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Guidelines for Reasonable and Appropriate Care in the Emergency Department 2 (GRACE-2): Low-risk, recurrent abdominal pain in the emergency department

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ORIGINAL CONTRIBUTION

CME

Guidelines for Reasonable and Appropriate Care in the Emergency Department 2 (GRACE-2): Low-risk, recurrent abdominal pain in the emergency department

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Abstract

This second Guideline for Reasonable and Appropriate Care in the Emergency Department (GRACE-2) from the Society for Academic Emergency Medicine is on the topic "low-risk, recurrent abdominal pain in the emergency department." The multidisciplinary guideline panel applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence and strength of recommendations regarding four priority questions for adult emergency department patients with low-risk, recurrent, undifferentiated abdominal pain. The intended population includes adults with multiple similar presentations of abdominal signs and symptoms recurring over a period of months or years. The panel reached the following recommendations: (1) if a prior negative computed tomography of the

The GRACE-2 writing group acknowledges the assistance of Tami Craig and Stacey Roseen at the Society for Academic Emergency Medicine for their administrative assistance coordinating and archiving GRACE-2 meetings. In addition, the GRACE-2 writing group appreciates the search strategies developed and completed by the medical librarians Michelle Doering and Danielle J. Gerberi.

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abdomen and pelvis (CTAP) has been performed within 12 months, there is insufficient evidence to accurately identify populations in whom repeat CTAP imaging can be safely avoided or routinely recommended; (2) if CTAP with IV contrast is negative, we suggest against ultrasound unless there is concern for pelvic or biliary pathology; (3) we suggest that screening for depression and/or anxiety may be performed during the ED evaluation; and (4) we suggest an opioid-minimizing strategy for pain control.

EXECUTIVE SUMMARY: The GRACE-2 writing group developed clinically relevant questions to address the care of adult patients with low-risk, recurrent, previously undifferentiated abdominal pain in the emergency department (ED). Four patient-intervention-comparison-outcome-time (PICOT) questions were developed by consensus of the writing group, who performed a systematic review of the literature and then synthesized direct and indirect evidence to formulate recommendations, following GRADE methodology. The writing group found that despite the commonality and relevance of these questions in emergency care, the quantity and quality of evidence were very limited, and even fundamental definitions of the population and outcomes of interest are lacking. Future research opportunities include developing precise and clinically relevant definitions of low-risk, recurrent, undifferentiated abdominal pain and determining the scope of the existing populations in terms of annual national ED visits for this complaint, costs of care, and patient and provider preferences.

KEYWORDS

abdominal pain, analgesia, anxiety, computed tomography, depression, emergency department, low-risk, opioid, recurrent, ultrasound

INTRODUCTION

Abdominal pain has consistently remained the most frequent chief complaint in U.S. emergency departments (EDs) from 2009 to 2018, accounting for 7.1%–8.8% of ED visits annually.[1–3] The evaluation of acute abdominal pain requires substantial ED resources, including imaging, laboratory studies, nursing care, time, and patient care space. Including computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), and plain radiography, more than 50% of ED abdominal pain patients undergo some form of imaging.[3] CT of the abdomen and pelvis (CTAP) use in ED visits for abdominal pain grew dramatically from 1996 to 2007, from 1.4% to 31.7%, and has remained at similarly high levels ever since.[2–5] By 2007, CTAP for the chief complaint of abdominal pain constituted 12.8% of all CT-associated ED visits in the United States.[6] CTAP use for abdominal pain remained high throughout the period 2007 to 2013, at 25.3% of abdominal pain visits in 2007, peaking at 30.1% in 2010, and reaching 28.6% in 2013.[3] In 2018, 10.7 million ED CTAPs were performed, representing 8.2% of all ED visits[2]—and notably indicating CTAP use not only for abdominal pain but also for related conditions such as trauma, flank pain, and hematuria.[5] Despite increasing rates of ED imaging for abdominal pain (CTAP from 10.1% in 2001 to 22.5% in 2005; ultrasound from 11.1% to 13.6% in the same period), the diagnosis of appendicitis, diverticulitis, and gallbladder disorders did not increase, and hospital admissions for abdominal pain did not decrease.[7] More than

RECOMMENDATIONS

Recommendation 1: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and prior negative computed tomography of the abdomen and pelvis (CTAP) within 12 months, there is insufficient evidence to accurately identify populations in whom repeat imaging can be safely avoided or routinely recommended in the ED. (No recommendation) [No evidence]

Recommendation 2: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and a negative CTAP with IV contrast in the ED, we suggest against ultrasound unless there is concern for pelvic or biliary pathology. (Conditional recommendation, against) [Very low certainty of evidence]

Recommendation 3: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain, we suggest screening for depression and/or anxiety may be performed during the ED evaluation. (Conditional recommendation, either) [Very low certainty of evidence]

Recommendation 4: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain, we suggest an opioid-minimizing strategy for pain control. (Conditional recommendation, for) [Consensus, no evidence]

85% of ED abdominal pain patients receive medications in the ED, including opioid analgesia in 34%.[3]

Despite the intensity of diagnostic testing, most patients presenting with abdominal pain do not receive a specific diagnosis in the ED. Between 2007 and 2013, the group of nonspecific diagnoses including "other gastrointestinal disorders," "nausea and vomiting," and "abdominal pain" totaled 40.8% (2007), 45.5% (2010), and 50.9% (2013).[3]

National data on ED presentations for recurrent abdominal pain are limited, but abdominal pain is a leading chief complaint among patients who have recurrent ED visits. ED superutilizers are defined as patients with annual ED visits >2 standard deviations (SDs) above the mean by age and payer group (e.g., patients aged 1–64 years covered by Medicare or Medicaid with six or more annual ED visits and privately insured patients aged 1–64 years or Medicare patients aged 65 years and older with four or more annual ED visits).[8] Within this group, abdominal pain was the most frequent first diagnosis for those aged 1–64 years and the third most frequent for those aged ≥ 65 years. In total, 15%–34% of ED visits by superutilizers are for abdominal pain.[8] Even though superutilizers represent only 2.6%–6.1% of all ED visits, the high representation of abdominal pain underscores the need for more evidence-based strategies to optimally manage this group of patients.

Recurrent ED visits for undifferentiated abdominal pain present opportunities that may benefit or harm patients. Benefits could include the identification of previously missed diagnoses, improved symptom management, addressing comorbidities such as depression and substance use disorders, and appropriately connecting patients with outpatient resources such as primary care and specialists. Risks of recurrent visits include repeated CT testing with its accompanying ionizing radiation and cancer risk,[9–13] the identification of false-positive or incidental findings resulting in unnecessary workup (with harms including iatrogenic pain, complications, fear, and cost),[14] and the potential to expose patients to opioid medications with opioid use disorder risks.[15–30] Negative health care system effects might include crowding and excessive wait times and length of stay (LOS), not only for those with abdominal pain but also for all patients.

High utilizers (with varying definitions), particularly young adults, have been observed to accumulate relatively large radiation doses and attendant estimated lifetime attributable risks of cancer from multiple CTs.[12,13,31–33] The Biological Effects of Ionizing Radiation (BEIR) VII report ("Health Risks from Exposure to Low Levels of Ionizing Radiation") suggests a linear effect of radiation exposure on cancer risk, with no safe threshold.[34,35] Consequently, each additional exposure to CT is believed to carry the same marginal/additional cancer risk. One study showed little effort by physicians to engage patients in shared decision making when considering CT for abdominal pain.[36] Another study suggested that patient requests for CT are an anticipated reason for emergency physician ordering practices.[37]

Visits for recurrent abdominal pain are also complicated by the diverse differential diagnosis for abdominal pain and the potential for similarity in presentations caused by very different pathology, such as ureteronephrolithiasis,[38] appendicitis,[39] cholecystitis,[40] mesenteric ischemia,[41] peptic ulcer disease,[42] abdominal aortic aneurysm,[43] bowel obstruction,[44] and ovarian pathology.[45] Patients with a history of previous episodes of abdominal pain cannot be assumed to have the same cause of pain when presenting anew; occasionally patients are diagnosed with new acute surgical disease on subsequent visits involving CTAP imaging.[46–48]

While guidelines from specialty organizations have targeted the management of patients with specific known or suspected disease processes (e.g., nephrolithiasis,[49,50] pancreatitis,[51] Crohn's disease,[52,53] or gastroparesis[54]) or focused on acute clinical presentations such as blunt abdominal trauma[55] or right lower quadrant abdominal pain with suspected appendicitis,[56,57] little guidance is available to emergency physicians evaluating and treating patients with recurrent and undifferentiated abdominal pain. Without guidelines for care, variance in practice could result in lower quality care, including risks of over- or undertesting, misdiagnosis, adverse effects of over- or undertreatment, higher costs, greater LOS, and lower patient satisfaction.

SCOPE AND PURPOSE

The purpose of the second Guideline for Reasonable and Appropriate Care in the Emergency Department (GRACE-2) is to provide an evidence-based, patient-centric approach for clinicians in their evaluation and management of adult patients with low-risk recurrent undifferentiated abdominal pain in the ED. The guideline is not intended for application to patients recognized by trained emergency physicians as having unstable vital signs, significant presenting history or physical examination findings suggesting acute abdominal pathology, or other risk factors for severe abdominal disease not specifically discussed here. The guideline is also not intended for patients with a new and acute presentation of abdominal pain with only short-term recurrence, such as might be seen in a patient with evolving appendicitis who presents on two or more occasions over a period of a few days as the disease progresses. The intended population includes adults with multiple *similar* presentations of abdominal signs and symptoms *recurring* over a period of months or years.

GRACE-2 is designed for application in the United States in settings with access to advanced diagnostic imaging and laboratory testing as well as specialty referral. The writing group discussed the possible application in international settings and rural settings within the U.S. patient populations, patterns of disease, ED resources, and health systems with access to primary care and referral may differ in other settings, making recommendations from this guideline less applicable.[58]

METHODS

Group composition

The GRACE-2 writing group included emergency physicians from geographically diverse academic medical centers in the United States and Canada, including those with research methodology expertise and content expertise in the diagnosis and treatment of abdominal pain,

opioid pain medications, and mental health. In addition, the panel included a patient representative and a board-certified psychiatrist with career specialization in pain management. As discussed in the limitations, the writing group did not include other specialists engaged in the care of patients with recurrent abdominal pain, although the guideline was submitted for external review by such groups. Future GRACE guidelines should consider inclusion of these stakeholders throughout the writing process. The Society for Academic Emergency Medicine (SAEM) supported the development of this guideline.

Group interaction and processes

From May 2020 until August 2021, the GRACE-2 writing group met monthly. The group applied the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology, a stepwise process that includes development of systematic reviews of priority questions; assessment of certainty in the evidence at the outcome level by explicit consideration of the GRADE criteria; and development of recommendations using the GRADE Evidence-to-Decision (EtD) framework. Recommendations are assigned direction (for, against, or either) and strength (strong vs. conditional/weak [the latter used interchangeably in GRADE]; Figure 1).[59–67]

Training

The methodologists had previously received GRADE training, and all writing group members were encouraged to watch online video content describing the GRADE methodology and its application to GRACE.[68]

Declaration and management of competing interests

All group members disclosed conflicts of interest using SAEM standard methods. No member of the group disclosed a significant conflict requiring management.

Definitions of the intended patient population

The GRACE-2 writing group deliberated extensively about the population of interest for this clinical practice guideline and focused on definitions of "low-risk," "undifferentiated," "recurrent," and "negative CTAP" throughout the development of the guideline. Table 1 summarizes definitions developed and used by the GRACE-2 writing group.

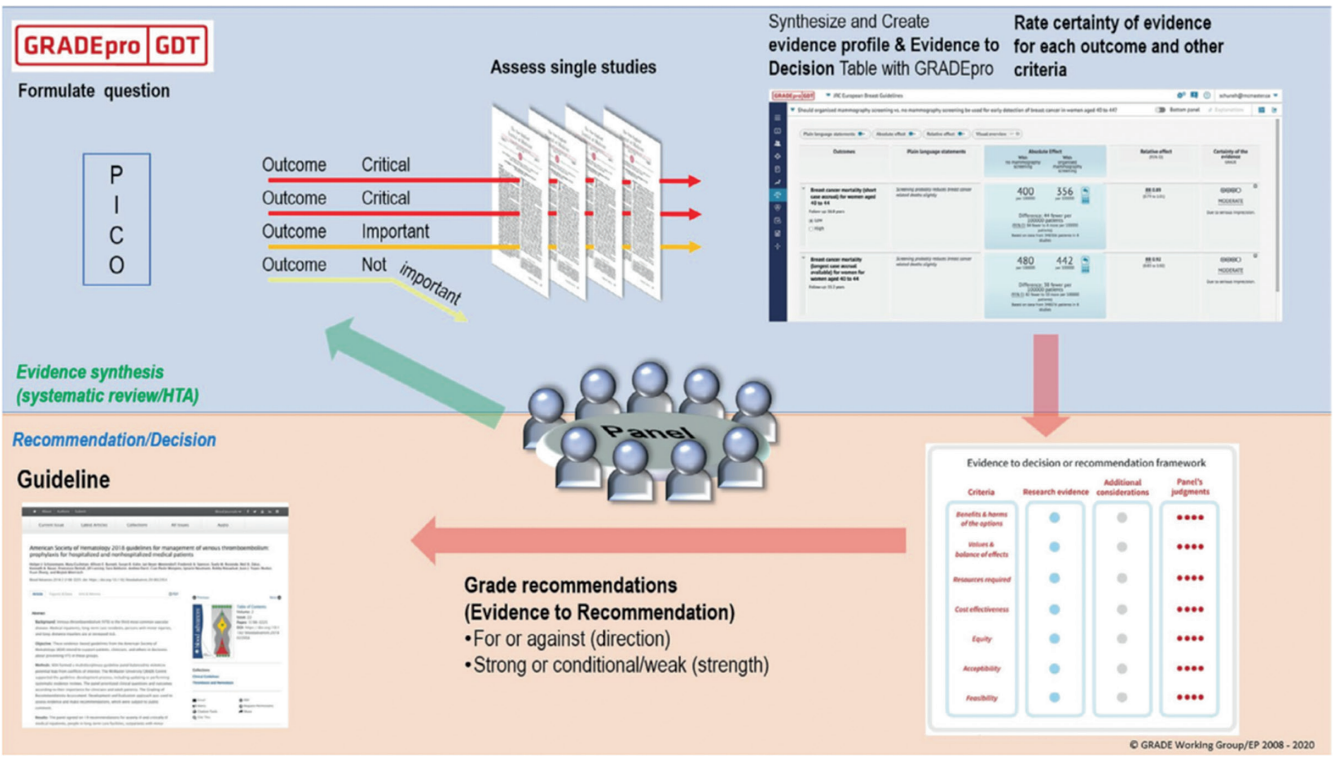

FIGURE 1 Schematic view of the GRADE approach for synthesizing evidence and developing recommendations. The top half describe steps in the process common to systematic reviews and making health care recommendations and the lower half describe steps that are specific to making recommendations including steps from panel members to make recommendations. *Reproduced with permission by the U.S. GRADE Network

TABLE 1 GRACE-2 definitions

Term	Definition
Low risk	Patients were *excluded* from the category of low risk for: • Unstable vital signs • History and physical examination findings suggesting acute abdominal pathology • Age < 18 years or ≥65 years • Pregnancy • Acute trauma within 7 days • Organ transplantation • Immunosuppression • Abdominal surgery within 30 days • Active cancer • Inflammatory bowel disease • Previous bowel obstruction • Severe active psychiatric illness
"Previously undifferentiated"	No clear etiology identified
"Previous workup"	CT of the abdomen and pelvis with IV contrast, complete blood count, hepatic function tests, lipase, urinalysis, and (when appropriate) human chorionic gonadotropin
"Negative CTAP"	No pathological abnormalities, related or unrelated to the current presentation
"Recurrent"	Two or more prior similar episodes within a period of 12 months, with the time elapsed from the first episode to the current episode being ≥30 days

Low risk

The GRACE-2 writing group identified clinically important outcomes of interest (identification of potentially life-threatening diagnosis, abdominal surgery or other invasive procedure within 30 days, hospital and intensive care unit [ICU] admission rates within 30 days, mortality within 30 days, and return ED visit within 30 days) and then sought to describe a patient population at low-risk of these. The selection process for clinically important outcomes is discussed in more detail later in this document and in Appendix S2.

In considering low risk, the GRACE-2 writing group identified specific populations that would not meet this definition and chose to exclude them prospectively. Excluded populations had the following characteristics and conditions: <18 years of age or age 65 years or older, pregnancy, acute trauma within 7 days, organ transplantation, immunosuppression, abdominal surgery within 30 days, active cancer, inflammatory bowel disease, previous bowel obstruction, and severe active psychiatric illness (specifically psychosis/mania). The writing group debated using the term "non–high risk," as the exclusion of the above assumed high-risk populations does not necessarily define the remainder as low risk. Without an evidence-based quantitative measure of risk, the writing group chose instead to adopt low risk as a convenient shorthand, rather than as an assertion.

The GRACE-2 writing group discussed the possibility of excluding other patients whose evaluation might be challenging and who therefore might be at increased risk of missed acute abdominal pathology without the use of extensive testing. Populations considered, but ultimately not excluded from, the guideline included undomiciled patients, patients with traumatic brain injury, non–English-speaking patients, patients with other communication barriers, and patients without a primary care physician, which could limit follow-up opportunities to evaluate causes of abdominal pain not pursued in the ED. Ultimately the GRACE-2 writing group chose not to exclude these populations, erring on the side of creating a clinical practice guideline with the broadest possible application. Excluding these patient populations could also introduce inequities in guidelines for the delivery of care (e.g., providing different guidance for emergency physicians caring for patients speaking different languages or those with socioeconomic disparities). Individual physicians may consider these patient populations to be at higher risk.

Recurrent abdominal pain

The GRACE-2 writing group debated the definition of recurrent abdominal pain, which was not clearly defined within the literature in relationship to ED patients. We defined recurrent as indicating two or more prior *similar* episodes within a period of 12 months, with the time elapsed from the first episode to the current episode being greater than or equal to 30 days. For comparison, the criteria for recurrent abdominal pain established by Rome IV for irritable bowel syndrome (IBS) require abdominal pain on average at least 1 day per week in the past 3 months, with symptoms beginning at least 6 months prior to diagnosis.[69] These criteria are based on a survey of U.S. adults with no previous physician diagnosis of an abdominal disorder, defining ≥90th percentile as abnormal. Our definition of recurrent pain was based on the consensus that recurrence was not intended to address repeated short-term presentations with an acute and evolving new abdominal syndrome. Such presentations may not represent a low-risk condition and likely require evaluation for evolving surgical disease such as appendicitis or bowel obstruction.

Undifferentiated abdominal pain without prior workup

GRACE-2 is not intended to apply to patients who have not yet undergone evaluation of potential causes of their abdominal pain. Medical workup for undifferentiated recurrent abdominal pain may be indicated, as patients may have serious and treatable causes such as malignancy, inflammatory bowel disease, nephrolithiasis, abdominal vascular disease, and endometriosis. GRACE-2 addresses patients who, despite prior medical evaluation for the cause of pain, have not had a cause identified. Ongoing or repeated medical evaluations may have risks and benefits that should be balanced, such as cost, radiation exposure, and identification of incidental findings prompting further workup with uncertain benefit.

Differentiated abdominal pain with prior workup

The GRACE-2 writing group also considered whether to include within the guideline those patients for whom the cause of recurrent abdominal pain has been identified or is very likely (differentiated pain), such as those with pancreatitis, inflammatory bowel disease, or nephrolithiasis. These populations may suffer the consequences of repeated radiation exposure from imaging and other negative effects of recurrent ED presentations that the clinical practice guideline is intended to address. However, ultimately we felt that existing guidelines from specialty organizations such as the American College of Gastroenterology,[53] the American College of Obstetrics and Gynecology,[70] the American Urological Association,[50] the American College of Radiology,[51] and the American College of Emergency Physicians[55,56] could provide sufficient disease-specific recommendations for management of these patients. Our search strategies, described later in this document, were not intended to capture these populations. However, some literature retrieved by the searches included patients with these conditions, and some publications were included as they provided context for comparison of outcomes in patients with undifferentiated abdominal pain in the ED. Patients with a history of nephrolithiasis, for example, may present with other abdominal conditions such as appendicitis and vascular pathology. Studies describing the yield of repeated CTAP in these populations could be relevant to those with more undifferentiated abdominal pain.

