinated afferent C fibers located on the walls of hollow viscera and capsules of solid organs and is perceived as a deep, diffuse pain.<sup>8</sup>

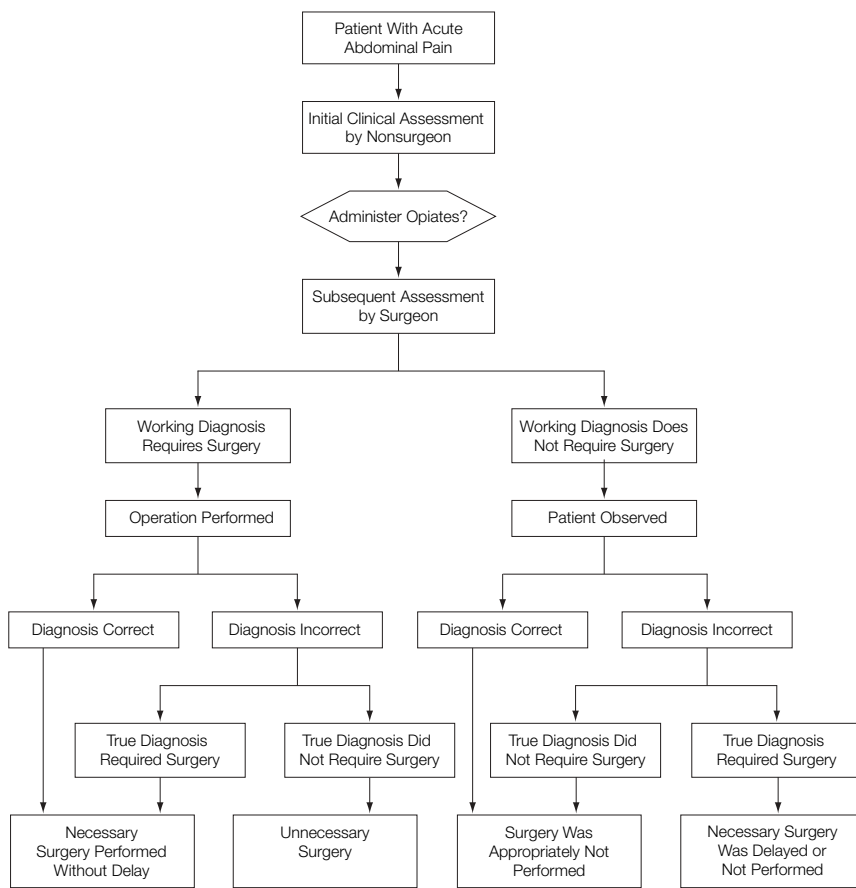
Thus, at the onset of an illness involving the viscera, the patient experiences pain that is difficult to describe or localize precisely, although the pain is often midline due to the bilateral sensory innervation of the spinal cord. As

the illness progresses, the peritoneum itself becomes affected. The peritoneum is richly innervated with larger myelinated A-delta fibers, which when stimulated transmit the sensation of sharper, more easily localized pain.<sup>7</sup> Exacerbating irritation of the peritoneum provides the basis for clinical maneuvers that elicit “peritoneal signs.” These maneuvers stretch the affected peritoneum, intensifying the pain.

**Possible Impact of Opiates on the Physical Examination**

Synthetic opiates, primarily through interaction with  $\mu$  receptors in the brain and spinal cord, produce analgesia by stimulating pain-inhibitory neurons and inhibiting pain-transmission neurons, thus blocking the pain cycle from afferent to central to efferent neurons.<sup>19</sup> Blocking the somatic efferent fibers that conduct messages to the abdominal muscles and skin may alter peritoneal signs, but predicting how opiates may affect the sensitivity and specificity of the overall physical examination is challenging. Voluntary guarding—ie, contraction of the abdominal muscles in response to palpation—may decrease if opiates have diminished a patient’s overall pain level. However, involuntary guarding or rigidity is thought to be a reflex spasm of the abdominal wall<sup>8</sup> and thus should not be affected by analgesia. The possible effect of opiates on rebound tenderness—ie, an increased pain response when abdominal pressure is removed suddenly during examination—is even more difficult to assess. If opiates help relax the patient without affecting the peritoneal signs, their administration could improve the reliability of results for some patients.

**Figure 1.** Diagnosis and Management Pathway in Patients With Acute Abdominal Pain Having Uncertain Diagnosis and Operative Decision After the Initial Examination



Patients may be given opiates between the initial examination and final examination when a decision is made about surgery. Opiates might alter the clinical findings and therefore affect the decision to proceed to surgery. Surgery may be required to establish the final diagnosis.

**METHODS**

We searched for studies that addressed 1 of 3 key questions: 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 manage-

ment of patients with acute abdominal pain?

