Effective Health Care Program

Comparative Effectiveness Review
Number 110

Wireless Motility Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation:

A Comparative Effectiveness Review

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Wireless Motililty Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation: A Comparative Effectiveness Review

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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The Evidence-based Practice Center wish to thank the Key Informants, Technical Expert Panel, Peer Reviewers, Associate Editor, and Task Order Officer.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Wireless Motililty Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation: A Comparative Effectiveness Review

Structured Abstract

Objectives. To systematically review the evidence comparing wireless motility capsule (WMC) with other diagnostic tests used for the evaluation of gastroparesis and slow-transit constipation, in terms of diagnostic accuracy, accuracy of motility assessment, effect on treatment decisions, effect on patient-centered outcomes, harms, and effect on resource utilization.

Data sources. We searched Medline ® and Embase ® from inception through July 2012. Additionally, we scanned reference lists of relevant articles and queried experts.

Review methods. We included studies in any language that compared WMC with other diagnostic tests among patients with suspected gastroparesis or slow-transit constipation. Two reviewers independently assessed articles for eligibility, serially abstracted data from relevant articles, independently evaluated study quality, and graded the strength of the evidence (SOE). We summarized results qualitatively rather than quantitatively because of the heterogeneity of studies.

Results. We included 12 studies (18 publications). Seven studies evaluated diagnosis of gastric emptying delay; we found low SOE that WMC alone was comparable to scintigraphy for diagnostic accuracy, accuracy of motility assessment, effect on treatment decisions, and effect on resource utilization. Sensitivity of WMC compared with gastric scintigraphy ranged from 59 to 86 percent and specificity ranged from 64 to 81 percent. We found two studies evaluating WMC as an add-on to other testing. The SOE was low for diagnostic accuracy and for the accuracy of motility assessment by WMC in combination with other modalities. The addition of WMC increased diagnostic yield. Nine studies analyzed colon transit disorders and provided moderate SOE for diagnostic accuracy, accuracy of motility assessment, and harms. WMC was comparable to radiopaque markers (ROM), with concordance ranging between 64 percent and 87 percent. Few harms were reported. The evidence was insufficient to justify conclusions about effects of WMC on treatment decisions and resource utilization.

Conclusions. WMC is comparable in accuracy to current modalities in use for detection of slow-transit constipation and gastric emptying delay, and is therefore another viable diagnostic modality. Little data are available to determine the optimal timing of WMC for diagnostic algorithms.

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Executive Summary

Gastroparesis

Definition and Prevalence

Gastroparesis is a condition in which patients experience symptoms of delayed gastric emptying in the absence of an actual physical blockage.[1] The most common symptoms are nausea, vomiting, early satiety, bloating, abdominal pain, and postprandial fullness.[2] Assessing gastric emptying delay is essential to diagnosing gastroparesis. In clinical research, the definition of gastroparesis is delayed gastric emptying as detected by clinical testing and the presence of symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months. Using this definition, the cumulative incidence of gastroparesis is 4.8 percent in people with type 1 diabetes, 1.0 percent in people with type 2 diabetes, and 0.1 percent in people without diabetes, who may have idiopathic gastroparesis or other etiologies.[2] A 2007 community-based study estimated the prevalence of gastroparesis to be 9.6 per 100,000 for men and 37.8 per 100,000 for women.[2] Newer estimates of prevalence report a higher rate of 24.2 per 100,000 inhabitants. Some experts estimate that more than 1.5 to 3 million Americans may have gastroparesis.[3,4]

Etiology and Clinical Course

The etiologies of gastroparesis are most often idiopathic, diabetic, or postsurgical, but can also be autoimmune, paraneoplastic, or neurologic. The condition is generally assessed in the outpatient setting, but some patients become severely ill with intractable vomiting and dehydration and are hospitalized. Hospitalizations for gastroparesis increased by 158 percent between 1995 and 2004.[5] In individuals with diabetes and gastroparesis, digestion of food is unpredictable, and wild swings in blood glucose can increase morbidity and necessitate medical care.

Evaluation of Possible Gastroparesis

A standard assessment for patients with typical symptoms (e.g., nausea, vomiting, bloating, abdominal pain, early satiety) of gastroparesis starts in the office of a physician, who takes a careful medical history and performs a physical examination.[6] First, the physician must rule out mechanical or medication-related dysfunction. Medications that commonly cause gastric emptying delay are opiates or glucagon-like peptide agonists. Second, the physician needs to test for gastric emptying. Methods of testing include gastric emptying scintigraphy, antroduodenal manometry, and now wireless motility capsule (WMC) technology. Motility disorders are difficult to diagnose. Multiple contributing factors make pathophysiology more complex, and physicians can have difficulty gathering a unifying diagnosis from a single test. In addition, most of the available tests have some inconsistency in performance, which can make their interpretation difficult.

Gastric Scintigraphy

Gastric scintigraphy is the ingestion of a meal commonly standardized to toast, jam, water, and radiolabeled egg whites. The egg whites are visible as they pass through the gastrointestinal

tract during subsequent timed imaging, ideally 4 hours.[7,8] Clinicians withhold interfering medications, such as opiates, motility agents, and glucagon-like peptide agonists, for 5 to 7 days before scintigraphic testing. Full 4-hour testing is more commonly available at regional referral centers or tertiary care centers with established practices of motility specialists.[7] Generally, physicians diagnose delayed gastric emptying if less than 90 percent of the gastric content has emptied at 4 hours, meaning that the patient has retained more than 10 percent of the content.

Antroduodenal Manometry

Antroduodenal manometry can provide information about gastric physiology. A manometry catheter, inserted through the pyloric channel with endoscopic guidance and patient sedation, measures pressure. Antroduodenal manometry may help differentiate myopathic and neuropathic etiologies of symptoms. Myopathy is present if amplitude muscle pressure falls below 30 mmHg, and neuropathy is present if uncoordinated bursts of muscle activity occur.

WMC

The United States Food and Drug Administration (FDA) approved WMC for identifying motility disorders. This device is a portable, one-time use, ingestible capsule that, when swallowed, records and transmits data to a receiver as it travels through the gut. A single device can detect specific transit times in the stomach, small bowel, and colon in a single test. The capsule can measure pH, pressure, and temperature to track location, gastric contents, and expulsion time from different regions of the bowel. The American Neurogastroenterology and Motility Society (ANMS) recommends its use and the American College of Gastroenterology considers it a technology that has great promise and should be watched.[9]

The patient takes the pill after eating a standardized meal and wears a small monitor that makes telemetry recordings. The established cutoff point for gastric emptying time is 300 minutes.[10] Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass (requiring serial x rays to document passage or endoscopic or surgical removal, respectively). Another disadvantage is that it should not be used in patients with a possible stricture, altered anatomy, or severe pyloric stenosis.[11] Patients ideally should be able to tolerate not using proton pump inhibitors and histamine 2 blockers before testing.[11] Advantages include that it is wireless and painless and contains no radiation.[12,13]

Use of Gastric Emptying Testing To Guide Treatment

Effective gastric-emptying-delay testing guides physicians in their recommendations for nutrition, medication, and surgical therapies. Testing informs physicians about the length and severity of delay, and this information can guide changes in diet to accommodate better gastric emptying. Recommended changes in diet may include a lowfat diet, a low-residue diet (i.e., low fiber, easy to empty from the stomach), a liquid diet, or changing one's consumption pattern to multiple small meals per day. Testing can also inform physicians about the use of prokinetic medicines like metoclopramide or erythromycin, which are often used to treat gastroparesis. This is important because of the FDA black box warning about the side effects of using metoclopramide for more than 3 months. Both metoclopramide and erythromycin can cause profound tachyphylaxis, limiting any intended benefit. Similarly, domperidone (Motilium®) is not FDA-approved but is available in many countries outside the United States and is used in clinical care and research in the United States through an Investigational New Drug Application. Therefore, clear documentation of gastroparesis is important to physicians who are considering

using a prokinetic. Patients with severe symptoms and severe emptying delay despite dietary changes may need feeding tubes, such as jejunostomy or gastrojejunostomy tubes, that bypass the stomach entirely. As patients undergo consideration for compassionate use of gastric stimulation therapy, one of the eligibility criteria is the presence of gastric emptying delay on testing. Thus, accurate diagnosis of gastroparesis is integral to decisions about management.

Outcomes

Major outcomes of interest are assessment of motility and diagnosis of gastric emptying delay. Other outcomes include the ability of testing to influence treatment decisions (e.g., changes in medications, nutrition), or to affect patient-centered outcomes (e.g., symptom improvement, need for surgery, quality of life, patient satisfaction). It is important to consider potential harms of testing such as capsule retention, radiation exposure, and mortality. Clinicians and policymakers may also be interested in the effects on resource utilization, such as the need for additional tests, physician services, or hospitalizations.

Constipation

Definition and Prevalence

Constipation is common, occurring in 15 to 20 percent of the U.S. population.[11,14,15] Multiple professional societies define constipation (with slight variation) as fewer than two bowel movements per week or a decrease in a person's normal frequency of stools accompanied by straining, difficulty passing stool, or passage of hard solid stools.[11] Physicians must assess patients with symptoms of constipation via their medical history and a physical examination to exclude malignant or organic causes of constipation. Clinicians should ask about warning signs such as new onset of symptoms, obstructive symptoms, rectal bleeding, unintentional weight loss, or family history of early colon cancer. A rectal examination can help to delineate rectal function and tone and exclude a low rectal cancer. Clinicians should perform a colonoscopy on all patients over 50 who have never received a screening colonoscopy, and those who have fecal occult blood, iron deficiency anemia, or any other warning signs.[16] However, the yield of colonoscopy in patients with constipation with warning signs is low. Once a physician has eliminated all organic causes for constipation, a diagnosis of functional constipation is appropriate. Physicians do not need to test an individual less than 50 years old and without "red flag" symptoms in order to diagnose constipation if the patient meets the Rome III criteria.