Undifferentiated abdominal pain despite workup

We addressed the guideline to patients with previously undifferentiated abdominal pain despite workup. "Previously undifferentiated" indicates no clear etiology identified (e.g., cholelithiasis, Crohn's disease, pancreatitis). "Workup" refers to commonly available laboratory and imaging tests that are often used in combination in the ED setting to identify the cause of abdominal pain, such as complete blood count (CBC), hepatic function tests, lipase, urinalysis, human chorionic gonadotropin (when appropriate), ultrasound, and CTAP with intravenous (IV) contrast.

"Negative" CTAP

We considered multiple descriptors of a prior CTAP. Negative CTAP was defined as not demonstrating pathological abnormalities, related or unrelated to the current presentation. For example, evidence of prior surgery such as staples, or benign abnormalities such as renal cysts, would be allowed. "Normal" was considered but not selected, as this could be construed as not including asymptomatic, nonpathological, and/or incidental findings such as anatomic variants. Normal also would exclude expected postoperative findings such as surgical clips, as these are not normal human anatomy. "Nondiagnostic" was considered but not adopted, as this might be interpreted to mean that the CTAP image quality was not sufficient for evaluation or that structures of interest were not visualized within the field of view. "No acute findings" was not adopted, as some nonacute findings such as abdominal aortic aneurysm or chronic inflammatory findings might explain ongoing or recurrent abdominal pain.

CTAP contrast requirements

The GRACE-2 writing group discussed whether a patient with undifferentiated abdominal pain should be considered to have been adequately evaluated if previous CTAP had been performed without IV contrast. CTAP performed with IV contrast is more likely to detect some causes of abdominal pain including vascular dissections and occlusions and conditions requiring enhancement for diagnosis, such as small malignancies or abscesses.[71] In clinical practice, some patients may not receive IV contrast for reasons such as contrast allergy, inadequate vascular access, or renal dysfunction. IV contrast is not required for evaluation of all conditions, and emergency physicians routinely consider the context of each individual patient's differential diagnosis. When abdominal pain remains undifferentiated despite previous workup using CTAP without IV contrast, physicians should consider the limitations of noncontrast CTAP in relationship to the differential diagnosis to determine whether CTAP with IV contrast is indicated.

Timing of repeat CTAP evaluations

For application of the guideline, we chose to study yield of repeat CTAP within 1 year of a previous CTAP for recurrent, undifferentiated abdominal pain. Clinician judgment must be applied because pathological conditions may develop at different rates, and therefore the differential diagnosis under consideration may differentially impact the ability of a previous CTAP to exclude pathology. For example, an abdominal aortic aneurysm is generally a slowly evolving condition (e.g., median annual growth rate is 0.22 cm for aneurysms ≤5 cm diameter; for aneurysms <4 cm diameter, maximum 6 month increase is 0.7 cm).[72] Therefore, a negative CTAP as many as 12 months prior to the patient's current presentation may be

adequate to rule out aneurysm, depending on aortic size on the first evaluation. In contrast, appendicitis may evolve over an interval of just hours,[73] meaning that a negative CTAP 1 month prior likely has little relevance if the patient's current presentation suggests acute appendicitis. In one study, appendicitis was diagnosed in 6.8% of patients with a negative CTAP ≤ 1 month prior, 6.1% of those with prior CTAP between 1 and ≤6 months, and 11.5% of those with CTAP repeated between 6 and ≤12 months.[46]

Availability of prior CTAP images and reports

We did not specify the requirements for available information (e.g., images, reports, summaries) to determine whether a prior CTAP was negative. Patients may present to multiple medical centers over the course of repeated evaluations, and the availability of CTAP images, complete CTAP reports, and/or summary information from the medical record or from patients (e.g., "CTAP was negative") may vary depending on the degree of integration of medical record systems. Some studies suggest a low rate of misinterpretation of CTAP (i.e., false-negative studies resulting from human error in interpretation), so review of original images may not have a high yield if reports can be reviewed.[48] To further safeguard against the possibility of missed findings, when original previous CTAP images are available, review of images as well as interpretations in the context of the patient's presentation is prudent, before a decision to repeat CTAP. Although siloed medical record systems may be an impetus for repeat imaging, the availability of an electronic medical record system was not associated with decreased repeat CT utilization in one retrospective study.[74] In the setting of suspected renal colic, visits to different EDs were associated with higher rates of repeat short-term CTAP, although the availability of images and/or reports was not evaluated.[75]

In summary, our working definitions of abdominal pain that is low risk, recurrent, and undifferentiated framed the profile of the patient population to guide our subsequent literature searches for relevant literature. In reality, studies applied variable inclusion criteria, which often did not specify patient risk factors, differentiated or undifferentiated etiology of pain, or the duration or frequency of signs or symptoms.

Selection of questions

The GRACE-2 writing group discussed the target population and considered management challenges, attempting to maintain the perspectives of treating physicians, health systems, and patients. We generated categories for discussion including diagnosis, treatment, and disposition. We considered a wide range of topics including risk stratification; utility of laboratory tests; utility of imaging including first-time and repeated CT/MRI/x-ray/ultrasound; endoscopy; acid suppression medications and motility agents; high-risk medications such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs); referrals to outpatient follow-up including primary care, gastroenterology, and mental health; minimum previous workup advisable before ceasing further search for physical causes of abdominal pain; best practices such as review of previous images or imaging reports before ordering additional testing; conditions that might be missed in an ED workup such as cancer, inflammatory bowel disease, interpersonal violence, or mental health conditions; and high-risk diagnoses for abdominal pain that should not be missed during an ED evaluation such as abdominal aortic aneurysm or acute appendicitis.[76] Prior research finding an association between moderate to severe depression and repeat ED visits for abdominal pain prompted consideration of a more systematic approach to this topic.[77] We considered the possibility of abdominal pain as a manifestation of depression and depression as a consequence of unremitting abdominal pain. The ongoing opioid epidemic in the United States, as well as clinical experience and studies noting frequent opioid prescribing in the ED setting of recurrent abdominal pain, prompted consideration of opioid use disorder screening and alternative methods of pain control.[3,17–26,28–30,78–86]

An important consideration for the GRACE-2 writing group was the feasibility of the guideline for physicians and patients in various practice settings. We debated including recommendations for testing for conditions such as *Helicobacter pylori* but noted that some forms of testing such as exhaled carbon dioxide or immunological testing might not be available within an ED time frame in some settings.[87,88] Similarly, we chose not to investigate the utility of MRI of the abdomen and pelvis in the ED for patients with recurrent and undifferentiated abdominal pain, as many sites might not have availability of this testing on a regular basis. Based on 2005 data, on-site MRI was available in 66% of a random sample of U.S. EDs, but only 13% reported 24 hours/7 days per week (24/7) availability with an on-site technologist and an additional 26% with 24/7 on-call technologist. In contrast, CT is widely available (96% of surveyed U.S. EDs, with 94% reporting 24/7 access for ED patients).[89]

All GRACE-2 writing group members, including the patient representative, had the opportunity to submit candidate questions and outcomes of interest, using the standard PICOT format.[90,91] Candidate questions shared features such as patient-oriented benefits (improved diagnosis, reduced radiation risk, cost) and impact on health system and societal resource utilization. We rank-ordered these using an online survey instrument, blinded to the submissions of other members of the group. The results of the PICOT survey are shown in Appendix S1. Box 1 details the four key priority questions.

Selection of outcomes of interest

We scored outcomes of interest using an online survey with a 0-to 100-point scale (maximum importance 100), blinded to others' scores (Appendix S2, Box 2). The chosen outcomes, while perceived as having greatest importance by the writing group, were often not reflected in outcomes measured by the identified literature. Published research instead tended to focus on readily measured process-oriented outcomes, such as frequency of positive findings on CTAP, the clinical relevance of which was not always clear. Identifying a diagnosis alone

BOX 1 Priority questions of GRACE-2

Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive a repeat CTAP after a negative CTAP within the last 12 months?
Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain with a negative CTAP receive additional imaging with abdominal ultrasound?
Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive screening for depression/anxiety?
Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive non-opioid and/or non-pharmacologic analgesics?

BOX 2 Priority outcomes of GRACE-2

Abdominal surgery or other invasive procedure within 30 days
Mortality within 30 days
Identification of potentially life-threatening diagnosis
Hospital and ICU admission rates within 30 days
Return ED visit within 30 days

might have patient-, physician-, and system-level benefits such as alleviating the frustration of having no explanation for symptoms or providing a direction for outpatient follow-up.[92,93] The absence of many of the highly rated, clinically relevant outcomes in the existing literature identifies an important target for future research.

Evidence synthesis and development of clinical recommendations

Systematic and scoping reviews

The GRACE-2 writing group divided into four subgroups, each focused on a single PICOT question for which a systematic review was executed. Medical librarians at Mayo Clinic (Rochester, MN) and Washington University (Saint Louis, MO) created and performed an individualized search strategy for each of the four PICOT questions, querying multiple databases from inception to December 2020. Databases included Ovid Medline (1946+, including epub, ahead-of-print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid EBM Reviews and Web of Science Core Collection (1975+), Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus (1970+). The full search strategies are available in Appendix S3.

Following the literature search, each subgroup screened the titles and abstracts, selecting articles for inclusion (as either direct or indirect evidence) or exclusion. Articles selected for inclusion during this initial screening were reviewed in full-text and abstracted. Each subcommittee then performed an evidence synthesis and created draft recommendations. We found zero studies directly addressing any of the selected PICOT questions, providing no direct evidence. For this reason, each subgroup synthesized pertinent indirect evidence as described below. The individual subcommittee evidence synthesis documents were then circulated among the group in July 2021 for review and commentary.

Certainty of evidence for outcomes

The GRACE-2 writing group attempted to abstract the priority outcomes selected earlier (Box 2). When these outcomes were unavailable in the literature, each subgroup evaluated the certainty for other relevant outcomes. After the available evidence was synthesized, certainty was assessed at the outcome level by each subgroup using GRADE methodology when appropriate.[59–65,94] GRADE applies eight criteria including risk of bias (methodological flaws), inconsistency (heterogeneity across studies), indirectness (studies conducted in populations other than the intended ED population), imprecision (wide confidence intervals [CIs] resulting from underpowered studies/studies with small sample sizes), publication bias, effect size magnitude, dose–response effects, and opposing bias/confounders.[59] A level of certainty was assigned to each effect estimate evaluated (Figure 2). The lowest level of certainty across critical outcomes determined the overall certainty of evidence supporting the guideline recommendation.

EtD framework

Using the GRADE EtD framework[59] for each PICOT question, a methodologist presented the evidence synthesis followed by a structured group discussion of each of the framework criteria: certainty of

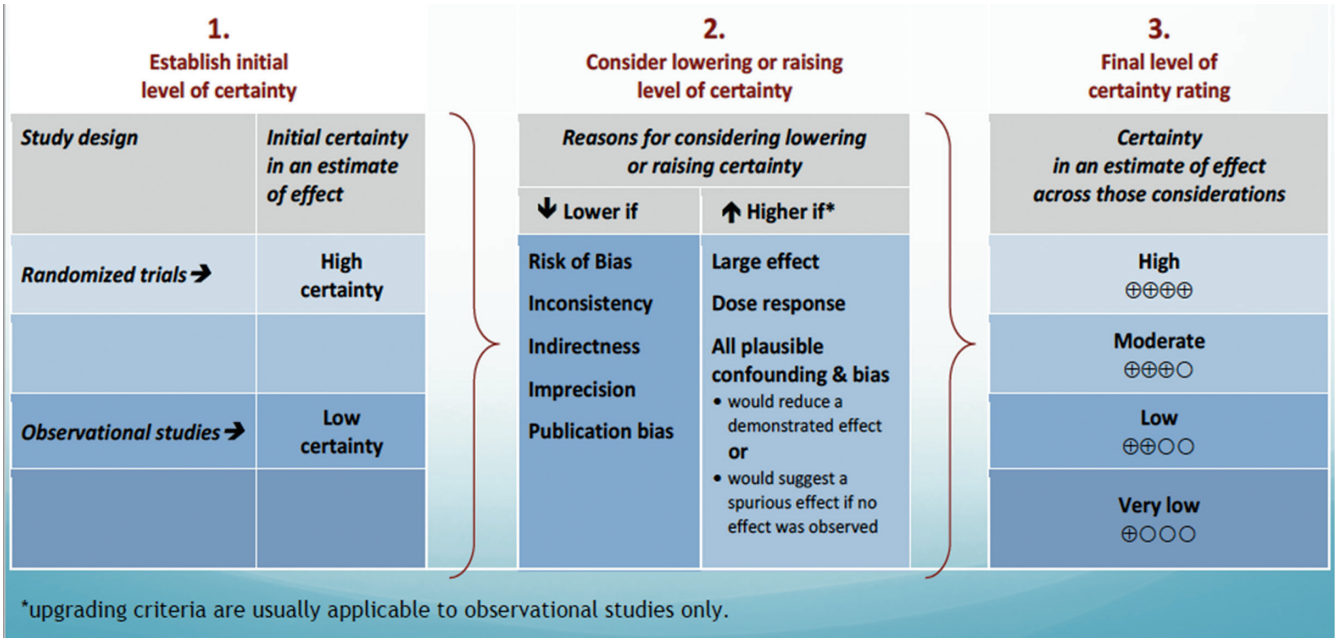

FIGURE 2 Rating the certainty in the evidence using the GRADE methodology. *Reproduced with permission by the U.S. GRADE Network

BOX 3 Recommendations of GRACE-2

Recommendation 1: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and prior negative CTAP within 12-months, there is insufficient evidence to accurately identify populations in whom repeat imaging can be safely avoided or routinely recommended in the ED. (No recommendation) [No evidence]

Recommendation 2: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and a negative CTAP with IV contrast in the ED, we suggest against ultrasound unless there is concern for pelvic or biliary pathology. (Conditional recommendation, against) [Very low certainty of evidence]

Recommendation 3: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain, we suggest screening for depression and/or anxiety may be performed during the ED evaluation. (Conditional recommendation, either) [Very low certainty of evidence]

Recommendation 4: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain, we suggest an opioid-minimizing strategy for pain control. (Conditional recommendation, for) [Consensus, no evidence]

evidence, balance of benefits and harms (desirable and undesirable effects of the intervention, balance of effects), values, resources, acceptability, feasibility, and equity. We then developed recommendations for each PICOT question (Box 3, Table 2). Recommendations for which no evidence was found received a label of "No evidence."

Use of indirect evidence

The GRADE methodology[59] allows the use of indirect evidence, which was necessary because our literature search did not identify direct evidence for any PICOT question. We decided a priori that "direct evidence" must match each element of the PICOT question. If any element of the published research differed from the PICOT question, that manuscript was considered "indirect evidence." In the GRADE evaluation, concerns for indirectness downgraded the certainty in the evidence, limiting the strength of conclusions and recommendations that were drawn.

QUESTION 1

Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive a repeat CTAP after a negative CTAP within the past 12 months?

Recommendation 1: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and prior negative CTAP within 12 months, there is insufficient evidence to accurately identify populations in whom repeat imaging can be safely avoided or routinely recommended in the ED. (No recommendation) [No evidence]

TABLE 2 Interpretation of strong and conditional (weak) recommendations for patients, clinicians, and health care policymakers

Implications of strong and weak recommendations for different users of guidelines		
	Strong recommendation	**Conditional weak recommendation**
For patients	Most individuals in this situation would want the *recommended* course of action and only a small proportion would not.	The majority of individuals in this situation would want the *suggested* course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Note: Reproduced with permission from the GRADE Handbook.

Summary of the evidence

Details of the literature search, selection of studies, and outcomes are described elsewhere.[95] An electronic search strategy was developed in collaboration with a professional medical librarian using keywords for repeat CTAP imaging in the ED. The search was performed in December 2020 using Ovid Medline, Embase, and clinicaltrials.gov. A total of 637 potentially relevant publications were identified. In a first-phase review, each of four committee members reviewed approximately one-fourth of the selected publications. Titles and abstracts were reviewed and noted for inclusion or exclusion. If a reviewer chose to exclude an article, a single reason for exclusion was recorded from a standardized list (e.g., not adult, not ED patients, not abdominal pain related, not recurrent, not repeat CT, initial CT not normal, review article, case report, trauma related, not a clinical study, immunocompromised, or other excluded subjects). More than one exclusion might apply. In the second phase of review, articles that had not been excluded in Phase 1 were further designated for inclusion (as direct or indirect evidence) or exclusion. To be chosen for inclusion as direct evidence, a publication was required to meet the following criteria:

1. Adult ED patients
2. Low risk (Table 1)
3. Recurrent similar undifferentiated atraumatic abdominal pain
4. Negative-index CTAP
5. Interval to repeat CTAP 30 days to 12 months after index CTAP

Zero studies met all criteria for direct evidence. Thirteen studies met some criteria and were included as indirect evidence.[12,46–48,74,75,96–102]

We attempted to abstract the *a priori* defined outcomes of interest (Box 2), but most studies did not provide these. The reviewers identified four alternative outcomes:[95]

1. Frequency and timing of repeat CTAP
2. Ionizing radiation exposure of repeat CTAP
3. Diagnostic yield of repeat CTAP
4. Predictors of repeat CTAP

The frequency and timing of repeat CTAP showed substantial heterogeneity. By design, some studies examined repeat CTAP at very short intervals (e.g., 0–72 h [including some during the index ED visit],[100] within 7 days,[96] or within 1 month of the index CTAP[47]). Time-limited studies of this type often did not capture the potential high frequency of repeat CTAP identified by studies with longer durations (e.g., up to 1 year,[46,48] up to 6 years[12]), which found a range of repeat CTAPs, including three or more CTAPs within 1 year in 6.3% of patients undergoing repeat CTAP in one study,[46] and with an average of 2.7 CTAPs per patient (range 2–10) in another.[12]

Ionizing radiation exposure of repeat CTAP was explicitly reported in one study,[12] although estimates could be derived from the frequency of CTAP in other studies. Among patients aged 18 to 45 years with abdominal pain at a single Italian hospital, 20% underwent more than one CTAP over a 6-year period. The mean cumulative effective radiation dose was 70.1 mSv (range 14–437 mSv). A total of 41% of patients with repeat CTAP had a cumulative dose > 50 mSv.[12] In another study, the median radiation exposure from a CTAP with IV contrast was 16 mSv.[10]

Diagnostic yield of repeat CTAP was heterogeneous, likely reflecting the different time courses, inclusion criteria, and patient populations in the identified studies.[95] Some studies included patients with *abnormal* index CTs (as opposed to *negative* CTs targeted by our PICOT), with very short term (e.g., <7 days) repeat CTAPs (which might reflect an evolving acute illness, rather than a chronic recurrent condition), and with uncertain risk profiles (not described in any study). Repeat CTAP positivity rates varied

widely from 5% to 67%. Some studies reported the stepwise yield of repeat CTAPs in the ever-diminishing population of patients remaining with prior negative CTAP results. The positive CTAP rate plateaued around 5% in one study, with some surgical disease continuing to be identified on repeat CTAPs in patients with previously negative CTAPs.[48] Studies did not apply a uniform definition of clinically relevant CTAP results, sorting CTAP-based diagnoses into emergent (e.g., appendicitis, mesenteric ischemia), urgent, or nonurgent (e.g., ovarian cyst) categories. These categories have not been validated and authors did not report follow-up of patients for operative interventions, ICU admission, mortality, or other clinically important outcomes. Some CTAP-based diagnoses defy easy categorization, as they may be medically treated or surgically treated or require no treatment at all (e.g., diverticulitis).[103] Some reported diagnoses that likely reflect information not derived from CTAP (e.g., fever, musculoskeletal pain, dysuria, hematuria, viral syndrome, varicella zoster). Finally, some CTAPs initially interpreted by radiologists as negative may actually have demonstrated abnormal findings recognized on repeat CTAP. Studies identified in our search varied in their methods to determine this. Some used only the initial CT report and therefore did not address the possibility of initial misinterpretation.[47] Others indicated that initial CTAP images were reviewed again to independently verify the original interpretation.[48,96] One study reported that 0 of 18 initially negative CTAPs had been misinterpreted, based on independent rereview.[48] Nonetheless, human error in CTAP interpretation is a potential problem in clinical practice and could justify rereview not only of prior CTAP reports but also of original CTAP images before repeating CTAP.