We systematically searched MEDLINE by combining Medical Subject Headings title and text words targeting abdominal pain (eg, *abdomen*, *acute*, *abdominal*, *appendicitis*) with terms related to analgesia (eg, *analgesics*, *opioid*, *analgesia*) (full search strategy available from the authors on request). The MEDLINE search covered articles published through May 2006. We also searched EMBASE and scanned article bibliographies for potentially relevant studies. Two investigators (S.R.R., L.E.G.) independently reviewed each article and systematically abstracted the required data. A third investigator (K.G.S.) independently resolved discrepancies.

### Inclusion Criteria and Outcomes

We included placebo-controlled trials of opiate analgesia in patients with acute abdominal pain that assigned treatment using a randomized or quasi-randomized design (eg, alternating patients). We included trials that provided data on changes in the history, physical examination, or clinical management of patients. We abstracted 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. Similarly, we abstracted data on the incidence of all management errors. When we abstracted the data, we 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.

Delivering optimal surgical care necessitates performing a certain number of operations in patients who do not ultimately have surgical pathology. For instance, to avoid perforated appendicitis due to delaying surgery, a certain percentage of patients will undergo laparotomy in which the surgeon finds no pathology and removes a normal appendix. Our definitions of manage-

ment errors do not take this into account and may include cases in which the purported error falls within the scope of acceptable surgical practice. However, by using a conservative definition of management error, any conclusions about the impact of administering opiates become more robust. If opiates do not increase management errors when a conservative definition of error is used, then one can more confidently conclude that opiates do not adversely affect patient outcomes.

### Statistical Analysis

We constructed  $2 \times 2$  tables from the raw data and calculated the risk ratios (RRs) for history or physical examination changes and risk differences for management accuracy. For calculations of RRs, 0.5 was added to each cell of the table when any single cell had zero events. We used a random-effects model to generate conservative summary RRs, risk differences, and confidence intervals (CIs) and calculated the  $I^2$  statistic to assess for heterogeneity. All analyses were performed using Stata version 8.2 (StataCorp, College Station, Tex).

For history or physical examination changes, an RR with a point estimate greater than 1 and a lower 95% confidence limit excluding 1 suggests that opiates are more likely than placebo to affect the history or physical examination results. For management accuracy, the risk difference represents the absolute difference between management errors with opiates and with placebo. A risk difference with the point estimate and upper 95% confidence limit greater than 0 favors placebo and suggests that opiates might be harmful. We calculated the number needed to harm (NNH) as  $1/(\text{risk difference})$ ; the NNH represents the number of patients who would need to receive opiates to result in 1 management error in excess of the number associated with withholding opiates.

### RESULTS

The search strategy yielded 492 citations, of which 11 met the above cri-

teria.<sup>12,20-28</sup> Review of the reference lists from these articles yielded 1 additional abstract.<sup>29</sup> The 275 citations identified by the EMBASE search did not yield any additional trials. The final data set consisted of 12 studies reporting a total of 15 comparisons (TABLE 1 and TABLE 2). Nine studies<sup>20-25,27,29,30</sup> enrolled adult patients, and 3<sup>26,28,31</sup> enrolled pediatric patients. Three studies<sup>24,25,30</sup> enrolled only patients with right lower quadrant pain; all others enrolled patients with undifferentiated acute abdominal pain.

Three studies<sup>22,26,27</sup> reported data from multiple examiners who evaluated the patients before and after administration of opiate or placebo (eg, an emergency medicine physician and a surgeon). In these studies, we used results only from the initial examiner, reasoning that the assessments of subsequent examiners would likely not be independent.

### Effect of Opiates on Patient History

None of the included studies explicitly evaluated the effect of opiate administration on the patient history. Alteration of the history by provision of analgesia could potentially decrease its accuracy (by sedating the patient and minimizing previously concerning symptoms) or increase its accuracy (by calming the patient, allowing a clearer history). All studies<sup>20-31</sup> assessed patients' perceptions of changes in pain after receiving opiate or placebo. Analgesia was significantly greater in the opiate group compared with the placebo group in 11 of 15 comparisons.<sup>21-24,27-31</sup> Five studies<sup>13,18-20,28</sup> addressed the adequacy of blinding by having the examiner guess whether the patient had received opiate or placebo; in all cases, blinding was deemed adequate. Although the available evidence does not directly address the effects of opiates on the history, the adequacy of blinding in studies in which opiates provided significant pain relief provides some indication that administering opiates does not substantially alter the history.