The Rome III criteria define functional constipation as follows:[17]

1. Two or more of the following:
    a. Straining during at least 25 percent of defecations
    b. Lumpy or hard stools in at least 25 percent of defecations
    c. Sensation of incomplete evacuation for at least 25 percent of defecations
    d. Sensation of anorectal obstruction/blockage for at least 25 percent of defecations
    e. Manual maneuvers to facilitate at least 25 percent of defecations (e.g., digital evacuation, support of the pelvic floor)
    f. Fewer than three defecations per week
2. Loose stools rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

A patient must have two or more of the above criteria for the last 3 months, with symptom onset being at least 6 months prior to diagnosis.

Clinically, patients with slow-transit constipation, also known as colonic inertia, often have the most severe symptoms of those patients with constipation, with prolonged periods of time between bowel movements. Often, standard medical therapies have failed these patients. The definition of slow-transit constipation is retention of greater than six radiopaque markers after 5 days from ingestion.[11,18] The reported incidence of slow-transit constipation is 1 in 3,000 or 0.033 percent. Other studies list a prevalence of 0.17 percent.[19] The true incidence is likely unknown.

Etiology and Clinical Course

There are several types of chronic constipation including slow-transit, normal-transit, and dyssynergic defecation. There is also constipation-predominant irritable bowel syndrome.[11] Physicians should recommend lifestyle changes and medical management for all patients with symptoms of constipation. Lifestyle changes include drinking appropriate quantities of liquid, removing all possible offending medications, and eating the U.S. Department of Agriculture's recommended amount of vegetables, fruit, and fiber. Medical management includes avoiding constipating medications and initiating bulking agents (e.g., fiber supplements), stool softeners (docusate, mineral oil), osmotic and stimulant laxatives (e.g., lactulose, milk of magnesia, magnesium citrate, polyethylene glycol [Miralax®], PEG-3350, senna), or prokinetics (e.g., bisacodyl), and secretagogues/prokinetics (e.g., lubiprostone, linaclotide), or in other countries prucalopride (not yet FDA-approved), as indicated. Thus, the initial evaluation of constipation symptoms does not often involve colonic transit testing.

Evaluation of Possible Slow-Transit Constipation

For certain individuals with suspected slow-transit constipation, colon transit testing can provide valuable insight into the etiology of the constipation. Testing can explain why a patient fails basic therapy and can help identify or exclude patients as surgical candidates.[11] However, a single test may not reflect the full complexity of a patient's motility disturbances. For example, anorectal dysfunction can impact colonic transit, but must be assessed by anorectal manometry separate from other transit testing. Furthermore, most of the available tests have some inconsistency in performance, which makes their interpretation difficult in some cases. Transit disorders include slow colonic transit or colonic inertia, a hypomotile disorder of the colon where transit in the proximal colon is slow without evidence of retropulsion of the markers from the left colon and without evidence of anorectal dysfunction. Defecatory dysfunction (or functional outlet dysfunction) is the presence of uncoordinated motion of the anorectum muscles causing ineffective or weak expulsion of stool. Idiopathic megacolon (primary or secondary), a pathological enlargement of the colon, can also be present and may occur in conjunction with longstanding neurological diseases or Hirschsprung's disease, a failure of the development of the nerve cells within the colon wall.[20] The main diagnostic methods used to test for colonic motility are radiopaque marker (ROM) examination, colonic scintigraphy, colonic and anorectal manometry, and WMC testing.[21,22] The nonreference standard is ROM.

ROM

The nonreference standard of ROM testing (commonly known as Sitz Markers) defines slow-transit constipation.[21,22] In its simplest form, a patient ingests the ROMs on day zero and then

receives an x ray at day 5, using overpenetrated films (110 kiloelectron volts) in order to reduce x-ray exposure. Gastroenterologists no longer focus on the areas of colon that have the greatest delays, since studies have shown that this does not predict pathophysiology or treatment. The only exception to this statement is the patient who accumulates markers in the rectum and does not pass them; this would strongly suggest a defecation disorder. Marker retention identifies patients with slow transit.[11,18] One disadvantage to ROM testing is x-ray exposure. However, the test is valid and in practice since the late 1960s.[18]

Colonic Scintigraphy

Colon scintigraphy is rarely available outside of highly-specialized motility research centers. It follows an ingested radiolabeled meal or radiolabeled tracer from the upper to lower gastrointestinal tract. A disadvantage is that testing requires several days and entails radiation exposure. Studies have assessed the validity of colon scintigraphy relative to ROM.[23,24] The ANMS guidelines endorse colon scintigraphy as a potential test for evaluating colon transit.

WMC

WMC testing assesses colonic transit time by measuring the time between cecal entry and rectal exit. Cecal entry produces a sustained drop in pH of greater than 1 unit that occurs more than 30 minutes after gastric emptying. Rectal exit produces a large temperature reduction.[11] One disadvantage is that 5 percent of tests do not record cecal entry time data, thus limiting the diagnostic potential of the study.[18] Camilleri has reported the use of the combined small bowel and colon transit time to allow for interpretation of the tests that do not report cecal entry.[25] Other disadvantages are that clinicians must use radiographic imaging to identify capsule retention when it fails to pass spontaneously, and that the device can fail at a rate up to 3 percent according to some studies. In addition, prolonged colon transit time with this technology does not necessarily distinguish slow transit from defecatory dysfunction.

Use of Colon Transit Testing To Guide Treatment

Most patients with chronic constipation see symptom improvement with medical therapy and/or lifestyle changes. For some patients, all measures fail and physicians must use colon transit testing to better understand the motility disorders. Physicians use anorectal manometry to identify anorectal or outlet dysfunction, and treat with biofeedback therapy. Evidence of Hirschsprung's disease is an indication for surgical segmental resection. Megacolon requires medical therapy tailored to reducing gas formation, and reduction of fiber intake may paradoxically relieve symptoms. If these conservative measures fail, megacolon may require segmental or total colectomy. If testing confirms the presence of slow-transit constipation (colonic inertia) without the use of laxatives, then the next step in evaluation in some centers is transit testing with use of laxatives. Physicians should only consider surgery as a potential therapy after they have demonstrated colonic inertia.[26] Clear demonstration of severe total or segmental slow-transit constipation is an indication for colectomy; however, most clinicians reserve colectomy for patients with the most terminal or untreatable conditions.

Outcomes

A major outcome of interest to clinicians is the ability to characterize transit time and to diagnose slow-transit constipation. Other outcomes include the ability of testing to influence treatment decisions (e.g., change in medications, change in nutrition) or to affect patient-centered

outcomes (e.g., symptom improvement, need for surgery, quality of life, patient satisfaction). It is important to consider potential harms such as capsule retention, radiation exposure, and mortality. Clinicians and policymakers may also be interested in the effects on resource utilization such as the need for additional tests, physician services, and hospitalizations.

Scope of Review and Key Questions

Our objective was to summarize the evidence on how useful current testing modalities for gastric and colonic motility are for diagnosing disease. We sought to determine whether WMC testing is useful in conjunction with or instead of other testing modalities for diagnosing and managing motility disorders. We also sought to define the populations that would benefit most from motility testing, including WMC testing. We listed our Key Questions (KQs) below and displayed them in Figure A.