Predictors of repeat CTAP were reported in some studies. Some investigators[97] found that a prior CTAP (time interval not specified) was associated with a lower probability of undergoing CTAP on a repeat visit (odds ratio [OR] 0.44, 95% CI 0.30 to 0.65). The similarity of previous and current clinical presentations and the risk profile of the patients were not described. Other authors did not find an association between the availability of a prior CTAP within 6 months and the probability of a patient undergoing repeat CTAP.[101] One study reported leukocytosis >10,900 cells/mm^3 and APACHE II score 5–9 as independent predictors of positive repeat CTAP in multivariable analysis.[48] However, both high APACHE II score and leukocytosis might be seen as clinical indicators of high risk and therefore not reflective of the intended low-risk population of GRACE-2. APACHE II score includes components for history of severe organ failure or immunocompromise, age, temperature, mean arterial pressure, heart rate, respiratory rate, sodium, potassium, acute renal failure, hematocrit, white blood cell count, Glasgow Coma Scale score, and FiO_2.[104]

Benefits

We were unable to determine whether benefit occurs from repeating CTAP in low-risk adult patients with recurrent and undifferentiated abdominal pain. Repeat CTAPs sometimes identify clinically relevant disease, but it is unclear how often these findings occur in low-risk patients with recurrent pain, rather than in higher risk patients or those with new (not recurrent) abdominal pain syndromes. Potential benefits of repeat CTAP might include improved diagnosis or diagnostic certainty, more appropriately tailored therapy (e.g., percutaneous drainage of an abscess, rather than laparotomy), reduced mortality, and fewer return ED visits. Patients with abdominal pain, but not specifically recurrent pain, have been found to be more confident when CTAP is part of their medical evaluation, but patients have also been shown to have a poor understanding of radiation and risk and to underestimate their prior imaging exposure.[105]

Harms and burden

Potential harms and burdens of repeat CTAP are multiple, but the magnitude of these risks is likely manageable. The majority of U.S. EDs have CT available, in most cases 24 h/day, so a strategy involving repeat CTAP is feasible.[89] Individual patient harms include cumulative radiation doses and increased medical expenses as well as downstream burdens of overdiagnosis and overtreatment associated with incidental findings.[106]

Radiation risks of CTAP are small on a per-patient basis, with each single CTAP incrementally contributing an attributable estimated lifetime cancer risk of between one in 470 (20-year-old female) to one in 1320 (60-year-old female),[10] with a relative risk in exposed populations of around 1. Compared with even the lowest rate of repeat CTAP abnormalities (around 5%, though not all are of equal clinical significance),[48] these additional cancer risks are small. The panel recognizes that some outlier patients may undergo enough repeat CTs for the risk to the individual patient to become meaningfully increased,[33] although no threshold for safe or unsafe exposure exists.

Studies commonly report cumulative CTAP/radiation exposures within a fixed time (e.g., within 1 year[12]) and emphasize specific cumulative doses (e.g., 50 mSv[12]). However, using a specific time interval or dose may create a false sense of safety or risk that does not fit with the current leading model of biologic effects of ionizing radiation.[34,35] Within the range of exposures seen with diagnostic imaging, exposure and cancer risk are believed to follow a linear relationship, with no threshold.

Net costs to patients, payers, the health care system, and society at large of repeat CTAPs are unclear. Models would need to incorporate a wide range of variables including direct costs, costs related to LOS, or alternatives to CTAP (e.g., hospital admission or observation), costs of missed diagnoses (e.g., costs of prolonged hospitalizations, increased invasive procedures, and medical malpractice costs), life-years lost as a consequence of delayed diagnosis, and CTAP-related radiation exposures. Cost and price are not the same; the price range for CTAP is reported as $1750–$9500.[107]

Time requirements for repeated CTAP pose potential harms and burdens for already overcrowded EDs in the United States. Our review did not explicitly and systematically examine time metrics, but

studies find heterogenous results. In one study of ED patients undergoing CTAP, CT-related workflow accounted for a median of 2.67 h, or 29% of LOS.[108] Other authors found that performance of CT (not confined to abdominal pain, rather any CT in all ED patients) was associated with an additional 59 min in LOS.[109] Studies show that patients who undergo CTAP and are ultimately discharged from the ED have longer ED LOS than patients who do not undergo CTAP, but these are not randomized trials and are not controlled for severity of illness or other potential confounders. Patients undergoing CT may have had more severe pain and/or might have required greater LOS regardless of CT use for ongoing assessment and treatment.[110] ED CTAP is associated with shorter hospital LOS for patients admitted to a general ward with abdominal complaints;[110] the net time and bed resource effects in a health system are less clear. Some studies show that CTAP facilitates discharge or reduces admissions, which may be of particular value in contrast to pathways that require observation or hospital admission.[102,111,112] We did not identify randomized ED studies comparing these alternatives to determine ED time metrics for each. Admitted patients randomized to "early" CTAP within 24 h (vs. usual care) had reduced hospital LOS by about 1 day, but this difference was not statistically significant.[113]

IV contrast reactions and IV contrast nephropathy are additional potential harms of repeat CTAP. Recent research suggests that "contrast nephropathy" may be a misnomer, as prior studies did not include appropriate controls for confounders.[114–117] The term "contrast-associated acute kidney injury (AKI)" may better express the concept that patients undergoing CT with IV contrast may have an increased risk of nephropathy, not necessarily caused by IV contrast exposure but related to factors such as their comorbidities, severity of current illness, and exposure to concomitant nephrotoxic drugs. The American College of Radiology (ACR) summarizes these concepts in its 2021 ACR Manual on Contrast Media, calling the diagnosis "real, albeit rare."[118] The ACR also notes the paucity of evidence for independent risks of AKI in patients with eGFR ≥ 30 mL/min/1.73 m^2. Anaphylactoid (sometimes called "allergic-like") reactions are another historically important risk of iodinated IV contrast administration for CT. However, nonionic low-osmolality IV contrast media in routine use for CTAP have a very low rate of adverse reactions, 0.2%–0.7%.[118]

Decision criteria and additional considerations

The detailed EtD framework for Question 1 is available in Appendix S4. We found no direct evidence to answer the proposed PICOT, and the indirect evidence was heavily influenced by all of the factors above.

We were interested in understanding the utility of repeat CTAP following an initially negative CTAP in patients with low-risk features and similar recurrent episodes of abdominal pain. However, none of the included studies provided patient details that would allow determination of whether patients met our definition of low risk. No study provided detail of the qualitative similarity of previous and current clinical presentations, so we were unable to determine whether any of the studies applied to recurrent similar episodes or if repeated presentations represented unique new clinical syndromes with different underlying etiologies. For example, a patient might have presented previously with gastroenteritis and now presents with appendicitis. The reported outcomes did not match our prospectively chosen priorities. Instead, most studies provided either CTAP-based diagnoses or clinical diagnoses following CTAP, without clear definitions of clinical importance to patient outcomes. In addition, we had hoped to identify comparisons between pathways involving either repeat CTAP or no repeat CTAP. We did not find any ED studies randomizing patients to one pathway or another, and most studies simply reported results in patients who had undergone a repeat CTAP. Such studies are likely flawed by selection bias, as clinicians may have chosen to repeat CTAP in some patients for a variety of reasons including perceived higher risk.

We had also sought to identify studies of patients undergoing CTAP 30 days or greater after an index negative CTAP, to avoid inclusion of patients who were experiencing acute and evolving illness (e.g., appendicitis or bowel obstruction). Many of the identified studies included patients with a broad range of time intervals between index and repeat CTAP, ranging from hours to greater than 1 year, and likely included at least some patients who did not meet our intended population of those with recurrent low-risk pain. We hoped to identify evidence for patients with undifferentiated abdominal pain and negative initial CTAP. Instead, many studies included at least some patients whose initial CTAP was abnormal or who had differentiated abdominal pain with a specific diagnosis such as nephrolithiasis. We felt that inclusion of differentiated patients was less helpful, as condition-specific clinical guidelines exist. In addition, patients with defined disease processes with risks of complications, such as fistula formation in Crohn's disease or ureteral obstruction in patients with renal colic, may not meet our low-risk definition.

Equity in health care delivery

GRADE calls for assessment of equity in health care delivery. The included studies provided indirect evidence. One study found the median age of patients undergoing repeat CTAP was 42 years (range 19–95 years). Seventy-four percent of patients undergoing repeat CTAP were female, and female gender was associated with higher CTAP positivity rate and number of repeated CTAPs.[48] Gender as a factor in diagnostic imaging choices has been identified as a research priority in emergency medicine, with equity complicated by the competing goal of reducing radiation exposure in women of childbearing age and pregnant females.[119] Race and ethnicity were not reported in any of our 13 included studies, making assessment of disparities in these domains impossible. Outside of the studies identified by our systematic search, other studies have documented disparities in ED CT imaging based on insurance status,[120] race, and ethnicity.[120–122] Patients with Medicaid are 20% less likely than privately insured patients to undergo CTAP for acute abdominal pain (not specifically recurrent pain or repeat CTAP).[120] Black and Hispanic patients are 42% to 52% less likely than White patients to undergo CTAP for acute abdominal pain.[120,122]

Conclusions and research needs

Understanding potential benefits and harms of repeated CTAP in adult patients with low-risk, recurrent, undifferentiated abdominal pain requires the standardization of definitions for each component (e.g., low-risk, recurrent, undifferentiated), as well as clinically meaningful standardized outcome measures of interest.[95] In clinical practice, radiologists may focus attention on causes of acute abdominal pain when interpreting CTAP for ED patients, potentially overlooking or failing to comment explicitly on chronic or recurrent causes. Reviewing prior CTAP with a radiologist in the context of recurrent abdominal pain could have utility, although the included literature did not address this. Factors affecting equity in imaging decisions for recurrent undifferentiated abdominal pain require explicit study. Future studies need appropriate methodology including randomization to comparison groups, with and without repeat CT. Funding for future research is essential, and an NIH Institute for Emergency Care could be a crucial organizing mechanism.[123,124]

QUESTION 2

Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain with a negative CTAP receive additional imaging with abdominal ultrasound?

Recommendation 2: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain and a negative CTAP with IV contrast in the ED, we suggest against ultrasound unless there is concern for pelvic or biliary pathology. (Conditional recommendation, against) [Very low certainty of evidence]

Summary of the evidence

The search strategy is detailed in Appendix S3.2. A total of 5291 titles were reviewed and 92 articles selected for full-text review. Narrative summary and details of included studies are available in Appendix S5. In our search, we did not restrict the timing of the prior negative CT in relationship with the ultrasound imaging; however, all included studies had ultrasound performed in the same ED visit or within 72 h of a negative CTAP. We found no studies with direct evidence answering our question and no studies assessing point-of-care ultrasound by emergency physicians after a negative CTAP. No studies addressed mortality, hospitalization, life-threatening disease, or ED return visits. Four studies provided indirect evidence on the need for surgery or invasive procedure.[125–128] Three studies (699 patients) included patients who underwent ultrasound after a negative CTAP. The included patients had acute abdominal pain, but there was no information regarding recurrence or risk profiles.

Following negative CTAP, we estimate that 345 ultrasound examinations would be necessary for the diagnosis of one surgical case (approximately 0.3%) and 10 for the diagnosis of nonsurgical pathology (number needed to test = 8 for pelvic pathology and number needed to test = 16 for biliary/liver findings). A total of 90% of ultrasound examinations will not add diagnostic value after a negative CTAP.

***Need for surgery or invasive procedure*:** Following CTAP, ultrasound identified additional findings in a small percentage of cases (0%,[125] 0.4%,[126] 0%,[128] and 24.8%[127] [including simple and hemorrhagic ovarian cysts, gallstones, gallbladder polyps, fibroids, pleural effusion, ascites, among others]). However, when CTAP was negative, ultrasound findings required emergent intervention in <0.3% (0/126,[125] 1/238,[126] 1/335[127]). The GRADE evidence table for the proportion of patients who required surgery is displayed in Table 3. The heterogeneity of the data and lack of reporting on patient-centered outcomes precluded us from performing a meta-analysis. GRADE domains were evaluated without a single pooled estimate, meaning we rated the certainty in the evidence using narrative summaries of the effects across different studies.[129]

***Gallbladder and gynecological pathology*:** CTAP was described as very sensitive for gallbladder and uterine/tuboovarian pathology in four studies with indirect evidence.[125–128] Ultrasound showed an abnormality that was missed on CTAP in 1.3% (3/238), and only 0.4% (1/238) involved a change in management (a nonradiopaque common bile duct stone without ductal dilatation, managed by endoscopic retrograde cholangiopancreatography).[126] CTAP was noninferior to ultrasound for the diagnosis (both ruling in and ruling out) of cholecystitis.[126] In 0.3% (1/335), ultrasound showed cholecystitis requiring surgical intervention, missed by CTAP.[127] This is similar to other studies that did not meet our criteria for inclusion in this question, but also support the high sensitivity of CT for acute cholecystitis.[130,131] Nonsurgical findings on ultrasound not initially reported on CTAP included ovarian cysts (simple and hemorrhagic) in 8.7% (29/335), gallstones in 2.7% (9/335), gallbladder polyps in 1.2% (4/335), and endometrial abnormalities.[127] Other investigators also found endometrial abnormalities on pelvic ultrasound that were not diagnosed on CTAP in 3.2% (4/126), but none underwent surgical intervention.[125] Nonvisualization of the ovary on either pelvic ultrasound or CTAP was highly predictive of the lack of ovarian abnormality on short-term follow-up and suggested that additional imaging to exclude ovarian disease was not required.[128]

In a subset of patients who had CT after ultrasound (instead of ultrasound after CT), CTAP had higher diagnostic yield compared to right upper quadrant ultrasound, including higher likelihood of finding acute nongallbladder abnormality that was not seen with ultrasound in 32% (103/322). A total 25.2% had a change in clinical diagnosis, including enteritis, colitis, pancreatitis, ruptured ovarian cysts, ureteral calculus, pneumonia, pyelonephritis, and appendicitis.[126]

When adding findings for nonsurgical diagnosis that could explain abdominal pain, 10% of ultrasound examinations (88/880) added a new diagnosis after CT, with pelvis being the region adding information in 73% (64/88) of the ultrasound examinations with new findings. A total of 12.6% (64/506) of pelvic ultrasound added a diagnosis not seen with CT[125,127,128] compared with 6.4% (24/374) of right upper quadrant ultrasound.[126,127]

TABLE 3 GRADE evidence profile for Question 2 (ultrasound after negative CTAP)

Certainty assessment							No. of patients	
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abdomen/pelvis ultrasound	Certainty
Hospitalization, ICU admission–not reported								
—	—	—	—	—	—	—	—	—
Return ED visits–not reported								
—	—	—	—	—	—	—	—	—
Invasive procedure								
3[a]	Observational studies	Serious[b]	Not serious[c]	Serious[d]	Serious	None	2/699 (0.3%)	⨁◯◯◯ VERY LOW
Mortality–not reported								
—	—	—	—	—	—	—	—	—
ED LOS								
2[e]	Observational studies	Serious[f]	Not serious	Serious[g]	Not serious	None	MD: 120 min longer in one study and 365 min longer in the other.	⨁◯◯◯ VERY LOW

Abbreviations: CTAP, computed tomography of the abdomen and pelvis; LOS, length of stay; MD, mean difference.

[a]Harfouch et al.,[127] Hiatt et al.,[126] Gao et al.[125]

[b]Harfouch et al.[127] had low risk of bias in the selection of the cases and high risk of selection bias in the controls. Comparability of cases and controls in other variables was not reported. Adequate follow-up for cases. Hiatt et al.[126] had low risk of bias in the selection of participants; comparability variables were not reported. Method of follow-up not recorded.

[c]The direction and magnitude of effect were similar in both studies. Overall, the results showed low value added with ultrasound. Harfouch et al.[127] had 3/335 patients positive for cholecystitis, but 1/335 underwent cholecystectomy and the other two were dismissed home. In Hiatt et al.[126] 1/238 had an ultrasound finding not seen on CT that led to a change in management (nonradiopaque common bile stone without ductal dilatation managed by endoscopic retrograde cholangiopancreatography).

[d]Our question aimed to answer recurrent abdominal pain in the ED. The included studies provided indirect evidence for ultrasound after negative CTAP.

[e]In Harfouch et al.[127] mean (±SD) ED LOS was 387 (±135) min for patients who received CT alone and 507 (±147) min for those who received both CT and ultrasound (MD 120 min with CT + ultrasound, 95% CI 83 to 155 min longer). In Gao et al.[125] ED LOS was 968 min (16 h 8 min) for CT alone and 1333 min (22 h 13 min) for those who received both CT and ultrasound (MD 365 min).

[f]High risk of bias in the selection of controls.

[g]Indirect evidence of patients with ultrasound after negative CTAP, but not recurrent pain.

***ED LOS*:** Two studies compared ED LOS between patients with abdominal pain who received an ultrasound after a negative CTAP and those who received CTAP only. One study reported a mean (±SD) ED LOS of 387 (±135) min for patients who received CT alone and 507 (±147) min for those who received both CTAP and ultrasound (mean difference [MD] 120 min longer with CTAP + ultrasound approach).[127] Another study reported an ED LOS of 968 min (16 h 8 min) for CTAP alone and 1333 min (22 h 13 min) for those who received both CTAP and ultrasound (MD 365 min longer with CTAP + ultrasound approach).[125] Notably, the ED LOS for patients undergoing CTAP alone and for those with CTAP + ultrasound was more than twice as long in the latter study compared with the former,[125,127] suggesting other factors in addition to imaging choices are strong contributors to ED LOS. These studies were not randomized, and differences in LOS associated with a particular imaging pathway may reflect other confounders. These might include overcrowding in the ED and selection bias related to physician level of concern/pretest probability of disease, which may have influenced decisions to perform additional imaging. Physician risk-taking behavior has been shown to be associated with the use of imaging in ED patients with abdominal pain.[132] In addition, differences in LOS associated with imaging may include time spent treating and assessing the patient (e.g., repeated examinations). When applied to our target population, our certainty in this evidence was deemed very low given high risk of bias and indirectness.

Two studies that did not meet the inclusion criteria were also discussed by our group. One study[133] of patients with acute pain and abnormal CTAP (instead of negative CTAP) found 97.8% concordance between the initial CTAP and subsequent ultrasound findings. A second study[134] found that ultrasound was higher yield when the radiologist recommended it after CT.

Benefits

The primary benefit of ultrasound after CTAP is finding other causes of pelvic or abdominal pain that can be missed on CTAP. Improving diagnostic certainty at the time of evaluation in the ED may be an important patient-centered factor. An uncertain diagnosis like

"undifferentiated abdominal pain" may lead to increased ED utilization and may impact patient satisfaction, although more research is needed to confirm these hypotheses.

Ultrasound could be helpful for patients with possible biliary or pelvic pathology, allowing for a timelier referral without requiring yet another ED visit or subspecialty evaluation for additional testing. However, additional findings identified on ultrasound occur in a small percentage of ultrasound examinations and very rarely require emergent intervention. Most ultrasound examinations after negative CTAP could be deferred to outpatient follow-up, if performed at all.

Harms and burden

Harms of ultrasound after CTAP include longer ED LOS, increased cost to patients and the health care system (e.g., charges of $260–$1950 for abdominal ultrasound, $220–$3200 for pelvic ultrasound),[135] possible premature closure by misattribution of incidental findings (e.g., gallbladder polyp) as causal, and the potential for morbidity from additional downstream testing/procedures secondary to overdiagnosis and overtesting.[106]

The burden of transvaginal ultrasound on females with abdominal pain includes the discomfort of the procedure itself, the challenge of doing the examination in non–sexually active females or those with prior sexual trauma/abuse, and the need for additional resources such as a chaperone and private examination room. Sonography is also a finite resource with limited availability of ultrasound equipment, sonographers, and imaging rooms; low-yield use in patients with negative CTAP could delay care for examinations in other patients.