**Table 1.** Adult Studies Used to Determine the Impact of Opiates on Accuracy of Clinical Evaluation of Patients With Acute Abdominal Pain

Source	No. of Participants	Inclusion Criteria	Examiner	Blinding	Analgesic Administered	Analgesia Greater in Opiates Group	Examination Outcome	Diagnosis Outcome
Zoltie and Cust, <sup>20</sup> 1986								
Comparison 1	125	Age >16 y with acute abdominal pain Excluded renal colic, "emergencies"	Same surgical resident before and after opiate administration	Examiner blinded to treatment group; unclear if outcomes assessors blinded	Sublingual buprenorphine (200 mg) vs placebo	No	Yes	Yes*
Comparison 2	143	As above	As above	As above	Sublingual buprenorphine (400 mg) vs placebo	No	Yes	Yes*
Attard et al, <sup>21</sup> 1992	100	Age >16 y with acute abdominal pain (<48 h) Excluded suspected AAA	Surgical resident before; surgical registrar after	Examiners blinded to treatment group; unclear if second examiner blinded to prior findings; unclear if outcomes assessors blinded	Intramuscular papaveretum (5-20 mg) vs placebo	Yes	Yes	Yes
Pace and Burke, <sup>22</sup> 1996	75	Age >18 y with acute abdominal pain (<48 h) Excluded if SBP <90 mm Hg or if judged to need opiates by treating physician	Same EM physician before and after	Examiners and outcomes assessors blinded	Intravenous morphine sulfate (up to 20 mg) vs placebo	Yes	Yes	Yes
Garyfallou et al, <sup>23</sup> 1997 (abstract)	41	Age not specified Excluded "severe pain," renal colic	Same physicians (EM physician and surgeon) before and after	Unclear if examiners or outcomes assessors blinded	Intravenous fentanyl (1.5 µg/kg) vs placebo	Yes	Yes	No
LoVecchio et al, <sup>23</sup> 1997								
Comparison 1	29	Age >18 y with acute pain, peritoneal signs Excluded renal colic, suspected AAA	Same EM physician (attending or senior resident) before and after	Unclear if examiners or outcomes assessors blinded to treatment groups	Intravenous morphine sulfate (5 mg) vs placebo	Yes	Yes	Yes*
Comparison 2	35	As above	As above	As above	Intravenous morphine sulfate (10 mg) vs placebo	Yes	Yes	Yes*
Vermeulen et al, <sup>24</sup> 1999	350	Age >16 y with RLQ pain Excluded renal colic, patients with "symptoms not suggestive of appendicitis"	EM physician before; surgeon after	Unclear if examiners or outcomes assessors blinded to treatment group or prior findings	Intravenous morphine sulfate (0.1 mg/kg) vs placebo	Yes	No	Yes
Mahadevan and Graff, <sup>25</sup> 2000	68	Age >11 y with RLQ pain <1 wk	Same EM resident before and after	Examiner blinded to treatment group; unclear if outcomes assessors blinded	Intravenous tramadol (1 mg/kg) vs placebo	No	Yes	No
Thomas et al, <sup>27</sup> 2003	74	Age >18 y with "severe" pain <72 h Excluded biliary/renal colic, hypotensive, suspected AAA	Same before and after (unclear if surgical resident, EM resident, or attending)	Examiners and outcomes assessors blinded	Intravenous morphine sulfate (up to 15 mg) vs placebo	Yes	Yes	Yes
Wolfe et al, <sup>30</sup> 2004	22	Age >16 y with suspected appendicitis scheduled for operation	Same EM physician and surgical resident before and after	Examiners blinded; unclear if outcomes assessors blinded	Intravenous morphine sulfate (0.075 mg/kg) vs placebo (crossover design)	Yes	Yes*	No

Abbreviations: AAA, abdominal aortic aneurysm; EM, emergency medicine; RLQ, right lower quadrant; SBP, systolic blood pressure.  
\*Outcome reported, but insufficient information provided for quantitative analysis.

### Effect of Opiates on the Physical Examination

Fourteen comparisons (from 11 studies<sup>20-23,25-31</sup>) reported data on changes in the physical examination, of which 11 comparisons (from 9 studies<sup>20-23,25,27-29,31</sup>) provided data in a format amenable to quantitative synthesis (Tables 1 and 2). The 9 comparisons conducted in adult patients<sup>20-23,25,27,29</sup> showed a trend toward changes in the physical examination with opiate administration, with a summary RR of 1.51 (95% CI, 0.85 to 2.69) (FIGURE 2). The 2 pediatric studies that provided quantitative data<sup>28,31</sup> showed a similar trend toward changes in physical examination with administration of opiates (RR, 2.11; 95% CI, 0.60 to 7.35) (Figure 2). Across both pediatric and adult studies, the summary RR was 1.55 (95% CI, 1.02 to 2.36.)

These results exhibited significant heterogeneity ( $I^2=62.1\%$ ;  $P=.003$ ), in-

dicating 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 such nonrandom variation may have been the adequacy of analgesia for patients in the opiate group. In 3 comparisons,<sup>20,25</sup> pain relief reported by the opiate group did not differ significantly from that reported by the placebo group. Restricting the analysis to the studies with adequate analgesia resulted in the risk for examination changes with opiate administration becoming statistically significant (RR, 2.13; 95% CI, 1.14 to 3.98) (Figure 2), but significant heterogeneity remained ( $I^2=68.6\%$ ;  $P=.002$ ).