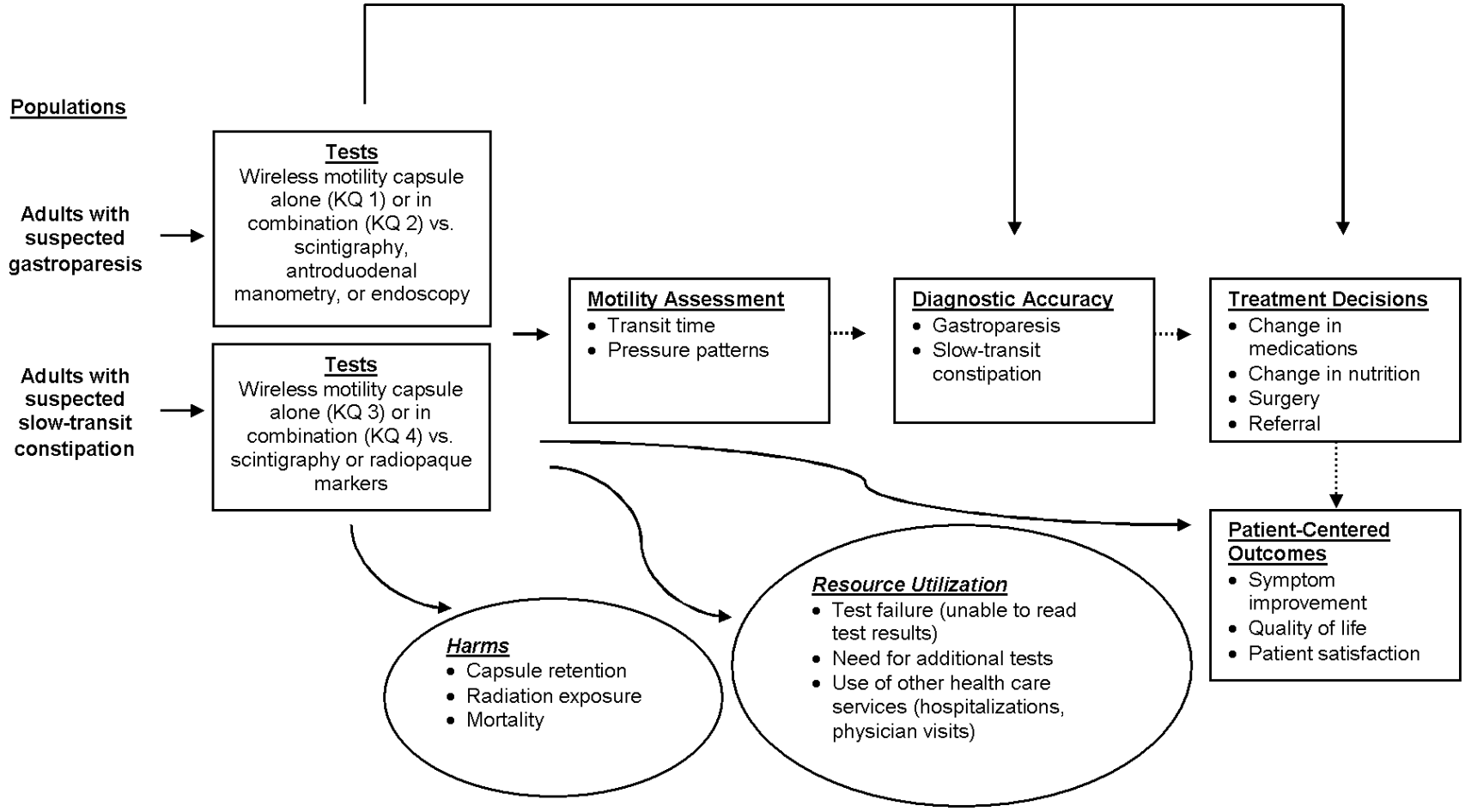
KQ 1. In the evaluation of gastric dysmotility, how does the WMC alone compare with gastric scintigraphy, antroduodenal manometry, and endoscopy, in terms of diagnostic accuracy of gastric emptying delay, accuracy of motility assessment, effect on treatment decisions,effect on patient-centered outcomes, harms, and effect on resource utilization?

KQ 2. When gastric scintigraphy, antroduodenal manometry, or endoscopy is used in the evaluation of gastric dysmotility, what is the incremental value of also using WMC, in terms of diagnostic accuracy of gastric emptying delay, accuracy of motility assessment, effect on treatment decisions, effect on patient-centered outcomes, harms, and effect on resource utilization?

KQ 3. In the evaluation of colonic dysmotility, how does WMC alone compare with ROM and scintigraphy in terms of diagnostic accuracy of slow-transit constipation, accuracy of motility assessment, effect on treatment decisions, effect on patient-centered outcomes, harms, and effect on resource utilization?

KQ 4. When an ROM or scintigraphy is used in the evaluation of colonic dysmotility, what is the incremental value of also using WMC, in terms of diagnostic accuracy of slow-transit constipation, accuracy of motility assessment, effect pm treatment decisions, effect on patient-centered outcomes, harms, and effect on resource utilization?

Figure A. Analytic framework for research on the comparative effectiveness of diagnostic technologies for evaluating gastroparesis and constipation



KQ = Key Question

Methods

Literature Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to July 1, 2012) and Embase® (1974 to July 1, 2012). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. Additionally, we reviewed the reference lists of included articles and any relevant review articles. We asked the manufacturer of WMC about any published or unpublished randomized controlled trials or observational studies that evaluated WMC. The manufacturer submitted comments on the draft report but did not submit any new materials. We searched ClinicalTrials.gov to identify any relevant trials.

Study Selection

Two independent reviewers evaluated each title, abstract, and full article. We included studies that compared WMC with other diagnostic tests among patients with suspected gastroparesis or slow-transit constipation, in terms of diagnostic accuracy, accuracy of motility transit time assessment, effect on treatment decisions, effect on patient-centered outcomes, effect on resource utilization, or harms. Other diagnostic tests were gastric scintigraphy, antroduodenal manometry, and endoscopy for the evaluation of gastroparesis, and scintigraphy and ROM for slow-transit constipation. There were no language restrictions. We resolved differences between investigators regarding eligibility through consensus adjudication.

Data Abstraction

We created and pilot tested standardized spreadsheets for data extraction. The study investigators performed double data abstraction on each article. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs that included personnel with both clinical and methodological expertise.

For all articles, the reviewers extracted information on study characteristics (e.g., study design, country, location of recruitment, start year of recruitment, multicenter vs. single center, length of followup, length of time in between diagnostic tests), characteristics of study participants (e.g., condition; age; gender; race; weight; prior diagnostic tests; blood sugar; smoking status; diabetes status; defecatory dysfunction status; and the use of prokinetics, opiates, antidepressants, proton pump inhibitors, and laxatives), eligibility criteria, characteristics of WMC testing (e.g., was the pill swallowed or placed; did the study provide a standardized meal; did the study provide Ensure® shakes, and if so, when?[a]), characteristics of the other diagnostic tests, outcome measures, definitions, and the results of each outcome, including measures of variability. For each of the diagnostic tests, we collected information on the criteria used to make a diagnosis of gastroparesis or slow-transit constipation, and on whether the study instructed patients to abstain from tobacco, prokinetics, opiates, antidepressants, proton pump inhibitors, or laxatives at the time of the test.

[a] Ensure® is a commercial nutritional drink that is given to subjects in some centers as part of the WMC protocol.

Quality Assessment

Two reviewers independently assessed article quality. We selected and modified the questions from the QUADAS-2 quality assessment tool.[27] We supplemented this tool with quality-assessment questions (i.e., to assess spectrum bias) based on recommendations in the Methods Guide for Medical Test Reviews.[28] Our quality assessment included items on: (1) whether the study excluded healthy subjects from the diagnostic accuracy comparison, (2) whether the study excluded severely affected patients, (3) whether the study enrolled a random sample of patients, (4) whether all patients received the same reference standard, (5) whether the study included all patients in the analysis, (6) whether the study interpreted results of the test independently, (7) whether the time period between tests was reasonably short (within 3 months) to ensure that the condition did not change, (8) whether the study established cut-off values for test positivity before the study started, (9) whether a stated aim of the study was to compare diagnostic accuracy between WMC testing and other diagnostic tests, (10) whether the study reported on conflicts of interest, (11) whether a commercial source related to motility testing funded the study, and (12) whether a commercial source related to motility testing employed or gave funding or fees to any of the authors. The two reviewers resolved differences in quality assessment.

Applicability

We assessed the applicability of studies in terms of the degree to which the characteristics of the study population (e.g., age, etiology, comorbidities, prior surgery or gastric pacer), diagnostic test procedures (e.g., use of opiates during testing, use of bowel motility-altering agents such as laxatives or prokinetic agents), outcomes, and settings (e.g., referral center) were typical for the treatment of individuals with suspected gastroparesis or slow-transit constipation.

Data Analysis and Synthesis

We had planned to conduct meta-analyses if sufficient data were available (at least five studies for hierarchical summary receiver operator characteristic curves for diagnostic accuracy and at least three studies for other outcomes) and if studies were sufficiently homogenous with respect to key variables (e.g., population characteristics, study duration, diagnostic test procedures). We qualitatively summarized studies not amenable to pooling.

We considered gastric scintigraphy and clinical symptoms to be reference standards and ROM to be a nonreference standard. For measures of diagnostic accuracy when there was a reference standard, we summarized the results in terms of sensitivity, specificity, and test concordance. For measures of diagnostic accuracy when there was a nonreference standard, we summarized the results in terms of positive percent agreement, negative test agreement, and test concordance.[29] When the reference standard was a clinical diagnosis, we chose a 10 percent difference between tests in sensitivity or specificity as a potentially important difference because key studies were powered to detect a 10 percent difference.[25] When the reference/nonreference standard was another diagnostic test, we considered it similar if WMC had a test concordance of at least 80 percent.

We conducted a sensitivity analysis where we included data that was reported only in a conference abstract.

Rating the Body of Evidence

At the completion of our review, we graded the strength of the available evidence addressing the KQs by adapting an evidence grading scheme recommended in the "Methods Guide for Medical Test Reviews"[28] and in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[30,31] Both of these evidence grading schemes are based on recommendations of the GRADE Working Group.[32] We applied evidence grades to the bodies of evidence about each diagnostic test comparison for each outcome. We assessed the strength of the available evidence by assessing the risk of bias, consistency, directness, and precision.