Decision criteria and additional considerations

The detailed EtD framework for Question 2 is available in Appendix S6. When discussing the balance of risk and benefits, we were divided. The group discussed physician risk tolerance and fear of litigation, the potential diagnostic benefit in the minority of cases, and the lack of need for surgical intervention in the additional findings provided by the ultrasound. The patient representative favored ultrasound after negative CTAP, even with its low diagnostic yield, if this might help find a cause for abdominal pain, and accepting longer ED LOS. Additional findings might not be the cause of the patient's pain. Finally, the benefits and harms do not accrue to the same people or to the same degree. A patient undergoing ultrasound after negative CTAP does experience additional LOS, but also a minority will have a potential diagnostic benefit. At the same time, the health care system as a whole would experience increased operational stressors, and patients in the waiting room would experience longer LOS (most without subsequent benefit for that additional delay). Delays in care for other patients to perform low-yield ultrasound for patients with negative CTAP could result in increased morbidity and even mortality for those with time-sensitive conditions; ED crowding has been associated with increased mortality, hospital LOS, and costs.[136,137]

Additional considerations included:

- In ill-appearing patients, or those with negative CTAP and ultrasound but continued concern for acute morbid pathology (e.g., ovarian torsion), clinician judgment must be used and consulting surgical specialties should be considered. For ovarian torsion, neither CTAP nor ultrasound is 100% sensitive, and variation in sensitivity between readers may occur—important in clinical practice. One study found CTAP sensitivity for ovarian torsion to be 90% for one of two readers and ultrasound sensitivity to be 80% for both readers.[138]
- *Contrast use in CTAP*: No difference in adnexa visualization were found based on use of IV contrast.[126,128] One study described higher sensitivity of CTAP compared to ultrasound in the older adult population with comorbidities.[139] Certain diseases like acalculous cholecystitis and particular findings like emphysematous cholecystitis are more common in older adults and better visualized on CTAP than ultrasound.[140,141]
- Ultrasound is operator dependent,[128] and all the included studies had ultrasound performed by a radiologist or radiology technician. One study reported that ultrasound after a negative CTAP was most likely to be helpful when specifically recommended by radiologists, with improved diagnostic yield in that setting.[133] The authors suggested involving radiologists to improve advanced imaging utilization management.

Conclusions and research needs

We found no direct evidence that ultrasound after negative CTAP for recurrent low-risk abdominal pain is better compared to not performing ultrasound. Based on indirect evidence, CTAP with IV contrast is sensitive for abdominal and pelvic surgical pathology, and ultrasound after a negative CTAP rarely (<0.3%) identifies pathology that requires immediate intervention. Ultrasound after negative CTAP may be beneficial in cases of suspected female pelvic pathology and/or gallbladder disease but could improve diagnostic certainty in <10% of cases.

We were surprised by the paucity of studies of ultrasound after negative CTAP, and future studies should clarify the role of ultrasound in improving both patient-centered outcomes (e.g., diagnostic certainty and cost of care) and health care–centered outcomes (e.g., LOS and ED throughput). Involving the patient through shared decision making was recommended by our panel, including the patient representative.

QUESTION 3

Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive screening for depression/anxiety?

Recommendation 3: In adult ED patients with low-risk, recurrent, undifferentiated abdominal pain, we suggest that screening for depression and/or anxiety may be performed during the ED

evaluation. (Conditional recommendation, either) [Very low certainty of evidence]

Summary of the evidence

Our scoping review provides details of the search strategy and inclusion processes.[142] We found no direct evidence on the effect of depression or anxiety screening strategies compared to usual care without screening in adult patients with recurrent and undifferentiated abdominal pain in the ED. Nevertheless, we synthesized four groups of relevant indirect evidence including a total of 35 studies. None of these studies evaluated our target population of interest (recurrent and previously undifferentiated abdominal pain in the ED). Synthesizing indirect evidence when direct evidence is lacking helps decision makers during guideline development.[64] Indirect evidence in the context of this question included studies evaluating the prevalence of depression and/or anxiety in ED populations (whether or not abdominal pain patients were included), diagnostic accuracy of screening tools, effectiveness of screening in other settings on outcomes of interest (e.g., recognition and referral rates), and natural course of patients with abdominal pain who were screened for these conditions while in the ED.

In ED populations, depression was reported in 8%–55% of patients (median 25%) across 19 studies, while anxiety ranged from 9% to 74% (median 27%) across 14 studies.[142] The wide-ranging prevalence estimates are partly explained by varying definitions, different diagnostic instruments, and heterogeneous ED populations. Two studies included in our evidence synthesis specifically evaluated patients with nonspecific abdominal pain, defined as those in which an organic cause for the pain was not identified during the ED visit. These studies evaluated the closest subset of patients to our population of interest in this guideline. One study reported that 25.3% of 83 patients screened positive for depression,[77] while another reported that 29.6% of 55 patients were positive for depression-related questions.[143] The latter also reported that 25.9% were positive for anxiety. Despite these two studies evaluating a population with undifferentiated abdominal pain, no studies specifically examined the subset of patients with recurrent abdominal pain in the ED. To address this evidence gap, we found two systematic reviews that evaluated the prevalence of depression and/or anxiety in patients with either IBS or functional dyspepsia. Recurrent abdominal pain is part of the Rome definition of IBS and is a common feature of functional dyspepsia.[144] The first review reported depression prevalence of 23.3% (19 studies, 409,967 patients) and anxiety prevalence of 23% (20 studies, 375,534 patients with IBS). The second review found higher prevalence: depression 36% (nine studies, 3637 patients) and anxiety 44% (eight studies, 3505 patients with IBS).[145] While direct comparisons are not possible, ED patient populations are at relatively high risk of depression. Twelve-month prevalence of major depression in the general population is approximately 5% worldwide[146,147] and 10% in the United States.[148]

Using the data above to estimate the pretest probability of depression and/or anxiety in our population of interest, we evaluated the diagnostic accuracy of pragmatic and short instruments for screening of depression and anxiety to assess potential misclassifications. For depression screening, we found one high-quality systematic review and individual patient meta-analysis evaluating the diagnostic accuracy of the Patient Health Questionnaire-2 (PHQ-2) and PHQ-9 using the reference standard of semistructured interviews (44 studies, 10,627 patients, various settings including both outpatient and inpatient).[142,149] The meta-analysis did not indicate whether ED studies were included. These tools can be self-administered by patients and involve questions associated with symptoms within the prior 2 weeks (Appendix S7). The pooled sensitivity and specificity of PHQ-2 and PHQ-9 for inpatients and outpatients (not necessarily individuals with abdominal pain or ED patients) alone or in combination are presented in Table 4. The strategy with the highest sensitivity was accomplished with the use of PHQ-2 with a cutoff of ≥2 (pooled sensitivity 92%, 95% CI 88% to 95%). Using an estimated pretest probability of depression at approximately 25%, this screening strategy would yield 25 false positives for every 100 screened patients due to relatively low specificity. Figure 3 illustrates other scenarios using different screening approaches with the same 25% pretest probability. The GRADE assessment for the use of PHQ-2 of ≥2 in our population of interest is detailed in Table 5. All other GRADE summary of findings tables, considering other possibilities of pretest probability and evaluation of certainty in the evidence, are available in the supplementary material of our evidence synthesis.[142] Our certainty in the evidence when applying these estimates to our population of interest was very low due to risk of bias, indirectness, and inconsistency.

For anxiety screening, we found one systematic review[150] evaluating the Generalized Anxiety Disorder Scale-7 (GAD-7; Appendix S8). Its sensitivity and specificity for the screening of generalized

TABLE 4 Diagnostic accuracy of depression screening strategies using the PHQ instrument[149]

Screening strategy	Sensitivity (95% CI)	Specificity (95% CI)
PHQ-9 ≥ 10 alone	86% (80%–90%)	85% (82%–87%)
PHQ-2 ≥ 2 alone	92% (88%–95%)	67% (63%–70%)
PHQ-2 ≥ 3 alone	72% (67%–77%)	85% (83%–87%)
PHQ-2 ≥ 2 followed by PHQ-9 ≥ 10	82% (76%–86%)	87% (84%–89%)
PHQ-2 ≥ 3 followed by PHQ-9 ≥ 10	70% (64%–75%)	91% (89%–93%)

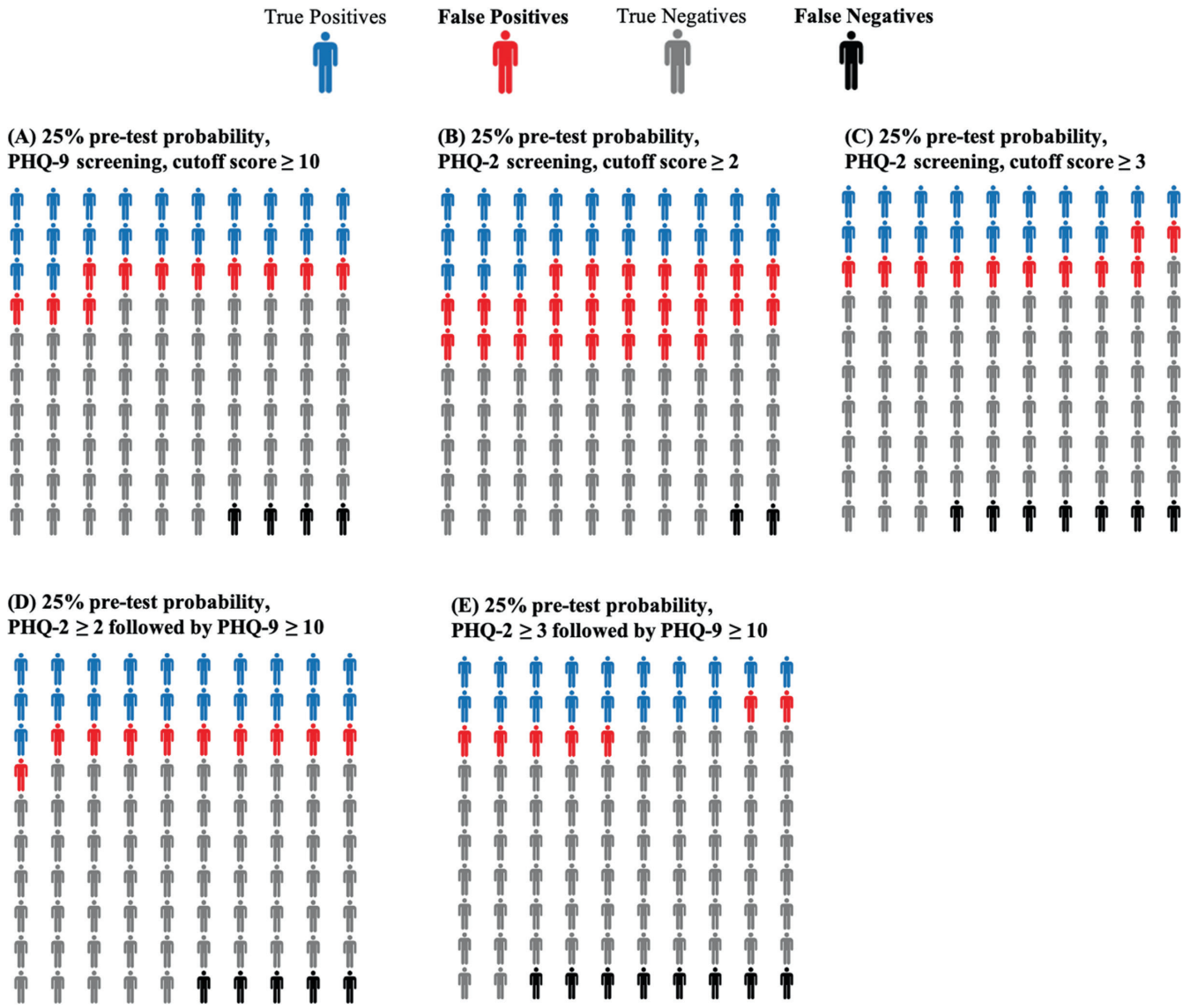

FIGURE 3 Pictogram on the number of false positives (red) and false negatives (black) using different approaches for depression screening with an estimated pretest probability (prevalence) of 25%. From Oliveira J. e Silva et al, reproduced with permission.[142]

anxiety disorder were estimated at 89% and 83%, respectively.[150] The GRADE summary of findings table illustrates the number of misclassifications and the certainty in the evidence when we applied its diagnostic accuracy estimates to different scenarios of pretest probabilities (Table 6). We also found studies evaluating the effectiveness of depression screening compared to usual care without screening and studies evaluating the natural course of screened patients. Importantly, none of these studies evaluated our target population of interest (recurrent and previously undifferentiated abdominal pain in the ED), yielding significant concerns for indirectness when evaluating this evidence.

One randomized trial evaluated the effect of depression screening on a composite outcome of depression recognition, psychiatric consultation, or referral by the emergency physician.[151] In this trial, when the provider was notified of screening results, a higher proportion of patients had the composite outcome, but the difference was not statistically significant (7.6% vs. 5.1%; risk ratio [RR] 1.49, 95% CI 0.49 to 4.53, very low certainty; Table 7). This was the only trial that we found in the ED-specific literature. A meta-analysis evaluated screening and case finding for depression compared to usual care and assessed recognition of depression by the clinician and change in management including referral.[152] A modest increase in recognition of depression by clinicians was associated with depression screening (11 randomized trials, 5996 patients; pooled RR 1.27, 95% CI 1.02 to 1.59, very low certainty). There was no difference in change in management between screening and usual care (10 studies, 2333 patients; pooled RR 1.30, 95% CI 0.97 to 1.76, very low certainty). Subgroups involving unselected patients versus patients at high risk of depression yielded similar results.[152] Our GRADE assessment is detailed in Table 7. Our certainty on these estimates when applying them to our target population was very low due to risk of bias, inconsistency, indirectness, and imprecision.

TABLE 5 GRADE summary of findings table for Question 3 (screening for depression using the PHQ-2 instrument with a cutoff of ≥2)

	Number of results per 1000 patients tested (95% CI)				
Test result	Prevalence 8%: Lowest prevalence estimate reported in ED studies with unselected patients	Prevalence 25%: Median prevalence estimate reported across all studies with ED populations (and in studies of undifferentiated abdominal pain)	Prevalence 55%: Highest prevalence estimate reported in ED studies with unselected patients	Number of participants (studies)	Certainty of the evidence (GRADE)
True positives	74 (70–76)	230 (220–238)	506 (484–523)	10627 (44)[a]	⨁◯◯◯ VERY LOW[b,c,d]
False negatives	6 (4–10)	20 (12–30)	44 (27–66)		
True negatives	616 (580–644)	503 (473–525)	302 (284–315)	10627 (44)[a]	⨁◯◯◯ VERY LOW[b,c,d]
False positives	304 (276–340)	247 (225–277)	148 (135–166)		

Abbreviation: PHQ, Patient Health Questionnaire.

[a]This is based on the individual-patient meta-analysis by Levis et al.[200] They compared the diagnostic accuracy of PHQ-2 and PHQ-9 with data from 44 studies and 10,627 patients (1361 with depression and 9266 without depression). They were able to compare the different screening approaches by examining their accuracy estimates in relation to the same reference standard (semistructured interviews, which are considered the "best" reference standard in depression screening studies).

[b]In the risk of bias assessment using the QUADAS-2 tool, Levis et al.[200] reported that only three of 48 (6%) studies that used a semistructured interview had low risk of bias across all four domains and for this reason we downgraded one level for risk of bias. To note, four of the 48 studies did not have the PHQ-9 item scores available and thus could not be included in the comparison of screening strategies.

[c]Levis et al.[200] reported moderate statistical heterogeneity across studies. Visual inspection of forest plots also raised concerns for moderate heterogeneity for both sensitivity and specificity. For this reason, we downgraded one level for inconsistency.

[d]For indirectness, for the patient selection domain, studies included in the meta-analysis of Levis et al.[200] were from a variety of settings including nonmedical, outpatient, and inpatient settings, and for this reason we considered serious concern for indirectness. For index and reference test, we considered most studies to have low concern for indirectness. For outcome, our guideline panel was interested in patient outcomes and therefore we had serious concern for indirectness when using accuracy data instead. We downgraded two levels for indirectness.

TABLE 6 GRADE summary of findings table for Question 3 (screening for anxiety using the GAD-7 instrument with a cutoff of ≥10)

	Number of results per 1000 patients tested (95% CI)				
Test result	Prevalence 9%: Lowest prevalence reported in an ED population	Prevalence 27%: Median prevalence reported in ED populations	Prevalence 74%: Highest prevalence reported in an ED population	Number of participants (studies)	Certainty of the evidence (GRADE)
True positives	80 (74–86)	240 (221–259)	659 (607–710)	965 (1)	⨁⨁◯◯ LOW[a,b]
False negatives	10 (4–16)	30 (11–49)	81 (30–133)		
True negatives	755 (728–774)	606 (584–620)	216 (208–221)	965 (1)	⨁⨁◯◯ LOW[a,b]
False positives	155 (136–182)	124 (110–146)	44 (39–52)		

Abbreviation: GAD-7, Generalized Anxiety Disorder Scale-7.

[a]The risk of bias for this study was assessed by Herr et al.[150] using the QUADAS tool and 13 out of 14 domains/questions were deemed at low risk of bias. Therefore, we did not downgrade for risk of bias.

[b]For indirectness, for the patient selection domain, this study was in the primary care setting, and for this reason we considered serious concern for indirectness. For index and reference test, we considered most studies to have low concern for indirectness. For outcome, our guideline panel was interested in patient-oriented outcomes and therefore we had serious concern for indirectness when using accuracy data instead. We downgraded two levels for indirectness.

Lastly, one observational study found that patients with undifferentiated abdominal pain who screened positive for depression in the ED were more likely to have had one ore more ED visit for abdominal pain in the prior year than patients who screened negative (61.9% vs. 33.9%; OR 3.17, 95% CI 1.14 to 8.85, very low certainty due to risk of bias and indirectness),[77] suggesting that these patients may have increased ED recidivism.

Benefits

Depression and anxiety are associated with reduced quality of life, increased risk of suicide, and increased risk of chronic physical illness (including chronic abdominal pain).[153–158] Screening may represent an opportunity for emergency physicians to proactively promote public health, especially in populations with high risk of mental health

disorders. However, the benefits of screening when applied to the ED setting are difficult to evaluate, especially in our target population where no direct evidence was available. We found no evidence on the potential benefits or harms of anxiety screening. Uncertainty remains regarding the effectiveness of depression screening strategies alone, without other enhancements in care (e.g., referral, treatment), on outcomes such as recognition of depression and change in management. No studies evaluated the priority outcomes identified by the GRACE-2 writing group. As shown in the summary of evidence above, recognition of depression by the clinician may slightly increase with active screening, but this does not necessarily result in changes in the behavior of ED clinicians. Screening alone is unlikely to have a large desirable effect.

It is crucial to note that the presence of depression and/or anxiety does not exclude a coexisting serious cause of abdominal pain, and physicians should not use mental health screening as a method to determine the need for further evaluation of abdominal pain. If recurrent abdominal pain is a symptom of depression or anxiety for some patients, active screening for these conditions during ED evaluation, followed by referral and treatment, might mitigate the recurrent pain burden—but research is needed to test these hypotheses. Screening for depression and/or anxiety in ED patients with recurrent abdominal pain might be the only opportunity for detection in cases where patients have limited access to health care services (e.g., undomiciled, uninsured, and underinsured patients).[159,160] Another potential benefit is the fact that a negative screening with a highly sensitive tool could help clinicians to reevaluate other potential causes of the recurrent abdominal pain by avoiding the cognitive bias of "psych out error" (i.e., misattributing patient somatic symptoms to psychiatric illness) and concomitant anchoring bias or premature closure.[161]

Harms and burden

We found no direct evidence on the harms of screening in our population of interest. However, we noted that misclassification with the use of existing screening tools may lead to a significant number of false positives. False positives could lead to unnecessary referrals to mental health services and other unnecessary interventions such as antidepressant treatment, potentially harming patients and misallocating already-scarce mental health system resources. Given the relatively low specificity of existing screening tools, it is important to note that a positive screen by itself does not make the diagnosis of either depression or anxiety. Figure 3 illustrates the frequency of misclassification with the different depression screening approaches.