Another potential source of heterogeneity may be that studies generally did not distinguish between potentially beneficial changes (such as improved localization of tenderness) and

potentially harmful changes (such as changes in peritoneal signs). Only 2 studies<sup>27,28</sup> specified changes in peritoneal signs as an outcome; loss of peritoneal signs after drug administration occurred in 5.6% to 18.7% of patients in the group receiving opiates and in 2.6% to 7.7% of those in the control group.

### Effect of Opiates on Potential Management Errors

Twelve comparisons (from 9 studies<sup>20-24,26-28,31</sup>) supplied quantitative data on diagnostic accuracy (Tables 1 and 2), though definitions of diagnostic errors varied across studies. We focused our analysis on the subset of studies that supplied sufficient information to apply our definition of potential management errors. Possible cases of delayed or unnecessary surgeries could be identified in 7 studies, 4 adult<sup>21,22,24,27</sup> and

**Table 2.** Pediatric Studies Used to Determine the Impact of Opiates on Accuracy of Clinical Evaluation of Patients With Acute Abdominal Pain

Source	No. of Participants	Inclusion Criteria	Examiner	Blinding	Analgesic Administered	Analgesia Greater in Opiates Group	Examination Outcome	Diagnosis Outcome
Kim et al, <sup>26</sup> 2002	Comparison 1	60 Age 5-18 y with pain <5 d Excluded if SBP <90, suspected biliary or pancreatic disease, IBD, sickle cell anemia	Pediatric EM attending before and after	Examiner blinded; unclear if outcomes assessors blinded	Intravenous morphine sulfate (0.1 mg/kg) vs placebo	No	Yes*	Yes
Green et al, <sup>31</sup> 2005	108	Age 5-16 y with abdominal pain of <48 h duration who required surgical consultation Excluded patients with hypotension, recent (within 4 h) opiate use, or opiate allergy	Pediatric EM physician before and after	Examiners blinded; unclear if outcomes assessors blinded	Intravenous morphine sulfate (0.05 mg/kg)	Yes	Yes	Yes
Kokki et al, <sup>28</sup> 2005	63	Age 4-15 y with abdominal pain of <7 d duration and >5 cm on VAS Excluded patients who had received analgesia prior to arrival at ED, patients with trauma, asthma, SBP <90 mm Hg, or contraindication to oxycodone	Same surgeon before and after	Examiners and outcomes assessors blinded	Buccal oxycodone (0.1 mg/kg)	Yes	Yes	Yes

Abbreviations: AAA, abdominal aortic aneurysm; ED, emergency department; EM, emergency medicine; IBD, inflammatory bowel disease; RLQ, right lower quadrant; SBP, systolic blood pressure; VAS, visual analog scale.

\*Outcome reported, but insufficient information provided for quantitative analysis.

3 pediatric<sup>26,28,31</sup> (TABLE 3). The specific management errors identified in each study are detailed in TABLE 4.

In adult studies,<sup>21,22,24,27</sup> meta-analysis indicated no significant change in the rate of incorrect management decisions among patients who received opiates (+0.3% absolute increase; 95% CI, -4.1% to +4.7%) (FIGURE 3). Analgesia was adequate in all these studies, and no significant heterogeneity was present ( $I^2=8.7\%$ ;  $P=.35$ ). The magnitude of this nonsignificant increase in incorrect decisions is very small. To illustrate, if it had been significant, 333 patients would need to receive opiates to result in 1 management error attributable to analgesia. These data are also compatible with fewer management

errors among patients receiving opiates, as the range of the 95% CI suggests that there may be no true underlying difference in effect between opiates and placebo. Moreover, these results reflect the conservative assumption that the 2 patients with missing data in 1 study<sup>24</sup> would have contributed to management errors in the opiates group. Excluding those 2 patients from the analysis results in a pooled risk difference of 0% (95% CI, -4.2% to +4.2%).

Meta-analysis of the 3 pediatric studies<sup>26,28,31</sup> indicated a nonsignificant absolute decrease in incorrect management decisions (-0.8%; 95% CI, -8.6% to +6.9%;  $P=0.0\%$ ;  $P=.71$ ). Across all studies (adult and pediatric), there was virtually no change in the manage-

ment error rate for those who received opiates (+0.1% absolute increase; 95% CI, -3.6% to +3.8%) (Figure 3), which translates to an NNH of 909. Analgesia was inadequate in 1 trial,<sup>26</sup> though eliminating this trial from the analysis had minimal impact on the estimated error rate (-0.2% absolute decrease in potential management errors with opiates; 95% CI, -4.0% to +3.6%).