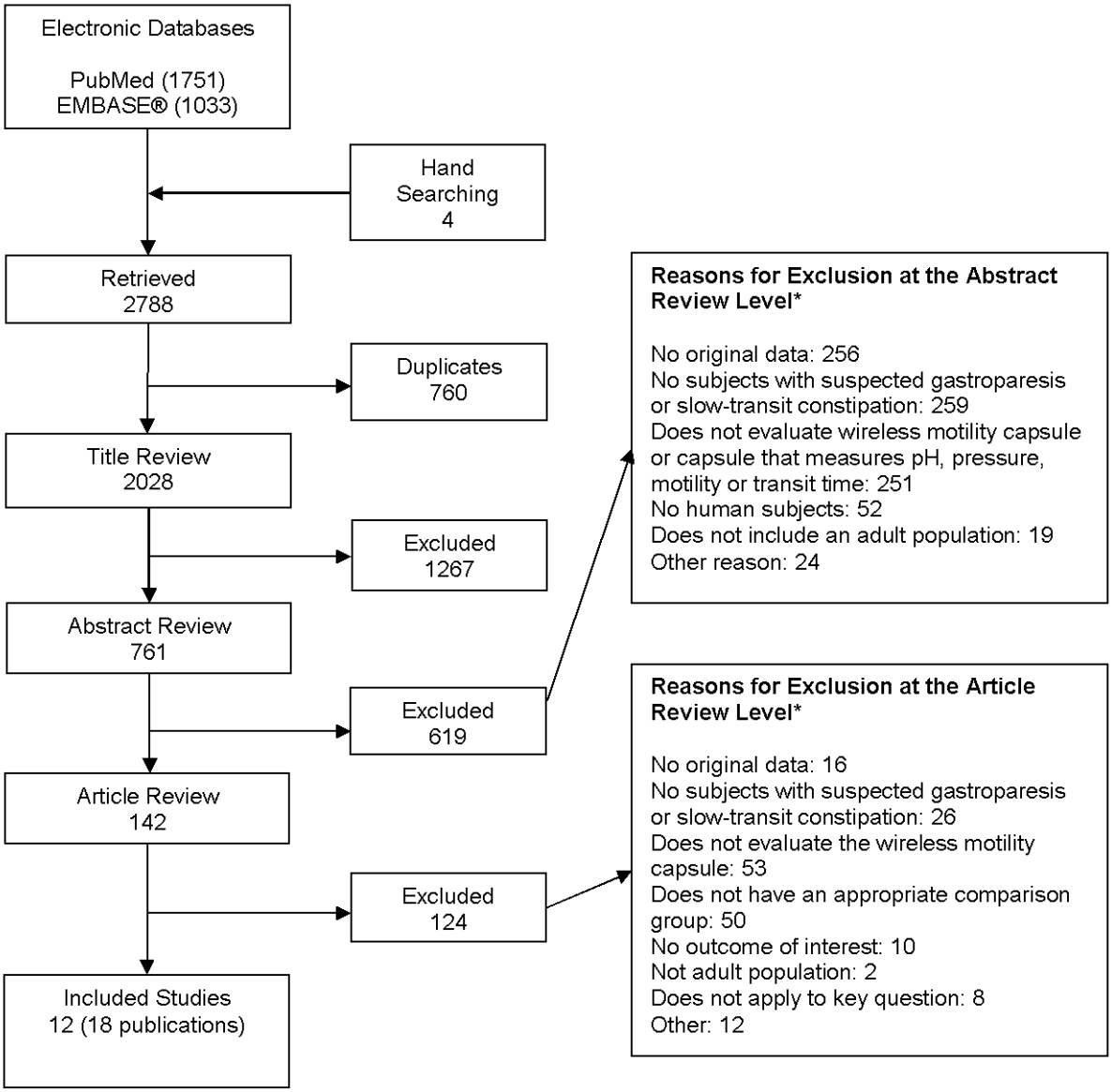
We classified evidence pertaining to the KQs into four basic categories: (1) "high" strength of evidence or SOE (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" SOE (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" SOE (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" SOE (indicating that evidence is unavailable or does not permit a conclusion).[32]

Results

Search Results

Figure B summarizes the results of our literature search. Our search retrieved 2,028 unique records. After reviewing the titles and abstracts, we considered 142 articles as potentially relevant and we reviewed the full text of the article for eligibility. We included a total of 12 studies (in 18 publications) in this review.[11,25,33-42] Seven studies (10 publications) evaluated WMC among patients with gastroparesis[33-39] and nine studies (14 publications) evaluated WMC among patients with slow-transit constipation.[11,25,33,34,36,38,40-42]

Figure B. Summary of literature search, with numbers of articles involved in each search step



*Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

Study Design Characteristics

Seven of the 12 studies were prospective,[10,11,25,35,37,41,42] 4 studies were retrospective,[33,34,36,38] and 1 did not specify a study design.[40] All prospective studies applied the tests concurrently. Six studies appeared in meeting abstracts,[35-38,40,41] the remainder were in peer-reviewed publications.

All studies that reported the study location occurred in the United States.[10,11,25,33-35,37,38] One study took place in multiple countries including the United States.[25] All studies that reported the location of recruitment occurred in tertiary centers.[11,33-38]

Length of followup for the prospective studies and those with unspecified designs included the day of the testing only,[35,37,38,40,43] 3 days,[10] 5 days,[41,42] 14 days,[25] and 21 days.[11]

Prospective studies included patients with known gastroparesis[10,35,37] or constipation.[11,25,42] Four retrospective studies included patients with suspected gastroparesis or constipation[33,34,36,38] and one included patients with known constipation exclusively.[40] Six of the prospective studies also included patients without gastroparesis or constipation,[10,11,35,37,41,42] whereas one study included only patients with known constipation.[25] Three studies that included patients with constipation used the Rome III criteria as inclusion criteria.[11,25,42] Three studies reported age restrictions. One allowed patients 18 to 80 years of age[25] and two others included patients older than 65 years of age.[41,42]

Study Population Characteristics

No gender restrictions were made in the inclusion criteria, although most of participants with gastroparesis or constipation were female. The mean age was 40 or greater in all studies that reported an average.[11,25,33,34,40,41] Three studies reported on race or ethnicity.[10,25,34] More than 80 percent of the participants were white in these studies. No study reported a measure of weight, blood sugar, or smoking status at baseline. Two studies reported on the percent of patients with diabetes,[33,39] reporting 15 and 37 percent with the disease, respectively. Two studies reported on defecatory dysfunction.[33,40] In one study, 20 of 32 subjects had defecatory dysfunction,[40] and in another study 64 percent of patients had this dysfunction.[33] Studies rarely reported on prior or concurrent use of medications, including prokinetics, opiates, antidepressants, proton pump inhibitors, and laxatives. Diagnostic testing prior to the study included scintigraphy[10,33,34,37] and ROM.[33,34]

Characteristics of Diagnostic Tests

We summarized the characteristics of the tests used in the studies, taking into consideration how the evaluation of gastrointestinal motility is dependent on multiple factors, including not only the types of test but also the specific protocols the studies employed, which were often not standardized. Our criteria for study assessment suggested that “best practice” studies would report on smoking, use of prokinetics, use of selective serotonin reuptake inhibitors, use of antacids, and the specific timing of ingestion of test meals. However, only a few of the studies with larger populations specified a predetermined meal and meal schedule for patients undergoing WMC testing. Several of the studies also specified that participants did not use prokinetics within the immediate timeframe of WMC testing. Clinicians most frequently performed gastric scintigraphy using the consensus protocol.[8] The community referral practice coordinated the ROM studies as per their local standards or the study made reference to a variation of the Metcalf protocol, wherein patients ingest ROMs and then receive an interval x ray and assessment of the marker location and number.[11,44-46] Few articles gave more specific test characteristics for ROM testing. Most abstracts did not report on any of these characteristics.

Study Quality

We reported study quality separately for the full-length publications and the abstracts, because the abstracts had limited information about study methods. Overall, study quality was fair among the 11 full-length publications we assessed.[10,11,25,33,34,39,42,47-50] Half of them used a uniform reference standard.[10,11,25,47,48] Only three studies interpreted the WMC results independently from the reference standard.[11,25,34] In another three studies that did not report

blinding, we were able to confirm, after contacting the authors, that the studies interpreted results independently.[10,39,47]

KQ 1. Evaluation of Gastric Dysmotility: WMC Alone Versus Other Diagnostic Tests; and KQ 2. Evaluation of Gastric Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

We summarized the results for KQ 1 and KQ 2 in Table A.

Table A. Summary of the strength of evidence (SOE) and main findings of studies comparing WMC alone (KQ 1) or in combination (KQ 2) with other diagnostic tests for the evaluation of gastroparesis

KQ	Comparison	Outcome(s)	SOE*	# of Studies	Main Findings
KQ 1	WMC vs. scintigraphy	Diagnostic accuracy	Low	7	Diagnostic accuracy of WMC is similar to scintigraphy. The sensitivity of WMC compared with clinical gastroparesis ranged from 65 to 68% and the specificity ranged from 82 to 87%. Sensitivity of WMC compared with gastric scintigraphy ranged from 59 to 86 percent and specificity ranged from 64 to 81 percent.
KQ 1	WMC vs. other modalities (antroduodenal manometry, endoscopy)	All outcomes	Insufficient	0	No studies addressed these comparisons.
KQ 1	WMC vs. scintigraphy	Motility assessment: Transit	Low	2	Transit data obtained via WMC are similar to scintigraphy.
KQ 1	WMC vs. scintigraphy	Motility assessment: pressure patterns	Low	3	WMC can measure pressure patterns and measurement of pressure patterns adds to diagnostic accuracy. (Scintigraphy does not measure pressure patterns.)
KQ 1	WMC vs. scintigraphy	Treatment decisions	Low	3	WMC testing alters management in patients with suspected gastroparesis (50-69% change in management for medicine, diet, or surgery).
KQ 1	WMC vs. scintigraphy	Resource utilization	Low	1	WMC testing may reduce the need for other studies, but this conclusion is based on one study with a high risk of bias. Need for anorectal manometry may not be reduced by WMC.
KQ 1	WMC vs. scintigraphy†	Harms	Low	2	Harms associated with WMC are minimal and no major safety issues were reported.
KQ 1	WMC vs. scintigraphy	Patient-centered outcomes	Insufficient	0	No studies reported on patient-centered outcomes for this comparison.
KQ 2	WMC in combination with other tests vs. scintigraphy	Diagnostic accuracy	Low	2	Adding WMC to conventional motility testing improves diagnostic accuracy in patients with suspected gastroparesis (sensitivity scintigraphy 42-51%; WMC 60-66%).