Patients might perceive the discussion of emotional factors as an invalidation of their primary complaints.[162] Emergency physicians might stop considering other potential causes of abdominal pain if they prematurely anchor on psychiatric disorders (anchoring bias), particularly if falsely supported by low-specificity screening tools.[161] Malpractice risk might arise with identifying a problem (e.g., depression and/or anxiety) without concomitant resources (e.g., access to outpatient services) to address these conditions. Emergency physicians might view screening for mental health disorders as a low-priority task given the multitude of other pressures.[163] While depression/anxiety screening may be simple with existing tools, the burden of many individually valid screening tasks (e.g., suicide, frailty, fall risk, delirium, dementia, immunization status, substance abuse, interpersonal violence, housing and food insecurity) upon ED teams may be overwhelming.

Decision criteria and additional considerations

Appendix S9 provides the detailed EtD framework for Question 3. Both depression and anxiety appear to be relatively common in our population of interest despite the indirectness and uncertainty of evidence. The risk of these conditions in this population is likely higher than the average non-ED population.[146–148] Active screening by providers may increase recognition but may also lead to misclassification (false positives and false negatives) that could have undesirable effects. It is uncertain whether ED screening of patients with recurrent and undifferentiated abdominal pain would meaningfully improve patient-oriented outcomes. We felt that the relative simplicity of screening and potential for increased recognition of conditions that are associated with significant morbidity in the long-term probably favors the intervention (screening). However, we noted that screening without appropriate mental health follow-up is unlikely to benefit patients. When discussing feasibility and acceptability, we also proposed that screening should not occur as part of the triage process but later in the ED evaluation, preferably after other priority workup has been completed and life-threatening causes of abdominal pain have been ruled out.

Despite one study suggesting significant variability of patients' interest in ED-initiated interventions for mood disorders,[164] the GRACE-2 patient representative noted that screening for these conditions in the setting of recurrent abdominal pain could have tremendous value despite current uncertainty regarding the balance of potential benefits and harms. However, stigma against depression is common in multiple cultures,[165,166] and the patient representative highlighted the importance of educating patients about mental health disorders to mitigate negative responses that might arise from screening. We emphasized that the coexistence of depression and abdominal pain does not prove a causal relationship, and complex interactions are possible. For example, chronic undifferentiated pain without an effective plan for diagnosis and treatment could result in or worsen depression; depression could manifest somatically as abdominal pain; or patients could have chronic abdominal pain and depression as two primary conditions. We felt it important to acknowledge these possibilities with patients.

Conclusions and research needs

Patients with recurrent and undifferentiated abdominal pain may have undetected depression and/or anxiety disorders that could be

TABLE 7 GRADE summary of findings table for Question 3 (effectiveness of screening strategies without enhancements of care compared to usual care)

				Anticipated absolute effects	
Outcomes	**No. of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)***	**Risk with usual care**	**Risk difference with screening of depression and/or anxiety**
Composite outcome of depression recognition, psychiatric consultation, or referral by the emergency physician	190 (1 RCT)[a]	⨁◯◯◯ VERY LOW[b,c,d]	RR 1.49 (0.49 to 4.53)	51 per 1000	25 more per 1000 (26 fewer to 180 more)
Recognition of depression by clinicians (overall patient population)	5996 (11 RCTs)[e]	⨁◯◯◯ VERY LOW[f,g,h,i]	RR 1.27 (1.02 to 1.59)	173 per 1000	47 more per 1000 (3 more to 102 more)
Recognition of depression by clinicians (unselected patients)	5469 (7 RCTs)[j]	⨁◯◯◯ VERY LOW[f,h,k,l]	RR 1.03 (0.85 to 1.24)	158 per 1000	5 more per 1000 (24 fewer to 38 more)
Recognition of depression by clinicians (high-risk patients)	527 (4 RCTs)[m]	⨁◯◯◯ VERY LOW[f,h,l,n,o]	RR 2.08 (0.90 to 4.78)	325 per 1000	352 more per 1000 (33 fewer to 1230 more)
Change in management of depression including referral (overall patient population)	2333 (10 RCTs)[e]	⨁◯◯◯ VERY LOW[f,h,l,p,q]	RR 1.30 (0.97 to 1.76)	327 per 1000	98 more per 1000 (10 fewer to 249 more)
Change in management of depression including referral (unselected patients)	1351 (5 RCTs)[j]	⨁◯◯◯ VERY LOW[f,h,l]	RR 0.97 (0.81 to 1.18)	251 per 1000	8 fewer per 1000 (48 fewer to 45 more)
Change in management of depression including referral (high-risk patients)	982 (5 RCTs)[m]	⨁◯◯◯ VERY LOW[f,h,l,n]	RR 1.50 (0.89 to 2.53)	444 per 1000	222 more per 1000 (49 fewer to 679 more)

Note: GRADE Working Group grades of evidence: *High certainty*—We are very confident that the true effect lies close to that of the estimate of the effect. *Moderate certainty*—We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low certainty*—Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. *Very low certainty*—We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: PICOT, patient-intervention-comparison-outcome-time; RCT, randomized controlled trial; RR, risk ratio.

[a]This RCT (Schriger et al.)[151] included ED patients with complaints likely to be associated with an occult psychiatric illness including nonspecific abdominal pain.

[b]This study was deemed to be at low risk of bias. The Cochrane Risk of Bias tool version 2 was used for the assessment.

[c]This study was in the ED but it included patients presenting with complaints likely to be associated with an occult psychiatric illness. The authors reported that vague abdominal pain was among those complaints but given the fact that several other complaints were included in this study population, we downgraded for indirectness one level. Our target population of interest was recurrent and previously undifferentiated abdominal pain.

[d]We downgraded two levels for imprecision due to the very wide confidence interval involving a large increase in the composite outcome (upper bound of the CI) and a large decrease in the composite outcome (lower bound of the CI). Also, the sample size of this study was <280 patients (optimal information size).

[e]This meta-analysis by Gilbody et al.[152] included RCTs in a general patient population including primary care and general hospital with no distinction regarding baseline risk of depression.

[f]Most studies in the systematic review by Gilbody et al.[152] did not report adequate allocation concealment or method of randomization, raising concerns for risk of bias.

[g]The I^2 for the pooled RR of the overall effectiveness of screening and case finding on the outcome of recognition of depression was 69%. Part of the heterogeneity was explained by method of scoring and patient randomization (randomizing unselected patients vs. high-risk patients). Visual inspection of forest plot presented by Gilbody et al.[36] raised concerns for inconsistency because results differed across published studies.

[h]This systematic review included studies on different settings (primary care and general hospital) with only one study in the ED (Schriger et al.[151]). Also, none of the studies were exclusively on abdominal pain patients. Therefore, we downgraded two levels for indirectness.

[i]The lower bound of the CI crosses the threshold of minimal clinically important difference of 10% in the increase of depression recognition. This threshold was obtained by consensus of the working group focused on this PICOT question of the guideline. Therefore, we downgraded one level for imprecision from the perspective of clinical guideline development. Please note that downgrade would not occur if this was a systematic review assessment only.

[j]This meta-analysis by Gilbody et al.[152] included RCTs in which the study population was unselected/undifferentiated patients (it does not include the trials who randomized screening vs. usual care among high-risk patients).

[k]I^2 greater than 60% and visual inspection of the forest plot presented by Gilbody et al.[152] raised concerns for significant heterogeneity.

[l]Wide CI.

[m]This meta-analysis by Gilbody et al.[36] included RCTs in which the study population was composed of high-risk patients (i.e., patients who had certain criteria to be deemed at high risk of depression before being randomization to screening vs usual care).

[n]Visual inspection of the forest plot raised concern for important inconsistency. Studies with CIs not overlapping with each other.

[o]No studies in the ED examining high-risk patients.

[p]The I^2 for the pooled RR of the overall effectiveness of screening and case finding on the outcome of change in depression management was 81%. Part of the heterogeneity was explained by method of scoring and patient randomization (randomizing unselected patients vs. high-risk patients). Visual inspection of forest plot presented by Gilbody et al.[53] raised concerns for inconsistency.

[q]Lower bound of the CI crosses the threshold of minimal clinically important difference of 5% in the increase of change in depression management. This threshold was obtained by consensus of the working group focused on this PICOT question of the guideline. Therefore, we downgraded one level for imprecision.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

identified during the ED visit. The recommendation by the GRACE-2 writing group reflects the fact that screening of depression and/or anxiety in this population is reasonable, but significant uncertainty remains around the balance of potential benefits and harms for patient-oriented outcomes. Our recommendation weighted heavily the perspective of our patient representative who highlighted this intervention as being potentially very important to patients.

The need for future research on this topic is clear. We suggest the following four priorities: (1) high-quality observational studies to understand the magnitude of mental health disorders in ED patients with recurrent and undifferentiated abdominal pain; (2) validation of screening instruments in the ED setting along with training for providers and patients (if self-screening is applied); (3) evaluation of the effect of ED-based screening along with other interventions (e.g., referral, treatment) for patients who screen positive, preferably through randomized controlled trials comparing screening and intervention versus usual care; (4) and evaluation of ED-initiated interventions (e.g., antidepressant therapy) for patients with positive ED-screens for depression and/or anxiety.

QUESTION 4

Should adult ED patients with low-risk, recurrent, and previously undifferentiated abdominal pain receive nonopioid and/or nonpharmacologic analgesics?

Recommendation 4: In adult ED patients with low-risk, recurrent, and undifferentiated abdominal pain, we suggest an opioid-minimizing strategy for pain control (Conditional recommendation, for) [Consensus, no evidence]

Summary of the evidence

Search strategies and review methods are detailed in Appendix S3.4. To be considered direct evidence, a publication must have met the following criteria:

1. Adult ED patients
2. Low risk
3. Recurrent undifferentiated abdominal pain
4. Received a nonopioid or nonpharmacologic intervention aimed to manage pain

We found zero publications meeting the criteria for direct evidence. Nine studies met some criteria and were included as indirect evidence (Appendix S10, Table 8). No studies assessed our priority outcomes (Box 2). Consequently, the following outcomes were evaluated:

1. Change in pain score
2. Need for rescue medications
3. Patient satisfaction with pain relief

Risk profiles of patients were not described sufficiently to determine whether these matched the intended low-risk group. Many studies specifically excluded patients with recurrent abdominal pain. Even by indirect measures, the included studies suffered from substantial limitations on multiple GRADE certainty and quality metrics, including risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size magnitude, and opposing bias and confounders. Some studies provided indirect evidence of inequities and potential areas for future research.

Pharmacologic analgesia for abdominal pain

Indirect evidence for pharmacologic therapies for acute abdominal pain are summarized below and in Table 8. Although specific abdominal pain pathologies such as renal colic and biliary colic were not our population of interest, several systematic reviews on these populations appeared in our literature search and provide indirect evidence. As described below, NSAIDs appear similar in efficacy to opioids for renal and biliary colic. Some nonopioid pharmacologic agents (including NSAIDs, acetaminophen, and lidocaine) are associated with short-term decrease in acute abdominal pain, often with a defined or suspected etiology (such as renal or biliary colic); their role in recurrent undifferentiated pain is unknown. Many studies did not compare opioids and nonopioids directly, instead using opioids as rescue therapy when first-line analgesics did not provide adequate pain relief. Some studies compared one nonopioid to another nonopioid. Studies did not consistently report potentially important delayed adverse effects that might accrue after an ED visit (e.g., AKI or gastrointestinal bleeding from NSAIDs or constipation, long-term opioid use, and overdose mortality from opioids). The heterogeneity of study populations, interventions, and outcomes, and their methodologic limitations are highlighted in some examples below.

Analgesics for renal colic. Three meta-analyses assessed NSAIDs for patients with acute renal colic, reaching similar conclusions on the magnitude of analgesic effects of NSAIDs, acetaminophen, and opioids.[167,168,169] We also compared findings with the minimum threshold for clinically significant changes in pain (13 mm on a Visual Analog Scale [VAS]).[170]

A meta-analysis (20 studies, 1613 patients) of patients with renal colic found no clinically significant difference in analgesia between opioids and NSAIDs (MD −10.5, 95% CI −19.9 to −1.1 on a 0–100 VAS).[167] Patients treated with NSAIDs required less rescue medication (19% vs. 25%, RR 0.75, 95% CI 0.61 to 0.93) and had less vomiting (6% vs. 20%, RR 0.35, 95% CI 0.23 to 0.53) than those treated with opioids.

Another meta-analysis (37 studies, 4483 patients with renal colic) found that NSAIDs were more effective than placebo in reducing pain by 50% within 60 min (65% vs. 27%, RR 2.28, 95% CI 1.47 to 3.51). Patients receiving NSAIDs were less likely to require rescue medication compared to placebo (23% vs. 67%, RR 0.35, 95% CI 0.20 to 0.60). NSAIDs also reduced pain more than antispasmodics (estimated VAS mean 33 vs. 46, MD −13.0, 95% CI −21.8 to −4.1).[168]

A third meta-analysis (36 randomized clinical trials [RCTs], 4887 subjects) compared NSAIDs, opioids, and acetaminophen for renal colic.[169] Compared to opioids, NSAIDs provided better pain relief at 30 min (MD −5.58, 95% CI −10.22 to −0.95), but this difference did not meet the clinically significant threshold.[170] Patients treated with NSAIDs required fewer rescue treatments than those treated with opioids (23% vs. 31%, RR 0.73, 95% CI 0.57 to 0.94) and had lower rates of any adverse event (RR 0.53, 95% CI 0.40 to 0.69). NSAIDs had lower rates of vomiting compared with opioids (5% vs. 20%, RR 0.41, 95% CI 0.24–0.70). Comparing NSAIDs to acetaminophen, pain relief was similar at 30 min, although those treated with NSAIDs required less rescue analgesia (11% vs. 20%, RR 0.56, 95%CI 0.42 to 0.74).

Analgesics for biliary colic. A systematic review of randomized trials for acute adult biliary colic found similar pain relief between NSAIDs and opioids, while NSAIDs outperformed antispasmodics and placebo. Inadequate pain relief or need for rescue analgesia occurred in 23% NSAIDs versus 18% opioids (RR 0.98, 95% CI 0.47 to 2.07), 30% NSAIDs versus 60% antispasmodics (RR 0.51, 95% CI 0.37 to 0.71), and 21% NSAIDS versus 78% placebo (RR 0.27, 95% CI 0.19 to 0.4).[171] However, all of the studies included in this analysis were found to have high risk of bias.

In a RCT of 87 patients with suspected biliary colic,[172] the combination of morphine 0.05 mg/kg IV and acetaminophen 1000 mg IV versus morphine 0.1 mg/kg IV provided similar decreases in mean VAS (0–10 scale) at 15 min (MD −0.35, 95% CI −1.15 to 0.45) or 30 min (MD −0.48, 95% CI −1.2 to 0.24). Both groups had a clinically and statistically significant reduction in mean pain score from baseline (from 8.73 ± 1.57 to 1.66 ± 1.59 in the combination group and 8.53 ± 1.99 to 2.14 ± 1.79 in the morphine alone group on a 0–10 scale). Rescue analgesia was required in 2.3% in the morphine plus acetaminophen group and none in the morphine alone group.

Nonopioids for undifferentiated abdominal pain (not necessarily recurrent or low risk). Three studies addressed treatment outcomes for nonspecific abdominal pain in the ED.[170,173,174] In an RCT of 154 adult ED patients with acute abdominal pain, hydromorphone 1 mg IV achieved a 50% reduction in pain at 90 min in 22% more patients than did lidocaine 120 mg IV (95% CI 7% to 37%). Hydromorphone reduced pain by 5.0 points versus lidocaine 3.8 points on a 0–10 pain scale (MD 1.2, 95% CI 0.3 to 2.2).[173] Patients treated with hydromorphone were less likely to require rescue analgesia (26% hydromorphone vs. 51% lidocaine, 95% CI 10% to 40%]) and more likely to be satisfied with treatment (90% hydromorphone vs. 64% lidocaine, 95% CI 13% to 39%). In post hoc analysis, patients weighing <73 kg had a more pronounced decrease in pain with lidocaine compared with patients of greater mass (mean improvement of 5.0 [95% CI 3.8 to 6.2] on a 0–10 pain scale compared to 3.0 [95% CI 1.7 to 4.3] for those weighing 73–85 kg or 3.1 [95% CI 2.1 to 4] for those weighing 85–120 kg). The authors suggested that a weight-based approach may improve the effects of lidocaine for pain. A total of 32% of patients were ultimately diagnosed with nonspecific abdominal pain (35% in lidocaine group vs. 29% in hydromorphone group).

Another RCT of 210 adult ED patients with acute abdominal pain compared tramadol 1 mg/kg IV, acetaminophen 15 mg/kg IV, and placebo.[174] Twenty-five percent of patients had a final diagnosis of nonspecific abdominal pain. Each analgesic was associated with a decrease in pain on a 100-mm VAS at 40 min (85 [95% CI 71 to 97] to 28 [95% CI 18 to 30] for tramadol, 83 [95% CI 73 to 97] to 33 [95% CI 30 to 37] for acetaminophen), while there was no decrease in pain among the placebo group, with an initial score of 84 (95% CI 73 to 97) and a final score of 85 (95% CI 74 to 93).

A third RCT of 132 adult ED patients with moderately severe undifferentiated abdominal pain compared acetaminophen 1000 mg PO to hyoscine butylbromide (a non–FDA-approved anticholinergic used as an antispasmodic agent) 20 mg IV or a combination of both medications.[170] Patients with a VAS pain score greater than 7 on a 0- to 10-point scale were offered opioids first and enrolled only if they declined opioids. All groups had an approximately 2 points decrease in pain at 30 min. At 60 min, pain scores decreased from baseline in all groups (−3.3 points for acetaminophen, −2.8 for hyoscine, and −1.9 for hyoscine + acetaminophen), without clinically or statistically significant differences among groups. There was no difference between treatment groups in the need for rescue analgesia, with <20% in all groups requiring it.

One additional RCT included 220 ED patients with diverse anatomic sites of acute pain including 79.5% with abdominal pain.[175] This RCT compared hydromorphone 1 mg IV to acetaminophen 1 g IV. Hydromorphone resulted in greater pain relief (difference of 2 points on a 0–10 pain scale, 95% CI 1.2 to 2.7). There was no difference in the number of patients receiving rescue analgesia within 60 min. More patients treated with hydromorphone declined additional analgesia after 60 min (65% vs. 44%, 95% CI 8% to 35%). Hydromorphone was associated with significantly more nausea (19% vs. 3%, difference 16%, 95% CI 4% to 28%) and vomiting (14% vs. 3%, difference 11%, 95% CI 0% to 23%) compared to acetaminophen.

Nonpharmacologic analgesics therapies (not specifically for abdominal pain)

We found no direct evidence for nonpharmacologic therapies in low-risk recurrent undifferentiated abdominal pain. No studies investigated acupuncture for nontraumatic abdominal pain in the emergency setting. Studies identified in our search utilizing nerve blocks for the treatment of abdominal pain were performed in the perioperative period, not ED, and not for recurrent pain. Studies focused on other modalities (e.g., cognitive behavioral therapy, yoga, biofeedback, herbal remedies) had small sample sizes, were performed over weeks or months in an outpatient setting, or suffered other methodological issues such as lack of comparator groups or adequate blinding.