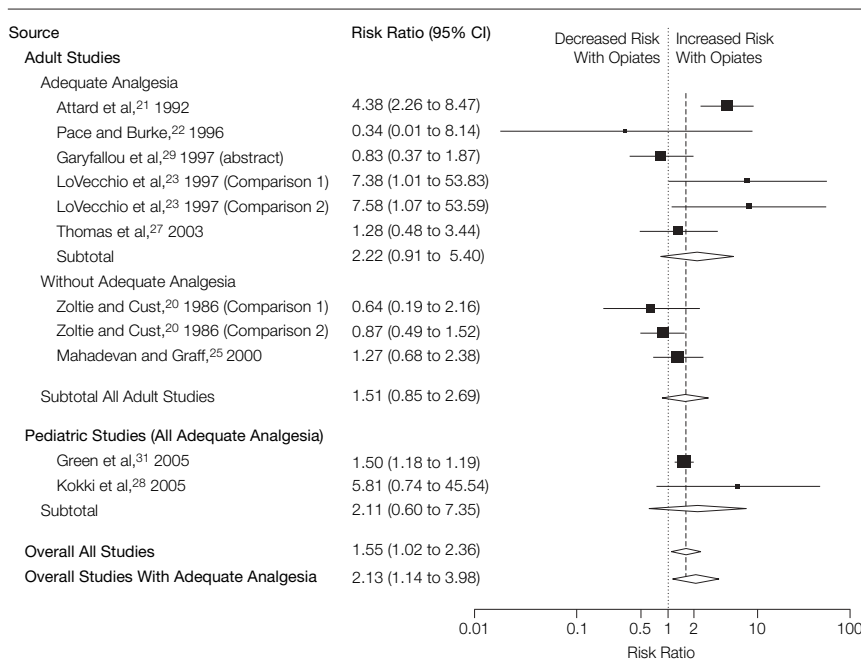
We further analyzed the 7 trials<sup>21,22,24,26-28,31</sup> by post hoc classification of errors into surgeries that were possibly delayed or unnecessary. Among a total of 816 patients, 7 in the opiate group and 4 in the control group may have experienced a clinically important delay in surgery (Table 3). Meta-analysis of the difference between groups was not informative, as the small number of outcomes produced wide CIs. On the other hand, the rate of delayed surgeries overall was only 1.3% (95% CI, 0.7% to 2.4%).

The frequency of possible unnecessary surgeries was 7.6% (95% CI, 5.2% to 10.6%) among patients who received opiates, compared with 7.9% (95% CI, 5.4% to 10.9%) among patients who received placebo. Meta-analysis showed a trend toward fewer unnecessary surgeries among patients who received opiates for both adults (-0.3%; 95% CI, -7.5% to +6.8%) and children (-2.6%; 95% CI, -9.1% to +3.8%). Among all patients, there was a nonsignificant decrease in the risk of unnecessary surgeries for patients receiving opiates (-0.8%; 95% CI, -5.6% to +4.1%).

**Methodological Limitations of the Studies**

The majority of included studies exhibited important methodological problems. Only 1 study<sup>28</sup> indicated adequate concealment of allocation of patients to treatment group, and the outcomes assessors were blinded to treatment assignment in only 4 comparisons<sup>22,27,28</sup> (Tables 1 and 2). Two methodological issues related specifically to the study questions at hand: the use of the same examiner before and after treatment and the adequacy of opiate analgesia.

**Figure 2.** Changes in Abdominal Examination Results After Administration of Opiates Compared With Placebo



The forest plot shows the studies of adult and pediatric patients providing data on physical examination changes, both for all studies and for those studies with adequate analgesia (ie, analgesia significantly greater in the opiate vs placebo groups). The combined risk ratio (RR) for all studies (1.55; 95% confidence interval [CI], 1.02 to 2.36) indicates an increased risk of changes in physical examination findings with opiates. The studies exhibited significant heterogeneity ( $I^2=62.1\%$ ;  $P=.003$ ). In studies with multiple examiners, the results of the initial examination were used, with the exception of Thomas et al,<sup>27</sup> for which individual examination data were not available. The RR for this study is based on 104 separate examinations performed on 74 patients. Reducing the weight accorded this study by 30% to compensate for this inflation of the sample size produced a negligible change in the summary RR. Deleting the study entirely had little impact on the summary result (RR, 1.60; 95% CI, 1.01 to 2.53). The combined RR for studies with adequate analgesia (2.13; 95% CI, 1.14 to 3.98;  $P=68.6\%$ ;  $P=.002$  for heterogeneity) indicates an increased risk of physical examination changes with opiates. Size of data markers is proportional to the weight of the individual studies in the meta-analysis. Error bars indicate 95% CIs.