Table A. Summary of the strength of evidence (SOE) and main findings of studies comparing WMC alone (KQ 1) or in combination (KQ 2) with other diagnostic tests for the evaluation of gastroparesis (continued)

KQ	Comparison	Outcome(s)	SOE*	# of Studies	Main Findings
KQ 2	WMC in combination with other tests vs. scintigraphy	Motility assessment	Low	5	Adding WMC to conventional motility testing improves assessment of motility parameters in patient with suspected gastroparesis. (Scintigraphy does not measure pressure patterns.)
KQ 2	WMC in combination with other tests vs. scintigraphy	Treatment decisions, utilization, patient-centered outcomes, harms	Insufficient	0	No studies addressed these outcomes for these comparisons.

KQ = Key Question; SOE = strength of evidence; WMC = wireless motility capsule

*The SOE was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

†Findings were based on observational studies that did not include a direct comparison of WMC with gastric scintigraphy.

KQ 3. Evaluation of Colonic Dysmotility: WMC Alone Versus Other Diagnostic Tests; and KQ 4. Evaluation of Colonic Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

We summarized the results from KQ 3 and KQ 4 in Table B.

Table B. Summary of the SOE and main findings of studies comparing WMC alone (KQ 3) or in combination (KQ 4) with other diagnostic tests for the evaluation of slow-transit constipation

KQ	Comparison	Outcome	SOE*	Number of Studies	Main Findings
KQ 3	WMC vs. ROM	Diagnostic accuracy	Low	5	Diagnostic accuracy of WMC is similar to ROM. Concordance between ROM and WMC was approximately 80% in 3 larger studies. The sensitivity for WMC compared with clinical suspicion ranged from 32 to 46% and specificity ranged from 95 to 100%. The sensitivity of day-5 ROM ranged from 28 to 37% and specificity ranged from 95 to 100%.
KQ 3	WMC vs. ROM	Motility assessment: Transit	Low	3	WMC was comparable with ROM in judgment of colonic transit time and identification of slow-transit constipation.
KQ 3	WMC vs. ROM†	Treatment decisions	Low	2	Very small numbers made comparison difficult for treatment decisions. Studies reported 7.1% change in nutrition, 21% referral to surgery, and 4% change in nutritional and behavioral therapies with WMC.
KQ 3	WMC vs. ROM	Resource utilization	Low	4	WMC testing may reduce the need for other tests, but this conclusion is based on one study with a high risk of bias. WMC does not replace anorectal manometry.
KQ 3	WMC vs. ROM†	Harms	Low	5	Harms and adverse events were infrequently reported for WMC or ROM. WMC is comparable to ROM with regard to harms. ROM involves exposure to at least one x ray. Day 21 x ray was required in a small proportion of patients who received WMC by protocol if the capsule had not spontaneously passed. Technical failures were reported in prototype devices the range of 3 to 10% in some series.[11]
KQ 3	WMC vs. ROM	Patient-centered outcomes	Insufficient	0	No studies addressed this outcome.
KQ 3	WMC vs. colonic scintigraphy	Diagnostic accuracy	Insufficient	0	No studies assessed the role of WMC versus these other modalities in the population of interest for this outcome.
KQ 4	WMC in combination with other diagnostic tests vs. other tests alone	Diagnostic accuracy	Insufficient	0	No studies addressed this question.

KQ = Key Question; ROM = radiopaque markers; WMC = wireless motility capsule

*The SOE was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

†Findings were based on observational studies that did not include a direct comparison of WMC with ROM.

Discussion

Potential Niche for WMC

WMC is a potential improvement over previous testing modalities for patients with possible gastroparesis or slow-transit constipation because it is small and can be transported to patients wherever they live. Also, the capsule does not contain any radioactive material or entail x-ray exposure, and can record information about pressure, transit, and location simultaneously. Other testing modalities for gastric emptying and colonic motility assessment do not share these characteristics. Certain academic centers use scintigraphy to assess gastric transit abnormalities and evaluate whole gut motility; however, this procedure involves radiation exposure, significant patient time, and significant cost. Antroduodenal manometry assesses gastric pressure parameters but has limited availability and is more invasive than other testing modalities; thus, physicians commonly use it as an investigative tool rather than as a clinical test. ROMs are portable and small, but require radiation exposure, access to fluoroscopy, and radiology interpretation. In addition, all other methods for evaluating either gastric or colonic motility evaluate either transit or pressure, but not both; yet both are involved in disease pathogenesis. Since WMC can evaluate both transit and pressure simultaneously, it could allow more optimal assessment of motility than evaluation of either parameter independently. Likewise, by recording both parameters, WMC has the potential to replace a combination of modalities and provide more accurate diagnosis with less resource utilization and enhanced patient convenience.

In light of this potential niche, WMC is becoming much more readily available in both academic and community centers. However, questions remain about the position of WMC in the diagnostic algorithm for suspected motility disorders such as gastroparesis and slow-transit constipation. Is WMC equivalent to conventional testing? Is it superior? Is it more likely to establish a concrete diagnosis or guide medical therapy than conventional motility testing? Should it be used as a stand-alone test? What should be done when WMC results are normal but clinical suspicion remains? Recommendations from the ANMS practice guidelines suggest that WMC can be useful in the diagnostic work up of patients with suspected gastroparesis and slow-transit constipation as well as those with more generalized motility disorders, but these are consensus guidelines. There is no specific or clear information about when or how physicians should utilize a WMC.

We must also consider potential limitations of WMC. The manufacturer lists severe gastroparesis as a contraindication to capsule placement due to fear of capsule retention. In addition, by definition, WMC evaluates motility at only a single point, as opposed to antroduodenal manometry, which has multiple recording points, or scintigraphy, which looks at transit of an entire meal. One assumes that the single point of measurement is representative of motility parameters as a whole; however, this is an assumption only and is not clearly established in the literature. When assessing constipation, one cannot distinguish patients with slow-transit constipation from those with defecatory dysfunction based on only colonic transit time, so we need further motility testing with anorectal manometry and clinical judgment to evaluate defecation. Finally, parameters of motility for a nondigestible solid are different from those for either liquids or a meal—so that patients can have abnormalities that would be detected with one modality but that would not be seen with another. In short, while the potential of WMC testing is exciting, many questions remain as to its appropriate place in the diagnostic algorithm.

Key Findings and Implications

Few studies met our criteria for evaluation. The paucity of full-length articles with independent data limited our ability to answer the KQs definitively.

Key Question 1. Evaluation of Gastric Dysmotility: WMC Alone Versus Other Diagnostic Tests

WMC Versus Scintigraphy

We found low SOE from seven studies[10,33-35,37-39] that WMC has comparable diagnostic accuracy with gastric scintigraphy. The sensitivity was moderately greater in some studies, but some studies reported slightly lower specificity. The test agreement and diagnostic gain were moderate. Diagnostic agreement between WMC and gastric scintigraphy ranged from 58 to 86 percent for positive test agreement and from 64 to 81 percent for negative test agreement.

We found low SOE from five studies[10,34,35,37,39] that transit data obtained via WMC testing correlates well with scintigraphic gastric emptying. The reporting of the results in these studies was heterogeneous. One study reported a correlation coefficient of 0.73 between gastric emptying time measured by the WMC and 4-hour gastric emptying measured by gastric scintigraphy.[10] When comparing WMC with gastric scintigraphy, one should keep in mind that WMC measures emptying of an indigestible object after the emptying of a meal, while gastric scintigraphy measures emptying of a meal. In a sense, then, WMC indirectly measures what gastric scintigraphy measures. Good correlation between the two tests indicates that delayed meal emptying generally translates into delayed indigestible object emptying. Other studies reported sensitivity, specificity, and device agreement between WMC transit data and gastric scintigraphy.[34,37,39] All three studies examining transit time showed similar sensitivity and specificity for WMC and scintigraphy, and some studies reported increased diagnostic gain of sensitivity with WMC.

Low SOE from two studies supports the utility of WMC versus scintigraphy in measuring pressure profiles.[37,39] A WMC detects pressure patterns, whereas scintigraphy cannot. It does appear, however, that abnormalities are more likely with WMC than scintigraphy--especially if one adds assessment of pressure patterns to the equation. However, based on the literature there remain questions as to whether increased diagnostic detection has clinical implications.

Overall, we had graded the SOE for many outcomes addressing KQ 1 to be low because we considered the evidence to have medium risk of bias, consistent reporting, direct nature of the data, and imprecise findings. The main limitation weighting the risk of bias was that studies did not prespecify patient enrollment or perform it in a random fashion; in fact many studies did not report how they selected patients for testing and study. Another limitation was the lack of advance prespecification of criteria and values of positivity of the tests the studies used. The final major limitation was that few studies mentioned whether they had selected a person without conflict of interest to manage data collection. Most studies had limited followup duration, which hampers our ability to draw conclusions about some of the outcomes that are really important to patients. A major strength of the full-length articles was that analysis involved an independent review of the results.

We could not conduct a meta-analysis because of the heterogeneity of the data and patient populations in the studies. Our ability to compare studies was limited by lack of consistency in the definition of reference standards. Studies often reported the reference standard as community-based gastric scintigraphy testing performed within 2 years of enrollment into a

study. Local standards for scintigraphy vary greatly, and this introduced heterogeneity into the patient populations under investigation. Many studies had different definitions for key outcomes such as diagnostic agreement, sensitivity, and specificity, as well as different diagnoses based on similar test results. This latter discrepancy is likely due to changes over time in cut-off values for detecting gastroparesis using a WMC. It is uncertain if the available examinations of motility testing captured the full spectrum of patients, as academic referral centers were the primary recruitment site for studies. Overall, seven studies with 560 patients addressed the question of diagnostic accuracy.[33-39] For a rare illness, the large number of patients that researchers have included for evaluation reflects the great lengths that they have gone to in order to assess the quality of this modality.