Two meta-analyses reviewed acupuncture for diverse forms of pain (not recurrent low-risk abdominal pain) in the emergency care setting, confounded by biases including inadequacy of blinding.[176,177] Studies used a range of practitioners (described as "nonacupuncturists trained in simple prescriptions," "emergency physicians with extra acupuncture qualifications," or "traditional Chinese medicine

TABLE 8 Evidentiary table for Question 4 (nonopioid analgesics)

Study, location, time frame	No. patients (median or mean age)	Inclusion criteria	Exclusion criteria
Afshar 2015[168]	37 studies	Randomized or quasi-randomized studies of adult patients with renal colic that included at least one nonopioid arm and reported a pain outcome	
Barnaby 2019,[175] 2 affiliated academic EDs, Jun–Nov 2017	220 patients, mean (±SD) age 42 (±12) years, large Hispanic population (67%), females 60% 82% in hydromorphone group had abdominal pain, 77% in acetaminophen group	Age 21–64 years, pain severe enough to warrant IV opioids	Prior adverse reaction to hydromorphone or acetaminophen, use of opioids or tramadol within 24 h, use of acetaminophen or NSAIDs in 8 h, chronic pain, intoxicated, vital sign abnormalities (sBP < 100 mm Hg, HR < 60, O_2 sat < 95% RA), pregnant, breastfeeding, use of MAOI, transdermal pain patch, medication that may interfere with study medications, medical condition that may affect metabolism of study medications
Chinn 2019,[173] single ED in the United States, between Jan and Aug 2018	154 (41 years)	Age 18–64 years, weight 60–120 kg, <7 days of severe abdominal pain (requiring opioids), requiring additional analgesia 1 h after receipt of ED pain medication	Cardiac conduction system impairment, known renal or liver disease, hemodynamic instability (as determined by the attending physician), pregnancy, breastfeeding, or allergy to either medication. Took opioids in the prior week, chronic pain disorder
Farnia 2016,[172] ED in Iran, Aug 2012 through Aug 2013	87, mean age 49 years	Age 18–65, new-onset upper abdominal pain with concerns for biliary origin, VAS > 3, gallstones in bile duct evidenced by ultrasound and labs	Previous or known hypersensitivity reactions to opioids or acetaminophen; unstable vital signs (systolic blood pressure <90 mmHg); evidence of peritoneal irritation; pregnancy; history of renal, liver or heart failure; patients undergoing kidney, lung, liver or heart transplantation; altered mental status (GCS < 15); patients who cannot cooperate in the study; VAS < 3; patients taking analgesics during the last 6 hours; substance or drug abuse and not giving consent to participate in the study
Fraquelli 2016[171]	12 trials of 823 participants age ranges 18–86 years	RCTs recruiting participants presenting with biliary colic and comparing NSAIDs vs. no intervention, placebo, or other drugs	

Study design	Factors assessed or primary outcome	Secondary outcome(s)	Prevalence of outcomes
Systematic review	Patient-reported pain	Time to pain relief, need for rescue analgesia, pain recurrence	• NSAIDs reduce pain compared to antispasmodics (MD −12.97, 95% CI −21.8 to −4.14), 5 studies, 303 participants • Combination NSAID plus antispasmodic is more effective for pain control than NSAID alone (MD −1.99, 95% CI −2.58 to −1.40), 2 studies, 310 participants • NSAIDs more effective than placebo in reducing pain by 50% in first hour (RR 2.28, 95% CI 1.47 to 3.51), 3 studies, 197 participants • Combination NSAIDs and antispasmodics not superior to NSAIDs alone (RR 1.00, 95% CI 0.89 to 1.13), 9 studies, 906 participants • Less likely to need rescue medication with NSAIDs than placebo (RR 0.35, 95% CI 0.20 to 0.60), 4 studies, 180 participants • No major events due to medications reported
RCT, double blind; acetaminophen 1 g IV vs. hydromorphone 1 mg IV	Between-group difference in change in numeric pain rating scale from baseline to 60 min	Difference in proportion of patients who declined further pain medication at 60 min, difference in proportion of patients who received additional analgesia before 60 min, difference in proportion of patients who developed side effects	• Difference of 2 points in decrease of pain score between groups at 60 min (95% CI 1.2 to 2.7), favoring hydromorphone • More patients in hydromorphone group declined pain medication at 60 min (difference of 21%, 95% CI 8% to 35%) • No difference in receipt of rescue analgesia (2 in hydromorphone group, 3 in acetaminophen) • More nausea in the hydromorphone group (difference of 16%, 95% CI 4% to 28%) • No difference in experiencing pruritis
RCT	Receipt of pain medication in ED over 1 h prior and requiring additional analgesia	Second analgesic dose required Satisfaction Return ED visit in 7 days	• Lidocaine pain improved less than hydromorphone (3.8-point vs. 5-point decrease) • Missing pain scores used average between score before and after missing value, carried forward value if end pain score missing. Of patients with nephrolithiasis, 3.4-point decrease with lidocaine, 6.4 with hydromorphone. Post hoc analysis revealed association between weight and lidocaine dose that led to pain relief • At 90 min, more hydromorphone patients (47/77, 61%) than lidocaine patients (30/77, 39%) reported a greater than 50% • Improvement in their pain (difference 22%, 95% CI 7% to 37%) • Need for off-protocol "rescue" analgesics occurred for 39 of 77 lidocaine patients (51%) and 20 of 77 hydromorphone patients (26%; difference 25%, 95% CI 10% to 40%; Table 3, Figure 3). More hydromorphone patients (64/71, 90%) than lidocaine patients (47/73, 64%) said they would want to receive the study medication again (difference 26%, 95% CI 13% to 39%) • Medication-associated symptomatology was comparable between the 2 study arms (Table 4) • The most commonly reported symptoms were dizziness, drowsiness, headache, nausea, and pruritis. No other symptom was reported by more than one patient • No serious adverse events. No patient required administration of naloxone
Randomized controlled trial	Acetaminophen 1 g with morphine 0.05 mg/kg versus morphine 0.1 mg/kg Pain	Rescue analgesia Adverse events	• The mean pain scores between the two groups at 0, 15, and 30 min demonstrated no significant difference • Mean VAS pain scores did not differ between administration of acetaminophen + low-dose morphine or morphine alone • There were no patients in the morphine arm but two (2.3%) patients in the acetaminophen + low-dose morphine arm who needed fentanyl as rescue analgesia • No significant adverse effects noted. Minimal rates of vomiting, nausea, and sedation and no difference in these minor adverse effects noted between the two groups
Systematic review	Pain relief	Adverse events	• Lack of pain relief—RR 0.27 (95% CI 0.19 to 0.4) NSAIDs vs. placebo, 208 participants from 5 studies, rated moderate-quality evidence by GRADE; Lack of pain relief—RR 0.98 (95% CI 0.47 to 2.07) NSAIDs vs. opioids, 459 participants from 4 studies, rated very-low-quality evidence by GRADE; Lack of pain relief—RR 0.51 (95% CI 0.37 to 0.71) NSAIDs vs. spasmolytics, 190 participants from 4 studies, rated low-quality evidence by GRADE • Only one trial comparing NSAIDs with opioids reported data on cholelithiasis-related complications and found no difference in the occurrence of events between the two groups • Two trials reported on cholelithiasis-related complications. When compared with spasmolytics, NSAIDs showed a significantly lower proportion of disease-related complications (RR 0.27, 95% CI 0.12 to 0.57; $I^2 = 0\%$)

TABLE 8 (Continued)

Study, location, time frame	No. patients (median or mean age)	Inclusion criteria	Exclusion criteria
Holdgate 2005,[167] academic ED in Australia, Sep 2002–Mar 2004	178 (no mean)	Age 18–75 years presenting with suspected renal colic as judged by ED physician	Received parenteral opioid analgesia or hyoscine butylbromide within 4 h before presentation, pregnant, glaucoma, urinary retention, or known allergy to morphine or hyoscine butylbromide Unable to be evaluated within 15 min, at which time analgesia would be ordered
Oguzturk 2012,[174] single ED in Turkey	210, 57% women, mean (±SD) age 33.8 (±12.2) years for men and 32.1 (±12.0) years for women	ED patients older than 17 years with abdominal pain <72 h	Trauma, pregnancy, allergy to opioids or acetaminophen, sBP < 100 mm Hg, self-medicated with analgesics
Pathan 2018[169]	36 studies, 4887 patients	Systematic reviews and controlled trials through Dec 2016 comparing NSAIDs to opioids or acetaminophen for renal colic, any route of administration, no language restrictions	
Remington-Hobbs 2012,[170] London, 2007–2008	132 (median age 28 years)	ED patients with acute, moderately severe, undifferentiated abdominal pain Patients ineligible for inclusion in the trial only because they had a VAS pain scores >7 were offered titrated IV opioid analgesia and if they declined this they were then offered the chance to participate in the study	Patients with mild abdominal pain without a known cause or with a dipstick positive urinary tract infection

Abbreviations: GCS, Glasgow Coma Scale; MD, mean difference; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; RR, risk ratio; VAS, Visual Analog Scale.

practitioners") to administer acupuncture, although it was unclear what training entailed.[177] A prospective study without randomization and using a historical control group found acupuncture to be acceptable to patients in the ED with pain of diverse locations/etiologies (58.5% musculoskeletal, 24.5% abdominal or flank),[178] which was also reported in a retrospective review.[179] An unblinded RCT comparing acupuncture to acetaminophen IV or diclofenac intramuscular for treatment of renal colic found acupuncture to be noninferior for pain control within 120 min, with the acetaminophen group experiencing a change in mean pain score on a 10-point VAS scale from 9.3 to 2.1, those with acupuncture improving from 9.0 to 4.5, and those receiving diclofenac changing from 8.8 to 2.8.[180]

Study design	Factors assessed or primary outcome	Secondary outcome(s)	Prevalence of outcomes
RCT	Hyoscine butylbromide (20 mg diluted to 10 ml) vs. 10 ml IV saline (placebo) Groups stratified by ability to receive NSAIDs Mean initial dose of morphine	Need for rescue analgesia Admission Adverse effects	• No difference between the 2 groups in the mean dose of morphine required to achieve initial analgesia, 0.13 mg/kg (95% CI 0.12 to 0.15) in the hyoscine butylbromide group and 0.12 mg/kg (95% CI 0.11 to 0.13) in the placebo group • No difference between the groups in the proportion of patients requiring further morphine (28 or 33% of hyoscine butylbromide group, 35 or 38% of placebo) or admitted to hospital (12 or 14% of hyoscine butylbromide group, 18 or 19% of placebo) or the number of adverse events (15 or 18% of hyoscine butylbromide, 17 or 18% of placebo) • No episodes of excessive sedation with no patient having a GCS < 14 at any time during the study
Randomized, placebo controlled	Pain severity	Abdominal examination, effect of medication on diagnosis	• Pain severity at 20 min decreased by 55% in tramadol group, 45% in acetaminophen, and 1% in placebo • Pain severity at 40 min decreased by 67% tramadol, 60% in acetaminophen, and 0% in placebo • No difference in abdominal findings between groups • Diagnostic accuracy was 96% for tramadol group, 94% for acetaminophen, and 94% for placebo • Side effects similar across groups
Systematic review	Change in pain at 30 min	Pain relief at 30 min, need for rescue analgesia, adverse events	• Opioids performed slightly better than NSAIDs for pain relief at 30 min (MD −5.58, 95% CI −10.22 to −0.95), 11 studies, 1985 patients, significant heterogeneity • No difference in proportion of patients with complete pain relief at 30 min between NSAIDs and opioids (RR 0.96, 95% CI 0.82 to 1.11), 13 studies, 943 patients • No difference in proportion of patients with >50% pain relief at 30 min between NSAIDs and opioids (RR 0.76, 95% CI 0.47 to 1.22), 4 studies, 1805 patients • NSAID groups required less rescue analgesia than opioids (RR 0.73, 95% CI 0.57 to 0.94), 17 studies, 2391 patients • Lower adverse events with NSAIDs compared to opioids (RR 0.53, 95% CI 0.40 to 0.69), 23 studies, 2703 patients • Lower rates of vomiting with NSAIDs compared to opioids (RR 0.41, 95% CI 0.24 to 0.70), 14 studies, 2300 patients
RCT	Compared the analgesic effect of IV hyoscine butylbromide, oral acetaminophen and the combination of both drugs using a VAS pain scoring tool Rescue analgesia was administered when pain was inadequately controlled by trial medication	None	• No difference in VAS at 30 min • Acetaminophen only had greater decrease in VAS at 60 min than did acetaminophen + hyoscine butylbromide • No differences noted between groups for need for rescue analgesia

Benefits

Our review found no direct evidence for nonopioid and nonpharmacologic analgesia in adult low-risk recurrent undifferentiated abdominal pain. The EtD framework is summarized in Appendix S11.

Pharmacologic analgesia (nonopioids vs. opioids)

We did not identify direct evidence in the population of interest. Nonopioid analgesics, particularly NSAIDs, reduce pain with similar efficacy to opioids in some forms of acute abdominal pain, such as suspected renal colic and biliary colic.[167,169] Their efficacy in

undifferentiated recurrent abdominal pain is uncertain. A potential benefit of nonopioid pharmacologic strategies to treating ED pain is reduction or avoidance of opioid exposure and downstream harms of long-term opioid use. While there is no known threshold for opioid exposure leading to opioid use disorder or harm, some evidence demonstrates ongoing opioid use after an initial prescription for opioids from the ED.[16,17,20,22,25,28,181–183] The American College of Emergency Physicians has recommended that nonopioid analgesic therapies (pharmacologic and nonpharmacologic) rather than opioids should be preferentially prescribed upon discharge from the ED, although this is a level C recommendation due to weak evidence.[24]

Nonpharmacologic analgesia

There were no studies identified that compared acupuncture or other nonpharmacologic alternatives to standard care that would allow conclusions regarding the benefits of these therapies in adult ED patients with low-risk, recurrent abdominal pain.

Harms and burden

Pharmacologic analgesia (nonopioids and opioids)

Indirect evidence did not report any serious short-term adverse effects from nonopioid analgesics. The common side effects of nausea and vomiting were observed at higher rates in the opioid treatment groups than in nonopioid groups. Without direct evidence for recurrent undifferentiated abdominal pain, a potential harm of nonopioid analgesia is inadequate pain control, as some studies show greater initial pain relief with opioids.[173] Studies did not report potentially important delayed adverse effects that might accrue after an ED visit. Because physicians may choose to prescribe the same class of medication used for ED analgesia when patients are discharged, longer term adverse effects (e.g., renal insufficiency or gastrointestinal bleeding from NSAIDs, long-term opioid use, and overdose) are important potential harms of all pharmacologic strategies.

In addition to direct pharmacologic effects, opioids and nonopioid analgesics may interact with other medications. None of the included studies discussed home medications of patients, and some classes of medications are contraindicated in combination or in at-risk populations (e.g., NSAIDs and anticoagulants, NSAIDs in patients >65 years of age, concomitant opioids and benzodiazepines).[185,186] However, use of NSAIDs at the lowest dose possible for the shortest duration possible may offer more benefit than harm.[187]

Nonpharmacologic analgesia

No studies directly assessed the harms or burdens of nonpharmacologic analgesia. Meta-analyses[176,177] found that <5% of patients treated with acupuncture had adverse events, most commonly minor pain, fainting, and breakage of needles. The burden of nonpharmacologic analgesia likely would arise primarily from human resources. No identified studies described the minimum training needed to deliver acupuncture, so we were unable to assess the resource burden or feasibility.

Decision criteria and additional considerations

Pharmacologic analgesia (nonopioids and opioids)

The lack of direct evidence for the PICOT question and the heterogeneity and uncertainty of indirect evidence posed substantial challenges for the GRACE-2 writing group. Abdominal pain may originate from a multitude of organ systems and structures, including extraabdominal sources.[187] Studies focused on a specific disease process such as renal colic therefore cannot be assumed to apply to undifferentiated abdominal pain.

Despite this crucial limitation, we felt that the overwhelming evidence of harms from opioid use (now a leading cause of mortality among Americans, accounting for 69,710 deaths in 2020)[188] must substantially influence the group recommendation. We deliberated extensively, choosing ultimately to recommend an "opioid-minimizing" strategy. In this context, opioid minimizing is meant to convey that the least amount of opioid possible should be used for each patient, including the possibility of none (similar to the "as low as reasonably achievable" [ALARA] concept for ionizing radiation use in diagnostic imaging, in which the benefits of diagnosis must be balanced against adverse effects).[189,190] We defined this in contrast to alternative approaches such as an "initial nonopioid" approach, which might suggest that failures of nonopioid analgesia require escalation to opioid therapy (in turn suggesting that opioids offer superior analgesia, a supposition not supported by any direct evidence in our review). We also did not wish to suggest without evidence that opioids are the preferred analgesic at any point in the timeline of patient care nor that the use of opioids is absolutely contraindicated in all instances. We selected "minimizing" rather than "sparing," as the latter term might be misconstrued to mean compete avoidance of opioids in all cases. This recommendation acknowledges the evidence that nonopioids can reduce some forms of abdominal pain, while empowering physicians and patients to individualize therapy to balance the need for analgesia with risks of treatment adverse effects. Inpatient opioid reduction strategies have shown satisfactory analgesia,[83] but validation is required in the ED setting.

We also extensively discussed equity considerations in analgesia for recurrent undifferentiated abdominal pain. In many settings, inequity in analgesia has been documented, with disparities associated with older age, female gender, and Black/Hispanic race. An observational prospective study found that in a cohort of older patients without the ability to communicate verbally (defined as patients with delirium, aphasia, cognitive impairment, and language barriers), including 34.5% with abdominal pain, only 31.9% received any pain medication.[191] A multicenter retrospective review found that being over the age of 85 was associated with a significantly decreased likelihood of receipt of any analgesia for abdominal pain (56% for those >85 years, vs. 77% <65 years), even more pronounced when specifically examining opioids (33% vs. 58%). However, these patients also had lower presenting pain scores and the greatest reduction in pain scores during the ED stay.[192] Another prospective observational study found that men and women had similar mean pain

scores, but women were less likely to receive any analgesia (60% vs. 67%, difference 7%, 95% CI 1% to 14%) and opioids (45% vs. 56%, difference 11%, 95% CI 4% to 17%). Women waited longer than men for administration of analgesia (16-min difference, 95% CI 3.5 to 33 min), despite reporting similar pain scores.[193] This is consistent with retrospective reviews demonstrating that being a woman with abdominal pain is associated with a lower likelihood of receiving pain medication and delayed time to administration of pain medication when compared to men.[194,195] A large retrospective study utilizing national data found that minorities had a decreased OR of receiving opioids in the ED when compared to non-Hispanic White patients, 0.50 for Black patients, and 0.85 for Hispanics.[196] While advocating for equity in analgesia, the writing group also recognized that medically appropriate differences in analgesia approaches may be warranted, based on factors such as pain mechanisms and adverse effects unique to individual patients (e.g., avoidance of NSAIDs in patients with advanced renal disease or gastrointestinal bleeding) or patient groups (e.g., use of Beers list to guide medication selection in older adults).[197]

Conclusions and research needs

Substantial unanswered questions remain about analgesic approaches in recurrent undifferentiated abdominal pain. Future research should attempt to further delineate the etiologies of such pain, allowing more mechanistically and individually tailored therapy. A wide array of pharmacologic and nonpharmacologic therapies should be compared. Studies should use rigorous RCT methods to identify effective therapies, using standardized metrics that characterize onset, magnitude, and duration of clinically important pain relief. Immediate and delayed clinically relevant adverse reactions should be systematically measured. Patient populations should be described in depth to identify and eliminate medically and ethically inappropriate disparities in therapy. The role of shared decision making and ascertainment of patient preferences should be investigated, particularly when clinically important benefits and risks of therapies must be balanced. Resources required for pharmacologic and nonpharmacologic therapies should be characterized.

GENERAL ISSUES NECESSARY FOR CORRECT INTERPRETATION AND IMPLEMENTATION OF RECOMMENDATIONS

Limitations

Topic selection and lack of direct evidence

The GRACE steering committee selected the topic of low-risk recurrent abdominal pain based on consensus agreement on the clinical importance, without feasibility assessment to determine the availability of definitions and evidence to address the topic. The GRACE steering committee felt that generating a guideline even the absence of strong evidence fills an important gap for clinicians. Identifying the paucity of evidence has its own value in directing future research efforts.