In all but 2 studies,<sup>21,24</sup> the same physician examined the patient before and after the study medication was administered. Physical examination results and differential diagnoses produced by the same examiner will likely be significantly correlated. This creates bias toward the null hypothesis, making it less likely that a significant difference would be found between opiates and placebo for any

aspect of the clinical examination. Using the same examiner in a before-after study design requires that clinicians consider whether the results generalize to the examination by a consultant after their patient receives opiates, especially since interrater agreement on the presence of a "surgical abdomen" is only moderate.<sup>32</sup> Blinding to study medication was adequate in the 5 studies<sup>13,18-20,28</sup> in

which it was assessed, providing some support for generalizing the results.

Analgesic agents varied across the studies and included opiates not routinely administered to treat acute pain in the emergency department setting. Seven studies<sup>22-24,26,27,30,31</sup> used intravenous morphine, but intravenous fentanyl,<sup>29</sup> intravenous tramadol,<sup>25</sup> intramuscular papaveretum,<sup>21</sup> buccal oxycodone,<sup>28</sup> and sublingual buprenor-

**Table 3.** Cases of Possible Management Errors, Defined As Delayed Surgery or Unnecessary Surgery

Study	No. of Participants*	Laparotomies, No. (%)	Final Diagnoses (%)	No. of Delayed Surgeries/ No. in Group		No. of Unnecessary Surgeries/ No. in Group	
				Opiates	Placebo	Opiates	Placebo
<b>Adult Studies</b>							
Attard et al, <sup>21</sup> 1992	100	NR	Nonspecific abdominal pain (22) Appendicitis (20) Perforated peptic ulcer (15) Cholecystitis/biliary colic (14) Diverticulitis (9) Bowel obstruction (6) Pancreatitis (4) Other (10)†	2/50	0/50	0/50	6/50
Pace and Burke, <sup>22</sup> 1996	75‡	28 (37.3) [13 opiates, 15 placebo]	Nonspecific abdominal pain (26.7) Appendicitis (12.0) Cholecystitis/cholelithiasis (12.0) Bowel obstruction (9.3) Ovarian cyst (5.3) Pancreatitis (5.3) Unperforated peptic ulcer (5.3) Perforated viscus (2.7) Kidney stone (2.7) Other (24)†	0/35	0/36	1/35	1/36
Vermeulen et al, <sup>24</sup> 1999	350§	205 (58.6) [113 opiates, 92 placebo]	Appendicitis (44.3) Other surgical pathology (4.6) Other final diagnoses not provided	2/175	0/165	19/175	15/165
Thomas et al, <sup>27</sup> 2003	74	18 (24.3) [11 opiates, 7 placebo]	Nonspecific abdominal pain (29.7) Diverticulitis (12.2) Genitourinary tract conditions (10.8) Appendicitis (9.5) Gastroenteritis (9.5) Cholecystitis/biliary colic (6.8) Pancreatitis (6.8) Bowel obstruction (5.4) Other (9.3)†	0/36	1/38	3/36	0/38
<b>Pediatric Studies</b>							
Kim et al, <sup>26</sup> 2002 (comparison 1)	60	44 (73.3) [21 opiates, 23 placebo]	Appendicitis (58.3) Nonspecific abdominal pain (20) Ovarian torsion (3.3) Constipation (3.3) Streptococcal pharyngitis (3.3) Other (11.8)†	0/29	0/31	3/29	2/31
Green et al, <sup>31</sup> 2005	108	62 (57.4) [32 opiates, 30 placebo]	Appendicitis (52.8) Nonspecific abdominal pain (41.7) Other (5.5)†	3/52	2/56	1/52	4/56
Kokki et al, <sup>28</sup> 2005	63	31 (49.2) [17 opiates, 14 placebo]	Nonspecific abdominal pain (61.9) Appendicitis (33.3) Other (4.8)†	0/32	1/31	4/32	4/31

Abbreviation: NR, not reported.

\*The presenting complaint was undifferentiated abdominal pain for all studies except Vermeulen et al<sup>24</sup> (right lower quadrant pain).

†Refers to a variety of conditions, which occurred in  $\leq 2$  patients in each study.

‡Only 71 patients completed the study (4 excluded for protocol violations).

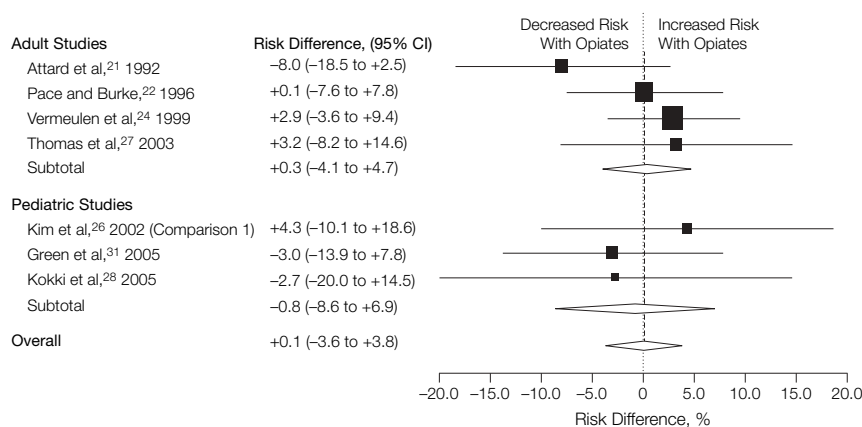
§Only 340 patients completed the study (8 excluded for protocol violations, 2 lost to follow-up [included in sensitivity analysis herein]).