Several studies suggested that there was some diagnostic gain with WMC as compared with scintigraphy, assuming that all the additional cases they identified were correct and not false positives.[10,33,34,37, 39] The investigators attempted to minimize the impact of having a heterogeneous population by employing simultaneous scintigraphy and WMC at the time of assessment; sensitivity and specificity for both scintigraphy and WMC compared with symptoms in these studies is expectedly low given the issues above and the fact that the denominator may not have truly represented only gastroparetic patients. Device agreement is a more useful parameter to measure in these papers than sensitivity and specificity.[28] However, agreement is likely to be imperfect because these two modalities look at different mechanisms of transit.

Regarding treatment decisions, we did find that, in three studies, WMC testing altered management in patients with suspected gastroparesis (50 to 69 percent change in management for medicine, diet, or surgery). However, the SOE was low (i.e., likely to be changed by future evidence).

The evidence was insufficient to permit conclusions regarding the differences or similarities between gastric scintigraphy and WMC with regard to patient-centered outcomes or resource utilization. Very little research examined resource utilization, and no studies specifically examined this outcome with any rigor.

The findings contained in the literature are consistent with what would be expected based on the pathophysiology of gastroparesis and the comparative methods of WMC and gastric scintigraphy. Comparing scintigraphy with WMC is fundamentally a challenging endeavor. Both modalities evaluate different parameters. Scintigraphy looks at transit of a test meal and does not assess pressure. When the stomach processes a meal, fundic accommodation is followed by antral contractions that break up the food into small particles that are then propelled from the antrum to the duodenum. In comparison, the WMC is not digested and is believed to exit the stomach when the gastric motility patterns change from a fed to fasting state and migratory motility complexes resume. As such, these two technologies are evaluating different parameters and a direct comparison may be challenging if one looks at transit alone.

WMC Anteroduodenal Manometry or Endoscopy

We did not find any head-to-head comparisons of antroduodenal manometry (which can record pressure patterns) and WMC in patients with suspected gastroparesis in our review. This makes it difficult to make a more definitive assessment of the ability of WMC to detect abnormalities in pressure patterns in our defined populations. Similarly, we did not find any studies that compared WMC with endoscopy among patients with suspect gastroparesis.

Key Question 2. Evaluation of Gastric Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

WMC Plus Gastric Scintigraphy Versus Gastric Scintigraphy Alone

Two studies[34,39] assessed the incremental value of using WMC with gastric scintigraphy. We found low SOE to suggest that WMC is associated with modest improvement in diagnostic accuracy over use of scintigraphy alone for patients with suspected gastroparesis. We also found low SOE to support the incremental benefit of WMC in evaluation of transit times and pressure patterns. The two studies that did attempt to address this question had a method of data collection that may not have allowed for full understanding of diagnostic discrepancy. Discrepancy exists when one test shows disease and the other test does not show disease. The authors assumed that in a population of patients with gastroparesis, diagnostic gain (when WMC was positive but scintigraphy was not) was always present when there was discrepancy with results.[34] This assumption is difficult to confirm without an independent gold standard for establishing the diagnosis.

While few studies addressed this question specifically, the ones that did were among the better-quality studies, and demonstrated independent review of WMC and scintigraphy. We assessed risk of bias as medium and felt these studies were consistent and direct. We felt that precision was low but this is difficult to gauge for this question. The overall SOE was low for this KQ. It is very hard to prove an incremental benefit of the test when studies use it in addition to other testing modalities because it is hard to determine how the study performed clinical decisionmaking. It may be unclear which test the clinician used to form an opinion of the case, and it may be unclear how much the incremental information contributed to the decisionmaking process. The retrospective nature of studies also limited the strength of evidence (SOE).

In addition, understanding the incremental benefit of WMC when added to gastric scintigraphy should take into account the fact that eligibility criteria for these studies required a previous positive test for gastric emptying scintigraphy and documented gastroparetic symptoms. Therefore, added WMC testing showed incremental sensitivity over scintigraphy alone in such a population, which one should take into account when judging these results' clinical applicability.

The incremental benefit for WMC in diagnostic evaluation of suspected gastroparesis is consistent with the nature of the disorder and the tests, since WMC offers pressure data and motility data that scintigraphy alone cannot detect, as well as lower gastrointestinal motility data, which can be implicated as a cause of symptoms in patients with combinations of motility disorders. One may obtain measurable benefit from the additional reported information in combination with scintigraphy, especially with regard to identification of a more diffuse motility disorder. The evidence was limited and there was no information to guide any conclusions regarding treatment decisions, utilization, patient-centered outcomes, or harms when evaluating the incremental value of also using WMC.

Incremental Value of WMC Compared with Antroduodenal Manometry Alone or Endoscopy Alone

We did not find any studies that evaluated the incremental value of adding the WMC test to testing with either antroduodenal manometry or endoscopy in patients with suspected gastroparesis.

Key Question 3. Evaluation of Colonic Dysmotility: WMC Alone Versus Other Diagnostic Tests

WMC Versus ROM

The SOE was low from five studies (306 total patients) comparing WMC with ROM in terms of their ability to accurately diagnose slow-transit constipation,[11,25,33,34,42] The diagnostic accuracy of WMC was similar to scintigraphy. (Concordance was about 80 percent in two of the larger studies.) Sensitivity and specificity were estimated to be 46 and 95 percent for WMC compared with a symptom-based diagnosis of clinical constipation, and 37 and 95 percent for ROM.[11] WMC was comparable to ROM in assessing diagnostic accuracy, and matched the sensitivity in different target populations in a reliable way.

The SOE was low to suggest that the colonic transit time estimated by WMC correlates well with the colonic transit times recorded by ROM. The correlation coefficients between these two measures ranged from 0.69 to 0.71.

The SOE was low regarding the effect of WMC testing on treatment decisions based on ROM testing. We graded the SOE as low because only two retrospective chart reviews offered information about change in management for WMC compared with ROM.[33,34] These two studies differed in the patient populations and the reporting of the outcomes. One of the studies reported few events, providing imprecise results. The data was further limited because not all patients underwent both diagnostic tests of interest. We found low SOE that WMC can affect resource utilization.

The SOE was low in the five studies reporting on any harms relevant to WMC or ROM.[11,25,34,40,42] Studies infrequently reported harms and adverse events for WMC or ROM. WMC is comparable to ROM with regard to low frequency of harms, as no studies reported serious adverse events or mortality. ROM testing involves exposure to at least one x ray by definition. A small proportion of patients who received WMC needed x rays on day 21 by protocol when the capsule had not spontaneously passed, but this may not be necessary in practice if someone witnesses capsule passage. Prototype devices suffered technical failure rates of 3 and 10 percent, depending on the study.[11] Studies also reported harms or adverse events, such as dysphagia, abdominal discomfort, bloating, or nausea, which happened infrequently. These all resolved spontaneously when reported.[25]

The SOE was insufficient to permit any conclusions about patient-centered outcomes like symptom improvement, quality of life, or patient satisfaction. No included studies addressed these outcomes of interest. These are difficult outcomes to assess without using dedicated symptom scores or mining large sources of data on hospital and physician visits. We will need longer-duration studies to address questions about change in quality of life or symptoms, which requires assessment along multiple time points.

Many factors contributed to the overall grading of evidence for outcomes we assessed as having low SOE in reference to KQ 3. We considered the evidence to have moderate risk of bias because many of the studies were retrospective, lacked random patient selection, did not report if there was blinding of assessment, and did not apply the same reference standard to all the patients. Furthermore, many studies recruited patients from academic referral centers; it is uncertain if the available examinations of motility testing captured the full spectrum of patients. Most studies had limited followup duration, which hampered our ability to draw conclusions about some of the outcomes that are important to patients such as patient satisfaction or change in symptom scores. We had only imprecise estimates of the effects on treatment decisions and

harms. Our conclusions were limited by how studies defined the nonreference standards. The non-reference standard test was often a community-based ROM study of varying protocol. The multiple protocols had different assessment methods, which could have influenced the results. We could not conduct a meta-analysis because of the heterogeneity of reported data and patient populations in the studies. Although the SOE was low, it is impressive how well these devices correlated given limitations of the studies.

Much like scintigraphy as compared to WMC, ROM and WMC assess different components of transit. Some of the points of assessment coincide and provide comparable data, but the additional pressure and transit data offered by WMC make it a different and possibly complementary modality. Overall, the studies showed diagnostic agreement between WMC and ROM for assessment and diagnosis of slow-transit constipation.

WMC Versus Colonic Scintigraphy

We found no evidence to evaluate the WMC in comparison with colonic scintigraphy in patients with suspected slow-transit constipation. We excluded existing studies on scintigraphy from our analysis because they compared testing in healthy subjects separately from those with constipation or slow-transit constipation and thus were not eligible for inclusion.

KQ 4. Evaluation of Colonic Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

No studies directly addressed any outcomes of interest related to KQ 4. The small amounts of data that were available from small trials about these outcomes were heterogeneous and did not specify the specific patient populations of interest; thus, it was impossible to generalize based on these data. One could use diagnostic gain to assess the incremental value of a new technology. However, when trying to judge whether a new test can be a replacement or an adjunct to an old test, it is difficult to get a clear picture of which test was most helpful in making a diagnosis without a blinded comparison or without a followup study capable of assessing the validity of the diagnosis and or treatment effects over time.