Within the topic chosen by the GRACE steering committee, the GRACE-2 writing team generated questions and outcomes of interest prospectively, before performing a literature search, and chose to abide by these decisions even when it was discovered that there was an absence of direct evidence to directly address these. Future GRACE cycles might perform feasibility assessment to determine whether a body of literature exists to address questions and outcomes before committing to guideline development or to develop a list of questions and outcomes, followed by final selection after literature searches determine which can be addressed through existing high-quality research. Ongoing surveys of topics of importance to patients and providers should be incorporated for future GRACE projects, as the writing group represents a small sample, though with specific topic expertise. Future updates might reevaluate point-of-care testing, the role of endoscopy (including capsule endoscopy), and MRI as these modalities become more widely available.

We considered the possibility that repeat CTAP or addition of ultrasound to CTAP, even with negative test results, might benefit patients and physicians by reaffirming the absence of a serious condition. However, prior research has not validated the effectiveness of "reassurance testing" in the presence of low-probability of serious disease. A systematic review (nine studies, 3828 patients) concluded that reassurance testing was not associated with statistically significant effects on patients' illness worry (OR 0.87, 95%CI 0.55 to 1.39), nonspecific anxiety (SMD 0.06, −0.16 to 0.28), or symptom persistence (OR 0.99, 0.85 to 1.15) in short (<3 months) or long (>3 months) time periods.[198] Of note, none of the included studies were conducted in ED settings with common ED complaints, where outcomes may be different than in primary care settings. It is unknown whether these results extrapolate to the ED setting and whether testing for low-risk clinical situations in the ED may change patient clinical outcomes, concerns, or expectations or may be needlessly wasteful. These gaps in patient expectations, concerns/anxieties, risk stratification for recurrent abdominal pain, and shared decision-making processes should be addressed in prospective ED research.

GRACE-2 writing team composition

The GRACE-2 writing team was selected for topic expertise related to abdominal pain, diagnostic imaging, analgesia, mental health, and methodology. Secondarily, efforts were made to include diverse representation. The final writing team lacked significant racial diversity and consisted of academic emergency physicians primarily from large suburban or urban centers (without rural or critical access practitioners). In the future, writing team composition might include a primary goal of diversity across many different factors including gender, race, ethnicity, sexual orientation, academic or community practice

settings, and geography. Early attention to diversity could improve the applicability to clinicians caring for diverse patient populations in diverse settings, including international care. While the GRACE-2 writing team did include a psychiatrist, our panel did not include primary care, experts in medical legal considerations, health economists, payers, insurers, surgeons, gastroenterologists, obstetrician-gynecologists, or radiologists who might participate in the care of patients with recurrent abdominal pain. Future GRACE writing teams might prospectively add specialists with expertise pertinent to guideline and PICO topics. Regarding representation in the writing team, a patient representative was included and participated in all phases of the guideline development, but physicians comprised the majority of the writing team, meaning that topics of importance to physicians were favored in the selection process, although the patient representative could influence discussion before voting occurred. In accordance with GRIPP-2 reporting standards, the patient representative was engaged in setting the aims of the guideline project, providing insights on values and preferences for clinical outcomes, reviewing and interpreting evidence reviews in PICO subgroups, and contextualizing results during EtD discussions based on lived experiences.[199]

Future GRACE cycles might consider broadening patient representation through various means, such as increasing patient membership on the committee or implementing representative surveys through SAEM to assess patient perspectives. Addition of other multidisciplinary writing team members to represent stakeholders such as physician assistants, nurses, social workers, and family members of patients could be considered.

Assumed values and preferences

The GRACE-2 writing team attempted to incorporate values such as diagnostic accuracy, pain control, risks of opioid medications, costs, ED LOS, adverse side effects such as radiation and iodinated contrast exposure, and health system–level concerns such as bed availability and impact on other patients. Nonetheless, shared decision making with individual patients is necessary to target treatment plans to the priorities of the patient at hand. Patients and practitioners may vary in their values and preferences with regard to these outcomes. Given the lack of any direct evidence to support the GRACE-2 recommendations, patient and physician preferences should be strongly considered. The guideline should also be applied in the context of local policies and resources, such as the availability of CT, ultrasound, hospital capacity, outpatient follow-up services, and mental health resources.

Plans for updating these guidelines

We suggest that these guidelines should be updated at an interval of approximately 5 years or when significant new evidence emerges for the management of low-risk recurrent undifferentiated abdominal pain. Given the absence of direct evidence identified during our review, new research targeting the specific population using rigorous methodology might substantially change recommendations.

Monitoring criteria for audit/feedback of implementation

Given that the GRACE-2 recommendations are conditional and supported only by low-level indirect evidence, an audit mechanism may be inappropriate, other than to gather new research data to support future guidelines. The GRACE-2 writing team does note that our review identified disparities in care including intensity of diagnostic resources and analgesia. The writing team discussed the possibility of implementing audit mechanisms to reduce these disparities. However, there may be medically indicated reasons for differences in care, such as avoidance of opioid medications in older adults or avoidance of ionizing radiation in children and young adults. Given the unknowns about the appropriateness of such differences, and recognizing that unequal care may not always represent harmful discrimination, audit mechanisms to evaluate disparities should be used with caution to identify areas for future research and to generate hypotheses, not to judge the quality of care.

CONCLUSIONS

No direct evidence exists to direct the care of patients with low-risk recurrent undifferentiated abdominal pain in the ED. Improved definitions are required to better define this population, and clinically relevant outcomes of interest should be described and studied with rigorous research methodology to inform future clinical guidelines.

CONFLICT OF INTEREST

All group members disclosed conflicts of interest using SAEM standard methods. No member of the group disclosed a significant conflict requiring management. C.R.C. and A.M.M. are members of the SAEM Board of Directors.

AUTHOR CONTRIBUTIONS

All authors participated in the writing and review of this manuscript.

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REFERENCES

1. *NAMCS and NHAMCS web tables: NHAMCS – emergency department summary tables*. National Center for Health Statistics. 2021. Accessed September 21, 2021. https://www.cdc.gov/nchs/ahcd/web_tables.htm
2. *National Hospital Ambulatory Medical Care Survey: 2018 emergency department summary tables*. Centers for Disease Control and Prevention National Center for Health Statistics. 2018. Accessed July 28, 2021. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2018-ed-web-tables-508.pdf
3. Meltzer AC, Pines JM, Richards LM, Mullins P, Mazer-Amirshahi M. US emergency department visits for adults with abdominal and pelvic pain (2007–13): trends in demographics, resource utilization and medication usage. *Am J Emerg Med*. 2017;35:1966-1969.
4. Kocher KE, Meurer WJ, Fazel R, Scott PA, Krumholz HM, Nallamothu BK. National trends in use of computed tomography in the emergency department. *Ann Emerg Med*. 2011;58:452-462.
5. *National Hospital Ambulatory Medical Care Survey: 2017 emergency department summary tables*. National Center for Health Statistics. 2017. Accessed September 21, 2021. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf
6. Larson DB, Johnson LW, Schnell BM, Salisbury SR, Forman HP. National trends in CT use in the emergency department: 1995–2007. *Radiology*. 2011;258:164-173.
7. Pines JM. Trends in the rates of radiography use and important diagnoses in emergency department patients with abdominal pain. *Med Care*. 2009;47:782-786.
8. Jiang HJ, Weiss AJ, Barrett ML. *Characteristics of Emergency Department Visits for Super-Utilizers by Payer, 2014: Statistical Brief #221*. Agency for Healthcare Research and Quality; 2017.
9. Berrington de Gonzalez A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med*. 2009;169:2071-2077.
10. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med*. 2009;169:2078-2086.
11. Takakuwa KM, Estepa AT, Shofer FS. Knowledge and attitudes of emergency department patients regarding radiation risk of CT: effects of age, sex, race, education, insurance, body mass index, pain, and seriousness of illness. *AJR Am J Roentgenol*. 2010;195:1151-1158.
12. Tonolini M, Valconi E, Vanzulli A, Bianco R. Radiation overexposure from repeated CT scans in young adults with acute abdominal pain. *Emerg Radiol*. 2018;25:21-27.
13. Griffey RT, Sodickson A. Cumulative radiation exposure and cancer risk estimates in emergency department patients undergoing repeat or multiple CT. *AJR Am J Roentgenol*. 2009;192:887-892.
14. Thompson RJ, Wojcik SM, Grant WD, Ko PY. Incidental findings on CT scans in the emergency department. *Emerg Med Int*. 2011;2011:624847.
15. Daniels J, Griffiths M, Fisher E. Assessment and management of recurrent abdominal pain in the emergency department. *Emerg Med J*. 2020;37:515-521.
16. Axeen S, Seabury SA, Menchine M. Emergency department contribution to the prescription opioid epidemic. *Ann Emerg Med*. 2018;71:659-667.e3.
17. Barnett ML, Olenski AR, Jena AB. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med*. 2017;376:663-673.
18. Beaudoin FL, Straube S, Lopez J, Mello MJ, Baird J. Prescription opioid misuse among ED patients discharged with opioids. *Am J Emerg Med*. 2014;32:580-585.
19. Borgundvaag B, McLeod S, Khuu W, Varner C, Tadrous M, Gomes T. Opioid prescribing and adverse events in opioid-naive patients treated by emergency physicians versus family physicians: a population-based cohort study. *CMAJ Open*. 2018;6:E110-E117.
20. Butler MM, Ancona RM, Beauchamp GA, et al. Emergency department prescription opioids as an initial exposure preceding addiction. *Ann Emerg Med*. 2016;68:202-208.
21. Daoust R, Paquet J, Cournoyer A, et al. Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study. *BMJ Open*. 2018;8:e022649.
22. Daoust R, Paquet J, Gosselin S, et al. Opioid use and misuse three months after emergency department visit for acute pain. *Acad Emerg Med*. 2019;26:847-855.
23. Duncan RW, Smith KL, Maguire M, Stader DE 3rd. Alternatives to opioids for pain management in the emergency department decreases opioid usage and maintains patient satisfaction. *Am J Emerg Med*. 2019;37:38-44.
24. Hatten BW, Cantrill SV, Dubin JS, et al. Clinical policy: critical issues related to opioids in adult patients presenting to the emergency department. *Ann Emerg Med*. 2020;76:e13-e39.
25. Hoppe JA, Kim H, Heard K. Association of emergency department opioid initiation with recurrent opioid use. *Ann Emerg Med*. 2015;65:493-499.e4.
26. Kyriacou DN. Opioid vs nonopioid acute pain management in the emergency department. *JAMA*. 2017;318:1655-1656.
27. Lynch MJ, Yealy DM. Looking ahead: the role of emergency physicians in the opioid epidemic. *Ann Emerg Med*. 2018;71:676-678.
28. Meisel ZF, Lupulescu-Mann N, Charlesworth CJ, Kim H, Sun BC. Conversion to persistent or high-risk opioid use after a new prescription from the emergency department: evidence from Washington Medicaid beneficiaries. *Ann Emerg Med*. 2019;74:611-621.
29. Poon SJ, Greenwood-Ericksen MB. The opioid prescription epidemic and the role of emergency medicine. *Ann Emerg Med*. 2014;64:490-495.
30. Upadhye S, Worster A, Valani R. Relevance of opioid guidelines in the emergency room (ROGER). *Am J Emerg Med*. 2019;37:538-539.
31. Broder J, Bowen J, Lohr J, Babcock A, Yoon J. Cumulative CT exposures in emergency department patients evaluated for suspected renal colic. *J Emerg Med*. 2007;33:161-168.
32. Tzou DT, Zetumer S, Usawachintachit M, et al. Computed tomography radiation exposure among referred kidney stone patients: results from the Registry for Stones of the Kidney and Ureter. *J Endourol*. 2019;33:619-624.
33. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology*. 2009;251:175-184.
34. Division on Earth and Life Sciences; Commission on Life Sciences. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII, Phase I, Letter Report (1998)*. National Academy of Sciences; 1998.
35. National Research Council; Division on Earth and Life Studies; Board on Radiation Effects Research; Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. National Academy of Sciences; 2006.
36. Ijaz H, Wong C, Weaver J, et al. Exploring the attitudes & practices of shared decision-making for CT scan use in emergency department patients with abdominal pain. *Am J Emerg Med*. 2018;36:2263-2267.
37. Broder JS, Bhat R, Boyd JP, et al. Who explicitly requests the ordering of computed tomography for emergency department patients? A multicenter prospective study. *Emerg Radiol*. 2016;23:221-227.
38. Moore CL, Carpenter CR, Heilbrun ME, et al. Imaging in suspected renal colic: systematic review of the literature and multispecialty consensus. *Ann Emerg Med*. 2019;74:391-399.

39. Wagner JM, McKinney WP, Carpenter JL. Does this patient have appendicitis? *JAMA*. 1996;276:1589-1594.
40. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? *JAMA*. 2003;289:80-86.
41. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: a systematic review and meta-analysis. *Acad Emerg Med*. 2013;20:1087-1100.
42. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? *JAMA*. 2006;295:1566-1576.
43. Lederle FA, Simel DL. The rational clinical examination. Does this patient have abdominal aortic aneurysm? *JAMA*. 1999;281:77-82.
44. Taylor MR, Lalani N. Adult small bowel obstruction. *Acad Emerg Med*. 2013;20:528-544.
45. Houry D, Abbott JT. Ovarian torsion: a fifteen-year review. *Ann Emerg Med*. 2001;38:156-159.
46. Hahn B, Akita A, Rankin L, et al. Incidence and pathology of repeat CT abdomen and pelvis in an adult emergency department population. *Clin Imaging*. 2016;40:861-864.
47. Lee LK, Reisner AT, Binder WD, et al. Repeat CT performed within one month of CT conducted in the emergency department for abdominal pain: a secondary analysis of data from a prospective multicenter study. *AJR Am J Roentgenol*. 2019;212:382-385.
48. Nojkov B, Duffy MC, Cappell MS. Utility of repeated abdominal CT scans after prior negative CT scans in patients presenting to ER with nontraumatic abdominal pain. *Dig Dis Sci*. 2013;58:1074-1083.
49. Coursey CA, Casalino DD, Remer EM, et al. ACR Appropriateness Criteria® acute onset flank pain--suspicion of stone disease. *Ultrasound Q*. 2012;28:227-233.
50. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol*. 2014;192:316-324.
51. Expert Panel on Gastrointestinal Imaging; Porter KK, Zaheer A, et al. ACR Appropriateness Criteria® acute pancreatitis. *J Am Coll Radiol*. 2019;16:S316–S330.
52. Kim DH, Chang KJ, Fowler KJ, et al. ACR Appropriateness Criteria® Crohn disease. *J Am Coll Radiol*. 2020;17:S81-S99.
53. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113:481-517.
54. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108:18–37; quiz 38.
55. Diercks DB, Mehrotra A, Nazarian DJ, et al. Clinical policy: critical issues in the evaluation of adult patients presenting to the emergency department with acute blunt abdominal trauma. *Ann Emerg Med*. 2011;57:387-404.
56. Howell JM, Eddy OL, Lukens TW, Thiessen EW, Weingart SD. Clinical policy: critical issues in the evaluation and management of emergency department patients with suspected appendicitis. *Ann Emerg Med*. 2010;55:71-116.
57. Garcia EM, Camacho MA, Karolyi DR, et al. ACR Appropriateness Criteria® right lower quadrant pain–suspected appendicitis. *J Am Coll Radiol*. 2018;15:S373-S387.
58. McCaul M, Clarke M, Bruijns SR, et al. Global emergency care clinical practice guidelines: a landscape analysis. *Afr J Emerg Med*. 2018;8:158-163.
59. Guyatt GH, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383-394.
60. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol*. 2011;64:1283-1293.
61. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence–indirectness. *J Clin Epidemiol*. 2011;64:1303-1310.
62. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. *J Clin Epidemiol*. 2011;64:1294-1302.
63. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence–publication bias. *J Clin Epidemiol*. 2011;64:1277-1282.
64. Murad MH, Chang SM, Fiordalisi CV, et al. Improving the utility of evidence synthesis for decision makers in the face of insufficient evidence. *J Clin Epidemiol*. 2021;135:170-175.
65. Mustafa RA, Cuello-Garcia CA, Bhatt M, et al. GRADE notes: how to use GRADE when there is "no" evidence? A case study of the expert evidence approach. *J Clin Epidemiol*. 2021;137:231-235.
66. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.
67. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. *J Clin Epidemiol*. 2020;122:129-141.
68. "Guidelines for Reasonable and Appropriate Care in the Emergency Department" Society for Academic Emergency Medicine. https://www.saem.org/publications/academic-emergency-medicine/grace. 5 May 2022.
69. Palsson OS, Whitehead WE, van Tilburg MA, et al. Development and validation of the Rome IV diagnostic questionnaire for adults. *Gastroenterology*. 2016;150:1481-1491.
70. Chronic pelvic pain: ACOG practice bulletin, number 218. *Obstet Gynecol*. 2020;135:e98-e109.
71. Expert Panel on Gastrointestinal I, Scheirey CD, Fowler KJ, et al. ACR Appropriateness Criteria® acute nonlocalized abdominal pain. *J Am Coll Radiol*. 2018;15:S217-S231.
72. Collin J, Araujo L, Walton J. How fast do very small abdominal aortic aneurysms grow? *Eur J Vasc Surg*. 1989;3:15-17.
73. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. *Ann Surg*. 1995;221:278-281.
74. Michael H, Gordon J, Chan SB. Impact of electronic medical record system on CT scan use in recurrent abdominal pain patients. *Ann Emerg Med*. 2016;68:S8.
75. Shah PK, Yan PL, Dauw CA, et al. Emergency department switching and duplicate computed tomography scans in patients with kidney stones. *Urology*. 2018;114:41-44.
76. Mills AM, Dean AJ, Hollander JE, Chen EH. Abdominal pain: a survey of clinically important outcomes for future research. *CJEM*. 2010;12:485-490.
77. Meltzer AC, Bregman B, Blanchard J. Depression is associated with repeat emergency department visits in patients with nonspecific abdominal pain. *West J Emerg Med*. 2014;15:325-328.
78. Van Winkle PJ, Ghobadi A, Chen Q, Menchine M, Sharp AL. Association of age and opioid use for adolescents and young adults in community emergency departments. *Am J Emerg Med*. 2019;37:1397-1403.
79. Sin B, Sikorska G, YauLin J, Bonitto RA, Motov SM. Comparing nonopioids versus opioids for acute pain in the emergency department: a literature review. *Am J Ther*. 2019;28:e52-e86.
80. Samuels EA, D'Onofrio G, Huntley K, et al. A quality framework for emergency department treatment of opioid use disorder. *Ann Emerg Med*. 2019;73:237-247.
81. Smith RJ, Rhodes K, Paciotti B, Kelly S, Perrone J, Meisel ZF. Patient perspectives of acute pain management in the era of the opioid epidemic. *Ann Emerg Med*. 2015;66:246-252.e1.
82. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA*. 2008;299:70-78.
83. Ackerman AL, O'Connor PG, Doyle DL, et al. Association of an opioid standard of practice intervention with intravenous opioid exposure in hospitalized patients. *JAMA Intern Med*. 2018;178:759-763.