**Table 4.** Examples of Delayed and Unnecessary Surgeries

Study	Delayed Surgeries	Unnecessary Surgeries
<b>Adult Studies</b>		
Attard et al, <sup>21</sup> 1992	Two patients with appendicitis who had delayed appendectomies; initial working diagnoses not provided	Preoperative diagnoses were appendicitis (5 patients) and perforated peptic ulcer (1 patient); postoperative diagnosis was nonspecific abdominal pain in all patients
Pace and Burke, <sup>22</sup> 1996	None	Preoperative diagnosis was appendicitis; postoperative diagnosis was nonspecific abdominal pain in both patients
Vermeulen et al, <sup>24</sup> 1999	Two patients lost to follow-up; in the main analysis, we treated these patients as if they represented cases of delayed surgery	Preoperative diagnosis was appendicitis; postoperative diagnosis was nonspecific abdominal pain in all patients
Thomas et al, <sup>27</sup> 2003	Delayed cholecystectomy: treating clinicians had noted "borderline evidence for cholecystitis" but discharged patient for outpatient follow-up, which resulted in cholecystectomy. Per study protocol, an independent surgeon unaware of study group assignment judged the patient's presentation as warranting cholecystectomy during hospitalization	Two patients with preoperative diagnosis of acute cholecystitis underwent cholecystectomy with no pathological findings; postoperative diagnosis presumed to be nonspecific abdominal pain in both cases One patient underwent operation that "might have been premature" for diverticular abscess
<b>Pediatric Studies</b>		
Kim et al, <sup>26</sup> 2002 (comparison 1)	None	Preoperative diagnoses not clear; indication for surgery listed as "exploratory laparotomy." Opiate group included 2 negative appendectomies, 1 patient with pelvic inflammatory disease Control group included 1 patient each with mesenteric adenitis and ovarian cyst
Green et al, <sup>31</sup> 2005	Three patients in the opiate group and 1 in the placebo group were admitted for observation and found to have perforated appendixes at laparotomy; 1 additional patient in the placebo group was discharged from the ED and readmitted 5 d later with acute appendicitis	Preoperative diagnoses not stated; in all cases, normal appendix found at laparotomy and no other surgical diagnosis identified
Kokki et al, <sup>28</sup> 2005	Delayed appendectomy; patient admitted for observation and at laparotomy was found to have perforated appendicitis with peritonitis	Preoperative diagnosis was appendicitis and postoperative diagnosis was nonspecific abdominal pain in all patients

Abbreviation: ED, emergency department.

**Figure 3.** Absolute Change in Risk of Incorrect Management Decisions With Opiates



The forest plot shows the trials that provided data on potential errors in clinical management, defined as possible delays in necessary surgery or the performance of possibly unnecessary surgery. The overall random-effects estimate shows almost no difference in the risk of incorrect management decisions (+0.1% absolute increase with opiates; 95% confidence interval [CI], -3.6% to +3.8%). The trials did not exhibit significant heterogeneity ( $I^2=0.0\%$ ;  $P=.67$ ). Size of data markers is proportional to the weight of the individual studies in the meta-analysis.

phine<sup>20</sup> were each used in 1 study. As noted previously, pain relief did not differ significantly between opiate and placebo groups in 5 comparisons (from 3 studies<sup>20,25,26</sup>) (Tables 1 and 2). Restricting the analysis to comparisons with adequate analgesia<sup>21-24,27-29,31</sup> lends credence to the argument that opiate analgesia induces physical examination changes; eliminating the single study that did not achieve adequate analgesia<sup>26</sup> from the analysis of management errors did not significantly change the results.

**SCENARIO RESOLUTION**

While the data suggest that opiates might change the physical examination findings, you decide to administer intravenous morphine sulfate. When examined by the surgical consultant, your patient is more comfortable com-

pared with when you evaluated her. The surgeon finds right lower quadrant tenderness on deep palpation without peritoneal signs. A computed tomography (CT) scan confirms the clinical impression of acute appendicitis. The patient undergoes an uncomplicated laparoscopic appendectomy and recovers uneventfully.