Applicability

Limiting the application of the literature is the fact that all studies occurred at referral centers and that all prospective studies involved patients with known disease (thereby providing no prospective testing of WMC as a diagnostic tool). When a study used a comparison group without constipation or gastroparesis, it included “healthy” controls instead of patients who may have similar presenting symptoms but who do not have constipation or gastroparesis. These controls tended to be college-age men compared with middle-age females with suspected disease. Additionally, it is unclear how previous treatments or comorbidity, including diabetes, affect test performance or how the test results ultimately affect management.

Limitations and Strengths of Our Review Process

Our review had three major limitations:

1. No standards exist in the field of motility assessment for determining the minimum improvement of diagnostic accuracy that will identify one test as superior to another test. There are also no standards to establish the equivalence of motility tests. We arbitrarily chose a 10 percent difference in sensitivity or specificity as a potentially important

difference between tests.[25] We felt that this threshold was a conservative minimum improvement over a reference standard with moderate diagnostic accuracy (between 50 and 80 percent). If the reference standard had a larger diagnostic accuracy (90 percent or greater), a 10 percent absolute difference is too large to expect.

2. We excluded studies that included non-diseased participants exclusively, because our review focused on studies that compared the diagnostic accuracy of the tests for patients with gastroparesis or slow-transit constipation. We recognize that many of the most commonly cited studies in the field included non-diseased participants exclusively.[12,13,51-64] Thus, we excluded a number of studies that evaluated characteristics of WMC.
3. Experts in the field acknowledge that scintigraphy and ROM have imperfect diagnostic accuracy. There are several options to account for the imperfection of the reference standard.[65] We chose to incorporate two of these in our review: (1) We presented the results as if the reference standard had no measurement error and acknowledged this imperfection. (2) We presented concordance of the test results when available. We did not attempt to adjust the results to correct for the measurement error. This adjustment would have required assumptions that we did not have sufficient data to justify. Another option is to examine patient outcomes according to WMC. We had included patient outcomes (need for medications, additional tests) as outcomes in our review. Unfortunately, we found few studies evaluating these outcomes.

The major strength of our review process was its comprehensiveness. We included abstracts, contacted industry for unpublished studies, and contacted study authors for missing data.

Limitations of the Identified Literature

Our aim was to compare the diagnostic accuracy of WMC with other testing modalities to diagnose and manage gastroparesis and slow transit constipation. The identified literature limited our ability to answer our KQs for several reasons:

1. No study directly addressed the incremental value of using WMC in addition to ROM or scintigraphy in the evaluation of colonic dysmotility (KQ 4). Only limited data addressed the incremental value of using WMC in addition to gastric scintigraphy, antroduodenal manometry, or endoscopy in the evaluation of gastric dysmotility (KQ 2).
2. All study sites were referral centers that tend to have patients with more severe disease. The study results have limited generalizability to general gastroenterology or primary care clinics where there is a greater spectrum of disease severity. The sensitivity and specificity of WMC may be different in referral center settings than in other settings, and the positive and negative predictive values will be different when the prevalence of disease is different.
3. Many studies included nondiseased patients in the comparison of the diagnostic accuracy of WMC with other tests, using a clinical diagnosis of disease as the reference standard rather than the results of the other diagnostic tests.
4. The non-diseased participants had demographic characteristics very different from the gastroparesis and slow-transit-constipation patients. For example, the majority of the non-diseased participants were college-age males, whereas the gastroparesis and slow-transit-constipation patients were middle-age women. Using clinical diagnosis as the reference standard, it is difficult to determine if WMC and other tests are distinguishing disease from non-disease or measuring differences in motility by demographic differences such as age and sex.

5. Variability in the administration of the motility tests and outcome assessments may explain some of the heterogeneity in the study results. Many studies used similar protocols to perform WMC testing and other tests, but with slight modifications such as the contents of the meal. Frequently, the timing of the motility assessment differed for WMC and the alternative test within and between studies, which may explain differences in the test results and the diagnostic accuracy differences between studies.
6. The abstracts we included did not report enough data to allow us to fully understand the study population, answer our KQs, and assess the quality of the studies.
7. We were unable to compare the results of studies with and without industry or investigator conflicts of interest because the company that manufactures the WMC sponsored most of the studies. The other studies did not report on conflicts of interest. No study stated that it was performed independent of industry sponsorship with authors who had no previous or current financial relationships with the manufacturer of the WMC.
8. Many studies included patients with gastroparesis defined by clinical symptoms and a prior abnormal gastric scintigraphy via local standards; however, symptoms of gastroparesis can be non-specific and many local facilities do not follow a standardized gastric scintigraphy protocol. As such, it is difficult, based on the data, to separate patients with gastroparesis from those with functional dyspepsia or other functional gastrointestinal disorders. This may have, to some degree, affected data with regards to sensitivity, specificity, and device correlation.
9. We attempted to assess publication bias by contacting the manufacturer of the WMC and requesting any unpublished data, but received no response.
10. Not all studies reported sufficient numbers to describe all the combinations of test results; some only provided means or medians. This hampered our ability to perform analyses, especially when analyzing combinations of tests.
11. Very few studies reported on patient-centered outcomes, limiting our abilities to draw conclusions on these outcomes.

Future Research Needs

Future research should ideally concentrate on finding a cure to these diseases that is nontoxic, cheap, easily available, and safe without major surgery or implanted devices. As far as diagnostic testing, the goal is always to find accurate, effective, and inexpensive tools to diagnose or exclude cases and qualify their severity in a reproducible way, especially when treatment is expensive, unavailable, or accompanied by great risks. Studies that compare the diagnostic modalities should have blinded interpretation of the results and make every attempt to classify patients by identical criteria and standardized protocols that other centers can repeat and verify. We recommend that research focus more on prospectively studied patients in larger numbers with an appropriate spectrum of symptoms and adequate followup to determine whether the diagnosis was accurate over time. Due to the difficulty enrolling patients, studies should carefully craft retrospective analyses.

We need research studies that evaluate how clinicians should use the WMC in combination with or instead of other testing modalities for evaluating slow-transit constipation. The studies we reviewed used alternative measures to assess anorectal function, such as anorectal manometry, as WMC does not capture data about this region reliably. Thus, clinicians will likely use WMC in combination with this test.

Eventually, we need outcomes studies to see if testing helps to improve quality of life or symptom control. It is unclear at present whether a more sensitive diagnostic test might just provide lead-time bias—or apparent superiority for an earlier diagnosis—but not actually change the outcomes or management steps overall for the patient. As we identify other targeted therapies, we will need to reassess the value of testing. We are aware that a new therapy is in Stage II trials for patients with diabetes and gastric emptying delay, which may increase the need for research into this area if it becomes available for use.[66] Currently, most patients with nausea- and vomiting-predominant symptoms of gastroparesis receive similar first-line treatment with antiemetics or prokinetics. As treatment options for gastroparesis expand (some at great expense), then more accurate detection of disease prior to initiation of therapy may play a more prominent role in disease management. The literature does not currently report resource utilization with and without WMC—we will need more studies evaluating these measures.

Little data is available to determine the optimal timing of WMC testing in the diagnostic and therapeutic approach to patients with symptoms of possible gastroparesis or slow-transit constipation. We need to do further work to classify the types of patients within subgroups of gastroparesis or slow-transit constipation in order to identify severe cases that may need more urgent evaluation. Finally, little is known about whether physicians should use testing to assess the effectiveness of treatment or if subsequent testing would offer any benefit in long-term management of patients. Currently, symptoms and symptom resolution guide therapeutic decisions, but these require careful interpretation.

Conclusions

Based on the current literature, WMC appears to be accurate in detection of gastroparesis and slow-transit constipation and may provide increased diagnostic gain as compared with standard motility testing. While the SOE is low, the data were relatively consistent and suggested that this modality is no less sensitive than conventional testing. The evidence is insufficient to determine whether use of WMC will improve outcomes of care.

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Introduction

Delayed gastric emptying and slow-transit constipation are disorders of gastrointestinal (GI) physiology that may cause persistent troubling symptoms. When patients present with their symptoms, clinicians frequently try empiric therapy first because it is often difficult to measure these disorders. When empiric therapy is unsuccessful or symptoms are severe enough to prompt immediate investigation, clinicians usually will recommend diagnostic evaluation of GI physiology with one or more of the available tests. Unfortunately, all of the traditional tests of GI physiology have limitations. Many of the traditional testing modalities have inconsistency in their performances that make interpretation difficult and complex for providers. To give patients and their clinicians another option, a new test is available and approved for use in the United States—the wireless motility capsule (WMC).[1]

Gastroparesis

Definition and Prevalence

Gastroparesis is a condition in which patients experience symptoms of delayed gastric emptying in the absence of an actual physical blockage.[2] The most common symptoms are nausea, vomiting, early satiety, bloating, abdominal pain, and postprandial fullness.[3] Diagnosing gastroparesis depends on the accurate detection and assessment of gastric emptying delay. Since the common symptoms for gastroparesis overlap with symptoms of functional GI disorders, such as dyspepsia, cyclical vomiting, and irritable bowel syndrome, researchers have established a more stringent definition of gastroparesis. They define it as delayed gastric emptying as detected by clinical testing and the presence of symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months.[4] Using this definition, the cumulative incidence of gastroparesis is 4.8 percent in people with type 1 diabetes, 1.0 percent in people with type 2 diabetes, and 0.1 percent in people without diabetes but who may have idiopathic gastroparesis or other rare etiologies.[3] A multicenter study revealed that 88 percent of patients with idiopathic gastroparesis were female, and the average age at the time of diagnosis was 41 years.[5,6] A 2007 community-based study estimated the prevalence of gastroparesis to be 9.6 per 100,000 for men and 37.8 per 100,000 for women.[3] Newer estimates of prevalence report a higher rate of 24.2 per 100,000 inhabitants. Some experts estimate that more than 1.5 to 3 million Americans may have gastroparesis.[7,8]

Etiology and Clinical Course

The etiologies of gastroparesis are most often idiopathic, diabetic, or postsurgical, but can be autoimmune, paraneoplastic, or neurologic. Idiopathic gastroparesis is the most common etiology, estimated by some small studies to range between 36 and 64 percent of patients with the condition. Diabetes mellitus is the primary cause of gastroparesis in 29 to 31 percent of patients. Clinicians usually assess gastroparesis in the outpatient setting, but some patients become severely ill with intractable vomiting and dehydration and must be hospitalized. Hospitalizations for gastroparesis increased by 158 percent between 1995 and 2004.[9] In individuals with diabetes and gastroparesis, food digestion is unpredictable, and wild swings in blood glucose can require medical care and increase morbidity. This unpredictability highlights the need for accurate diagnosis of gastroparesis so patients can receive appropriate care.