84. LaPietra AM, Motov S. A country in crisis: opioid sparing solutions for acute pain management. *Mo Med*. 2019;116:140-145.
85. D'Onofrio G, McCormack RP, Hawk K. Emergency departments – a 24/7/365 option for combating the opioid crisis. *N Engl J Med*. 2018;379:2487-2490.
86. Conrardy M, Lank P, Cameron KA, et al. Emergency department patient perspectives on the risk of addiction to prescription opioids. *Pain Med*. 2016;17:114-121.
87. Meltzer AC, Winter LE, Kulie P, et al. Treating gastritis, peptic ulcer disease, and dyspepsia in the emergency department: the feasibility and patient-reported outcomes of testing and treating for Helicobacter pylori infection. *Ann Emerg Med*. 2015;66:131-139.
88. Meltzer AC, Pierce R, Cummings DA, et al. Rapid (13)C urea breath test to identify helicobacter pylori infection in emergency department patients with upper abdominal pain. *West J Emerg Med*. 2013;14:278-282.
89. Ginde AA, Foianini A, Renner DM, Valley M, Camargo CA Jr. Availability and quality of computed tomography and magnetic resonance imaging equipment in U.S. emergency departments. *Acad Emerg Med*. 2008;15:780-783.
90. Gallagher PE, Allen TY, Wyer PC. How to find evidence when you need it, part 2: a clinician's guide to MEDLINE: the basics. *Ann Emerg Med*. 2002;39:436-440.
91. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64:395-400.
92. Asch DA, Patton JP, Hershey JC. Knowing for the sake of knowing: the value of prognostic information. *Med Decis Making*. 1990;10:47-57.
93. Croft P, Altman DG, Deeks JJ, et al. The science of clinical practice: disease diagnosis or patient prognosis? Evidence about "what is likely to happen" should shape clinical practice. *BMC Med*. 2015;13:20.
94. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol*. 2011;64:407-415.
95. Carpenter CR, Griffey RT, Mills A, et al. Repeat computed tomography in recurrent abdominal pain: an evidence synthesis for guidelines for reasonable and appropriate care in the emergency department. *Acad Emerg Med*. Forthcoming 2021. doi:10.1111/acem.14427
96. Asrani AV, Johnson JOF, Novelline RA. Benefit of follow-up CT in emergency department patients with persistent non-traumatic abdominal pain. *Emerg Radiol*. 2011;18:5-9.
97. Cross R, Bhat R, Li Y, Plankey M, Maloy K. Emergency department computed tomography use for non-traumatic abdominal pain: minimal variability. *West J Emerg Med*. 2018;19:782-796.
98. Goldstone A, Bushnell A. Does diagnosis change as a result of repeat renal colic computed tomography scan in patients with a history of kidney stones? *Am J Emerg Med*. 2010;28:291-295.
99. Ip IK, Mortele KJ, Prevedello LM, Khorasani R. Repeat abdominal imaging examinations in a tertiary care hospital. *Am J Med*. 2012;125:155-161.
100. Lamoureux C, Weber S, Hanna T, Grabiel AJ, Clark RH. Effect of intravenous contrast for CT abdomen and pelvis on detection of urgent and non-urgent pathology: can repeat CT within 72 hours be avoided? *Emerg Radiol*. 2019;26:601-608.
101. Seth N, Lu A, Chen HW, Hsieh M, Bielefeldt K. The utility of CT imaging in abdominal pain patients presenting to the ED: a tertiary-care center experience. *Am J Gastroenterol*. 2016;111:S404-S405.
102. Zwank MD, Mayeux GP, MacDonald J. Repeat abdominal computed tomography influences emergency department patient diagnosis and disposition. *Ann Emerg Med*. 2013;62:S40.
103. Daniels L, Ünlü Ç, de Korte N, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. *Br J Surg*. 2017;104:52-61.
104. Capuzzo M, Valpondi V, Sgarbi A, et al. Validation of severity scoring systems SAPS II and APACHE II in a single-center population. *Intensive Care Med*. 2000;26:1779-1785.
105. Baumann BM, Chen EH, Mills AM, et al. Patient perceptions of computed tomographic imaging and their understanding of radiation risk and exposure. *Ann Emerg Med*. 2011;58:1-7.e2.
106. Carpenter CR, Raja AS, Brown MD. Overtesting and the downstream consequences of overtreatment: implications of "preventing overdiagnosis" for emergency medicine. *Acad Emerg Med*. 2015;22:1484-1492.
107. How much does a CT scan cost? New Choice Health, Inc. 2021. Accessed September 1, 2021. https://www.newchoicehealth.com/ct-scan/cost
108. Wang DC, Parry CR, Feldman M, Tomlinson G, Sarrazin J, Glanc P. Acute abdomen in the emergency department: is CT a time-limiting factor? *AJR Am J Roentgenol*. 2015;205:1222-1229.
109. Kocher KE, Meurer WJ, Desmond JS, Nallamothu BK. Effect of testing and treatment on emergency department length of stay using a national database. *Acad Emerg Med*. 2012;19:525-534.
110. Li CJ, Syue YJ, Lin YR, et al. Influence of CT utilisation on patient flow in the emergency department: a retrospective 1-year cohort study. *BMJ Open*. 2016;6:e010815.
111. Rosen MP, Sands DZ, Longmaid HE 3rd, Reynolds KF, Wagner M, Raptopoulos V. Impact of abdominal CT on the management of patients presenting to the emergency department with acute abdominal pain. *AJR Am J Roentgenol*. 2000;174:1391-1396.
112. Rosen MP, Siewert B, Sands DZ, Bromberg R, Edlow J, Raptopoulos V. Value of abdominal CT in the emergency department for patients with abdominal pain. *Eur Radiol*. 2003;13:418-424.
113. Ng CS, Watson CJ, Palmer CR, et al. Evaluation of early abdominopelvic computed tomography in patients with acute abdominal pain of unknown cause: prospective randomised study. *BMJ*. 2002;325:1387.
114. Sinert R, Brandler E, Subramanian RA, Miller AC. Does the current definition of contrast-induced acute kidney injury reflect a true clinical entity? *Acad Emerg Med*. 2012;19:1261-1267.
115. Sinert R, Brandler E. Contrast-induced acute kidney injury: time for a step backward. *Acad Emerg Med*. 2014;21:701-703.
116. Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute kidney injury after computed tomography: a meta-analysis. *Ann Emerg Med*. 2018;71:44-53.e4.
117. Hinson JS, Ehmann MR, Fine DM, et al. Risk of acute kidney injury after intravenous contrast media administration. *Ann Emerg Med*. 2017;69:577-586.e4.
118. *Manual on Contrast Media*. American College of Radiology; 2021.
119. Ashurst JV, Cherney AR, Evans EM, et al. Research priorities for the influence of gender on diagnostic imaging choices in the emergency department setting. *Acad Emerg Med*. 2014;21:1431-1437.
120. Roberts B, Courington R, VerHage E, Ward-Peterson M, Lozano J. The association between insurance status and diagnostic imaging for acute abdominal pain among emergency department patients in the United States, 2005–2014. *Curr Med Res Opin*. 2019;35:1365-1370.
121. Shan A, Baumann G, Gholamrezanezhad A. Patient race/ethnicity and diagnostic imaging utilization in the emergency department: a systematic review. *J Am Coll Radiol*. 2021;18:795-808.
122. Mwinyogle AA, Bhatt A, Ogbuagu OU, Dhillon N, Sill A, Kowdley GC. Use of CT scans for abdominal pain in the ED: factors in choice. *Am Surg*. 2020;86:324-333.
123. Neumar RW, Blomkalns AL, Cairns CB, et al. Emergency medicine research: 2030 strategic goals. *Acad Emerg Med*. 2021;29:241-251.
124. Cherney AR, Marin JR, Brown J, et al. Funding research in emergency diagnostic imaging: summary of a panel discussion at the

2015 Academic Emergency Medicine Consensus Conference. *Acad Emerg Med*. 2015;22:1400-1405.
125. Gao Y, Lee K, Camacho M. Utility of pelvic ultrasound following negative abdominal and pelvic CT in the emergency room. *Clin Radiol*. 2013;68:e586-e592.
126. Hiatt KD, Ou JJ, Childs DD. Role of ultrasound and CT in the workup of right upper quadrant pain in adults in the emergency department: a retrospective review of more than 2800 cases. *AJR Am J Roentgenol*. 2020;214:1305-1310.
127. Harfouch N, Stern J, Chowdhary V, et al. Utility of ultrasound after a negative CT abdomen and pelvis in the emergency department. *Clin Imaging*. 2020;68:29-35.
128. Motuzko E, Solis M, Kazi M, Gefen R. Non-visualization of the ovary on CT or ultrasound in the ED setting: utility of immediate follow-up imaging. *Abdom Radiol (NY)*. 2018;43:2467-2473.
129. Murad MH, Mustafa RA, Schunemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22:85-87.
130. Jain A, Mehta N, Secko M, et al. History, physical examination, laboratory testing, and emergency department ultrasonography for the diagnosis of acute cholecystitis. *Acad Emerg Med*. 2017;24:281-297.
131. Wertz JR, Lopez JM, Olson D, Thompson WM. Comparing the diagnostic accuracy of ultrasound and CT in evaluating acute cholecystitis. *AJR Am J Roentgenol*. 2018;211:W92-W97.
132. Pines JM, Hollander JE, Isserman JA, et al. The association between physician risk tolerance and imaging use in abdominal pain. *Am J Emerg Med*. 2009;27:552-557.
133. Li D, Patlas M, McLean K, Duszak R. Relative diagnostic utility of radiologist-recommended abdominal ultrasound following emergency department abdominal and pelvic computed tomography. *Abdom Radiol (NY)*. 2018;43:3176-3183.
134. Adenaw N, Wen J, Pahwa AK, Sheth S, Johnson PT. Decreasing duplicative imaging: inpatient and emergency medicine abdominal ultrasound within 72 hours of abdominal CT. *J Am Coll Radiol*. 2020;17:590-596.
135. Specific ultrasound procedures and national cost averages. New Choice Health, Inc. 2021. Accessed September 27, 2021. https://www.newchoicehealth.com/ultrasound-cost
136. Sun BC, Hsia RY, Weiss RE, et al. Effect of emergency department crowding on outcomes of admitted patients. *Ann Emerg Med*. 2013;61:605-611.e6.
137. Berg LM, Ehrenberg A, Florin J, Ostergren J, Discacciati A, Goransson KE. Associations between crowding and ten-day mortality among patients allocated lower triage acuity levels without need of acute hospital care on departure from the emergency department. *Ann Emerg Med*. 2019;74:345-356.
138. Swenson DW, Lourenco AP, Beaudoin FL, Grand DJ, Killelea AG, McGregor AJ. Ovarian torsion: case-control study comparing the sensitivity and specificity of ultrasonography and computed tomography for diagnosis in the emergency department. *Eur J Radiol*. 2014;83:733-738.
139. Fagenholz PJ, Fuentes E, Kaafarani H, et al. Computed tomography is more sensitive than ultrasound for the diagnosis of acute cholecystitis. *Surg Infect (Larchmt)*. 2015;16:509-512.
140. Wang AJ, Wang TE, Lin CC, Lin SC, Shih SC. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. *World J Gastroenterol*. 2003;9:2821-2823.
141. Abbas SH, Ghazanfar MA, Gordon-Weeks AN, Reddy SR, Soonawalla Z, Silva MA. Acalculous cholecystitis: is an elective interval cholecystectomy necessary. *Dig Surg*. 2018;35:171-176.
142. Oliveira J e Silva L, Prakken SD, Meltzer AC, et al. Depression and anxiety screening in emergency department patients with recurrent abdominal pain: an evidence synthesis for a clinical practice guideline. *Acad Emerg Med*. Forthcoming 2022. doi:10.1111/acem.14394
143. Lexne E, Brudin L, Marteinsdottir I, Strain JJ, Nylander PO. Psychiatric symptoms among patients with acute abdominal pain. *Scand J Gastroenterol*. 2020;55:769-776.
144. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(P1393–1407):E5.
145. Hu Z, Li M, Yao L, et al. The level and prevalence of depression and anxiety among patients with different subtypes of irritable bowel syndrome: a network meta-analysis. *BMC Gastroenterol*. 2021;21:23.
146. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. *Sci Rep*. 2018;8:2861.
147. Andrade L, Caraveo-Anduaga JJ, Berglund P, et al. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) surveys. *Int J Methods Psychiatr Res*. 2003;12:3-21.
148. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75:336-346.
149. Levis B, Sun Y, He C, et al. Accuracy of the PHQ-2 alone and in combination with the PHQ-9 for screening to detect major depression: systematic review and meta-analysis. *JAMA*. 2020;323:2290-2300.
150. Herr NR, Williams JW Jr, Benjamin S, McDuffie J. Does this patient have generalized anxiety or panic disorder? The Rational Clinical Examination systematic review. *JAMA*. 2014;312:78-84.
151. Schriger DL, Gibbons PS, Langone CA, Lee S, Altshuler LL. Enabling the diagnosis of occult psychiatric illness in the emergency department: a randomized, controlled trial of the computerized, self-administered PRIME-MD diagnostic system. *Ann Emerg Med*. 2001;37:132-140.
152. Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ*. 2008;178:997-1003.
153. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002;68:167-181.
154. Tyrer P, Seivewright H, Johnson T. The Nottingham Study of Neurotic Disorder: predictors of 12-year outcome of dysthymic, panic and generalized anxiety disorder. *Psychol Med*. 2004;34:1385-1394.
155. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry*. 2005;58:175-189.
156. Hawton K, van Heeringen K. Suicide. *Lancet*. 2009;373:1372-1381.
157. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry*. 2014;171:453-462.
158. IsHak WW, Mirocha J, James D, et al. Quality of life in major depressive disorder before/after multiple steps of treatment and one-year follow-up. *Acta Psychiatr Scand*. 2015;131:51-60.
159. McGuire TG, Miranda J. New evidence regarding racial and ethnic disparities in mental health: policy implications. *Health Aff (Millwood)*. 2008;27:393-403.
160. Baillargeon J, Thomas CR, Williams B, et al. Medical emergency department utilization patterns among uninsured patients with psychiatric disorders. *Psychiatr Serv*. 2008;59:808-811.
161. Kane B, Carpenter C. Cognition and decision making. In: Fondahn E, Lane M, Vannucci A, eds. *Washington manual of patient safety and quality*. Wolters Kluwer; 2016.
162. Abar B, Hong S, Aaserude E, Holub A, DeRienzo V. Access to care and depression among emergency department patients. *J Emerg Med*. 2017;53:30-37.
163. Vu F, Daeppen JB, Hugli O, et al. Screening of mental health and substance users in frequent users of a general Swiss emergency department. *BMC Emerg Med*. 2015;15:27.

164. Boudreaux ED, Clark S, Camargo CA Jr. Mood disorder screening among adult emergency department patients: a multicenter study of prevalence, associations and interest in treatment. *Gen Hosp Psychiatry*. 2008;30:4-13.
165. Cook TM, Wang J. Descriptive epidemiology of stigma against depression in a general population sample in Alberta. *BMC Psychiatry*. 2010;10:29.
166. Blum GB, Bins RB, Rabelo-da-Ponte FD, Passos IC. Stigmatizing attitudes toward psychiatric disorders: a cross-sectional population-based survey. *J Psychiatr Res*. 2021;139:179-184.
167. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. *Cochrane Database Syst Rev*. 2004;(1):CD004137. doi:10.1002/14651858.CD004137.pub2/full
168. Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. *Cochrane Database Syst Rev*. 2015;(6):CD006027. doi:10.1002/14651858.CD006027.pub2/full
169. Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. *Eur Urol*. 2018;73:583-595.
170. Remington-Hobbs J, Petts G, Harris T. Emergency department management of undifferentiated abdominal pain with hyoscine butylbromide and paracetamol: a randomised control trial. *Emerg Med J*. 2012;29:989-994.
171. Fraquelli M, Casazza G, Conte D, Colli A. Non-steroid anti-inflammatory drugs for biliary colic. *Cochrane Database Syst Rev*. 2016;9:CD006390.
172. Farnia MR, Babaei R, Shirani F, et al. Analgesic effect of paracetamol combined with low-dose morphine versus morphine alone on patients with biliary colic: a double blind, randomized controlled trial. *World J Emerg Med*. 2016;7:25-29.
173. Chinn E, Friedman BW, Naeem F, et al. Randomized trial of intravenous lidocaine versus hydromorphone for acute abdominal pain in the emergency department. *Ann Emerg Med*. 2019;74:233-240.
174. Oguzturk H, Ozgur D, Turtay MG, et al. Tramadol or paracetamol do not effect the diagnostic accuracy of acute abdominal pain with significant pain relief – a prospective, randomized, placebo controlled double blind study. *Eur Rev Med Pharmacol Sci*. 2012;16:1983-1988.
175. Barnaby DP, Chertoff AE, Restivo AJ, et al. Randomized controlled trial of intravenous acetaminophen versus intravenous hydromorphone for the treatment of acute pain in the emergency department. *Ann Emerg Med*. 2019;73:133-140.
176. Jan AL, Aldridge ES, Rogers IR, Visser EJ, Bulsara MK, Niemtzow RC. Does ear acupuncture have a role for pain relief in the emergency setting? A systematic review and meta-analysis. *Med Acupunct*. 2017;29:276-289.
177. Jan AL, Aldridge ES, Rogers IR, Visser EJ, Bulsara MK, Niemtzow RC. Review article: does acupuncture have a role in providing analgesia in the emergency setting? A systematic review and meta-analysis. *Emerg Med Australas*. 2017;29:490-498.
178. Zhang AL, Parker SJ, Smit de V, Taylor DM, Xue CC. Acupuncture and standard emergency department care for pain and/or nausea and its impact on emergency care delivery: a feasibility study. *Acupunct Med*. 2014;32:250-256.
179. Reinstein AS, Erickson LO, Griffin KH, et al. Acceptability, adaptation, and clinical outcomes of acupuncture provided in the emergency department: a retrospective pilot study. *Pain Med*. 2017;18:169-178.
180. Kaynar M, Koyuncu F, Buldu I, et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. *Am J Emerg Med*. 2015;33:749-753.
181. Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health*. 2014;104:2023-2029.
182. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth*. 2018;120:1335-1344.
183. Jeffery MM, Hooten WM, Hess EP, et al. Opioid prescribing for opioid-naive patients in emergency departments and other settings: characteristics of prescriptions and association with long-term use. *Ann Emerg Med*. 2018;71:326-336.e19.
184. Dalgaard F, Mulder H, Wojdyla DM, et al. Patients with atrial fibrillation taking nonsteroidal anti-inflammatory drugs and oral anticoagulants in the ARISTOTLE trial. *Circulation*. 2020;141:10-20.
185. Kent AP, Brueckmann M, Fraessdorf M, et al. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;72:255-267.
186. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging Dis*. 2018;9:143-150.
187. Smith KA. Abdominal pain. In: Walls RM, Hockberger RS, Gausche-Hill M, eds. *Rosen's Emergency Medicine Concepts and Clinical Practice*. 9th ed. Elsevier; 2018:213-223.
188. Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. *National Center for Health Statistics*. 2021. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
189. ALARA – as low as reasonably achievable. Centers for Disease Control and Prevention. 2015. Accessed November 15, 2021. https://www.cdc.gov/nceh/radiation/alara.html#:~:text=The%20guiding%20principle%20of%20radiation,should%20try%20to%20avoid%20it
190. Allione A, Pivetta E, Pizzolato E, et al. Determinants of inappropriate acute pain management in old people unable to communicate verbally in the emergency department. *Turk J Emerg Med*. 2017;17:160-164.
191. Hwang U, Belland LK, Handel DA, et al. Is all pain is treated equally? A multicenter evaluation of acute pain care by age. *Pain*. 2014;155:2568-2574.
192. Chen EH, Shofer FS, Dean AJ, et al. Gender disparity in analgesic treatment of emergency department patients with acute abdominal pain. *Acad Emerg Med*. 2008;15:414-418.
193. Shabbir J, Ridgway PF, Lynch K, et al. Administration of analgesia for acute abdominal pain sufferers in the accident and emergency setting. *Eur J Emerg Med*. 2004;11:309-312.
194. Siddiqui A, Belland L, Rivera-Reyes L, et al. A multicenter evaluation of the impact of sex on abdominal and fracture pain care. *Med Care*. 2015;53:948-953.
195. Singhal A, Tien YY, Hsia RY. Racial–ethnic disparities in opioid prescriptions at emergency department visits for conditions commonly associated with prescription drug abuse. *PLoS ONE*. 2016;11:e0159224.
196. By the American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society. updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;2019(67):674-694.
197. Rolfe A, Burton C. Reassurance after diagnostic testing with a low pretest probability of serious disease: systematic review and meta-analysis. *JAMA Intern Med*. 2013;173:407-416.
198. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ*. 2017;358:j3453.
199. Levis B, Benedetti A, Thombs BD. DEPRESsion Screening Data (DEPRESSD) Collaboration. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ*. 2019;365:l1476.

200. Francisco MZ, Altmayer S, Verma N, et al. Appropriateness of computed tomography and ultrasound for abdominal complaints in the emergency department. *Curr Probl Diagn Radiol*. 2021;50:799-802.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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