### THE BOTTOM LINE

Despite methodological limitations, we conclude that opiate analgesics do alter the physical examination in patients with acute abdominal pain. Few studies specifically reported on examination changes that could alter the decision to operate (such as altered peritoneal signs), making it difficult to assess the significance of these changes. However, opiate administration seems to have negligible impact on clinical management. Despite using a definition in our analyses that would favor withholding opiate analgesia, 909 patients would have to receive opiates to result in 1 potential management error. The CI around this estimate includes the possibility that more liberal use of opiates reduces management errors, but it also includes the possibility of a 3.6% absolute increase in management errors. This error rate (associated with an NNH of 28) reflects a conservative definition in which surgeries labeled as either delayed or unnecessary may have met appropriate standards of care. As shown in Table 4, some of the cases termed management errors may fall within the scope of acceptable surgical practice. An exploratory laparotomy that reveals a non-surgical condition, or even no specific diagnosis, is not necessarily a management error. Labeling such practices as potential errors reflects the conservative nature of our analysis. None of the patients defined as having experienced a management error experienced significant morbidity or mortality.

Clinicians incorporate a complex series of inputs to arrive at a management decision, including the patient's history, physical examination, and

laboratory and radiological data. The debate in the literature has centered on the effects of opiates on physical examination findings. This focus runs counter to the generally accepted view that the history by itself provides the crucial information necessary for a diagnosis in many patients.<sup>33-36</sup> However, no study specifically addressed the effect of opiates on the accuracy of a patient's history. Thus, we do not know whether analgesic doses of opiates cloud a patient's memory or instead calm the patient so that he or she can provide a more coherent and accurate history.

Improvements in imaging have led to changes in practice patterns, whereby surgical diagnosis is increasingly predicated on the results of imaging (particularly CT scan).<sup>37,38</sup> Use of abdominal imaging may have decreased the emphasis in practice on the physical examination as a decision-making tool for patients with acute abdominal pain. Our results primarily pertain to patients in whom the initial clinical examination does not yield a specific diagnosis, necessitating reexamination, imaging studies, or both. Within this group, the subset of patients who have surgical problems but nondiagnostic imaging studies may be most susceptible to management errors caused by altered clinical examination findings. The size of this group of patients is not clear, nor is it known which diagnoses are likely to present in this fashion.

Greater reliance on imaging also raises the question of how opiate use affects the requests for, and interpretation of, abdominal ultrasound or CT scans. Two studies have evaluated the effects of opiate analgesia on the accuracy of ultrasound. One study<sup>24</sup> (included in our analysis) examined the influence of opiates on the accuracy of ultrasound in diagnosing acute appendicitis; administering opiates increased the specificity of ultrasound, while sensitivity decreased. Another study<sup>39</sup> found no change in the accuracy of the sonographic Murphy sign for diagnosing acute cholecystitis if pa-

tients had received opiates. No study has yet investigated the influence of analgesia on the use or interpretation of CT scanning in evaluation of abdominal pain.

What are the implications for clinical practice? While the theoretical possibility of harm from liberal administration of opiates exists, few empirical data document the extent of this harm. One retrospective study<sup>40</sup> found an increased incidence of significant morbidity in patients with an acute abdomen who were given opiates, but causality is difficult to determine, as the opiate effect may have been confounded by pain severity. The rate of perforated appendicitis is often used as an indicator of delayed surgery.<sup>41</sup> This rate appears to have remained stable at 15% to 20% of appendicitis cases over the last 3 decades,<sup>41,42</sup> despite some change in physicians' attitudes toward opiate use over that time. Two retrospective analyses of patients with proven appendicitis did not find any difference in the rate of perforated appendicitis between patients who received or did not receive analgesia.<sup>13,43</sup> Reports of analgesia administration leading to adverse consequences remain limited to case reports.<sup>15</sup>

While giving opiates to patients with acute abdominal pain appears to alter the physical examination, the use of opiates leads to virtually no increase in incorrect management decisions. Given the humane duty of physicians to relieve pain and the totality of the available evidence, clinicians should administer analgesia unless further studies document adverse events to patients directly attributable to opiates. Further studies should also clearly define and measure beneficial and harmful changes (both accuracy and delays) in the history, physical examination, and patient management. In addition, investigators should attempt to define the patient population in which physical examination changes are likely to influence management as well as consider whether opiates affect the need for CT scanning and if analgesia might im-

prove (or worsen) the accuracy of imaging studies.

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**Study concept and design:** Ranji, Simel, Shojania.

**Acquisition of data:** Ranji, Goldman.

**Analysis and interpretation of data:** Ranji, Goldman, Simel, Shojania.

**Drafting of the manuscript:** Ranji, Goldman, Simel, Shojania.

**Critical revision of the manuscript for important intellectual content:** Ranji, Simel, Shojania.

**Statistical analysis:** Ranji, Simel, Shojania.

**Administrative, technical, or material support:** Ranji. **Study supervision:** Simel, Shojania.

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