Evaluation of Possible Gastroparesis

Physicians generally assess gastroparesis in patients with typical symptoms (nausea, vomiting, bloating, abdominal pain, early satiety) in an outpatient setting, where they record a patient's medical history and perform a physical examination.[10] In the examination, physicians must first rule out medication-induced symptoms and mechanical causes. Medications, such as opiates or glucagon-like peptide agonists, are the usual cause of delay of gastric emptying. If there is any possible offending medication use, clinicians can stop medication and observe the patient for improvement of symptoms. If there is any clinical suggestion of mechanical obstruction, then imaging with x-rays or computed tomography can confirm obstruction and exclude gastric emptying delay as a primary etiology. Motility disorders are difficult entities to diagnose. Multiple contributing factors make pathophysiology more complex, thus physicians can have difficulty gathering a unifying diagnosis from a single test. Methods of testing include gastric emptying scintigraphy, antroduodenal manometry, and now wireless motility capsule technology. Electrogastrography is an older form of testing that clinics rarely use, even in academic centers.[2] Some patients with diagnosed gastroparesis may also have evidence of a diffuse GI motility disorder, as indicated by delayed small intestinal and/or colonic transit, in addition to the delayed gastric emptying. Management of these patients is different, as the prolongation of colonic transit in gastroparetic patients indicates dysmotility beyond the stomach, and this could be contributing to some of the patient's symptoms.[11,12]

Gastric Scintigraphy

The American College of Gastroenterology and the American Gastroenterological Association, recognize gastric emptying scintigraphy of a radiolabeled solid meal as the reference standard for determining delayed gastric emptying.[10] Gastric scintigraphy is the ingestion of a meal commonly standardized to toast, jam, water, and radiolabeled egg whites, which timed imaging can follow as the egg whites pass through the GI tract. Most radiology centers require that all possible interfering medications, such as opiates, motility agents, and glucagon-like peptide agonists, be withheld for 5 to 7 days before scintigraphic testing. In order to best detect more abnormalities among symptomatic patients, and for the test to be reproducible, a consensus statement issued by the American Neurogastroenterology and Motility Society (ANMS) and Society of Nuclear Medicine in 2011[13] recommends clinicians perform gastric scintigraphy over a period of 4 hours after a patient consumes a standardized meal. Motility specialists find that community-based radiology practices often provide shorter versions of the scintigraphic examination with durations between 60 and 120 minutes, whereas regional referral centers or tertiary care centers with established practices of motility specialists are more likely to offer full 4-hour testing.[13] The medical community has established clear standards of abnormal emptying for 1, 2, 3, and 4 hours. Generally, physicians diagnose delayed gastric emptying when less than 90 percent of the gastric content has not emptied at 4 hours, meaning that the patient has retained more than 10 percent of the content. There is little evidence to suggest that scintigraphy is a useful diagnostic tool for judging a patient's response to treatment. Scintigraphy has other disadvantages such as low-dose radiation exposure, lack of sensitivity in detecting delayed emptying, lack of a standardized protocol in widespread use, duration of up to 4 hours, a half-day lost from work for the patient, and a high cost of interpretation.

Antroduodenal Manometry

Antroduodenal manometry is a cumbersome technology that can provide information about gastric physiology, however, only a few specialized centers offer it. With the patient usually sedated, a physician inserts a manometry catheter through the pyloric channel, most commonly with endoscopic guidance. This test permits physicians to capture pressure measurements, which provide information about the small bowel and gastric pressure patterns during resting, mealtime, and after administering medication. Antroduodenal manometry may help differentiate myopathic and neuropathic etiologies of symptoms. Myopathy is present when there are amplitude muscle pressures of less than 30 mmHg, and neuropathy is present when there are uncoordinated bursts of muscle activity. These are patterns of small bowel disease. Many gastric neuropathies show a flat line pattern similar to myopathic disease.

WMC

The U.S. Food and Drug Administration (FDA) recently approved and made available a new modality for identifying motility disorders, the wireless motility capsule.[1] This new modality is a one-time use, portable, ingestible capsule that, when swallowed, records and transmits data to a receiver as the capsule travels through the gut. The capsule can measure pH, pressure, and temperature to track location, gastric contents, and expulsion time from the different regions of the bowel. Small trials to assess gastric emptying have tested wireless motility capsules. The ANMS recommend its use and the American College of Gastroenterology considers it a technology that has great promise and should be watched.[14] The patient takes the pill after eating a standardized meal and wears a small monitor that makes telemetry recordings. The device assesses gastric emptying time from ingestion of the capsule (a point at which there is a low pH reading) to after it moves into the small bowel (when there's an abrupt rise in pH).[15] A tandem scintigraphic study of the capsule alone, in comparison with a radiolabeled meal, established a cutoff point for gastric emptying time of 300 minutes.[16] Disadvantages of the capsule include failure to capture data (requiring repeat testing) and delay or total failure to pass. When the capsule fails to pass and patients have symptoms, then a patient may need x-rays to detect retention. In rare cases, endoscopic or surgical removal may be necessary. The capsule is not viable for patients with a possible stricture, altered anatomy, or severe pyloric stenosis.[17] Most patients do not mind wearing the data receiver during testing, but this may limit some patients in their daily life. Also, patients ideally should be able to tolerate not using any proton pump inhibitors and histamine 2 blockers before testing.[17] Advantages of testing with the capsule include that it is wireless and painless, can be used in an office setting without sedation or radiation, and provides information for the whole gut in addition to the area of interest for gastric emptying.[18,19] The capsule can assess gastric emptying, small bowel transit, and colonic transit in a single test. The only other single test that assesses transit in all areas of the gut is whole gut transit scintigraphy, which is available at only select centers. Alternatively, multiple tests, such as gastric emptying scintigraphy and radioopaque markers, can be combined to attempt to assess the transit in multiple locations of the gut.[11,12]

Most physicians would assess patients for evidence or history of stricture before using the capsule; this assessment might include additional imaging studies that physicians might not perform otherwise.

Use of Gastric Emptying Testing To Guide Treatment

Gastric emptying delay testing helps physicians choose appropriate nutrition, medication, and surgical therapies. Testing can provide useful information for adjusting diets to accommodate better gastric emptying, such as: a low-fat diet, a low-residue diet (i.e., low fiber, easy to empty from the stomach), a liquid diet, or increasing consumption to multiple small meals taken 4 to 6 times per day. Testing can also help physicians gauge whether or not to prescribe prokinetic treatments, like metoclopramide or erythromycin, which are common treatments for gastroparesis. This is especially important for oral, intravenous, and sublingual preparations of metoclopramide, since there is a FDA black box warning about side effects in patients who use metoclopramide for more than 3 months. Studies have linked both metoclopramide and erythromycin to profound tachyphylaxis, limiting any intended benefit. Similarly, domperidone is not FDA-approved, but is available in many countries outside the U.S. Clinical care and research studies in the U.S. use domperidone through an Investigational New Drug Application encouraged by the FDA. As such, most physicians would be reluctant to prescribe domperidone without documentation of gastroparesis. Testing can help guide physicians when treating patients with severe symptoms and severe emptying delay (despite dietary changes) who need feeding tubes such as jejunostomy or gastrojejunostomy tubes that bypass the stomach entirely. Testing is also helpful in patients with total failure of gastric emptying who can't tolerate feeding tubes and require intravenous nutrition. Documentation of gastric emptying delay is a key eligibility criterion for both of these treatments. Thus, accurate diagnosis of gastroparesis is integral to decisions about care management.

Outcomes

The main outcomes of interest are assessment of motility and diagnosis of gastric emptying delay. Other outcomes include the ability of testing to influence treatment decisions (e.g., medication, nutrition) or affect patient-centered outcomes (e.g., symptom improvement, need for surgery, quality of life, patient satisfaction). Clinicians and policymakers should consider the potential harms of testing, such as capsule retention, radiation exposure, and mortality. They should also consider the effects on resource utilization such as the need for additional tests, physician services, or hospitalizations.

Controversy

The 2011 ANMS conference addressed controversy surrounding the accuracy of the cutoff point for scintigraphy in differentiating patients with true gastroparesis from those with more functional symptoms. Experts debated the need for stricter criteria for diagnosing gastroparesis and whether greater retention of gastric content was likely to relate to greater severity of disease, which recent literature has questioned.[20] Nevertheless, this may still have implications for how physicians use capsule testing to treat patients with abnormal gastric emptying. Previous consensus recommendations from 2008 established baseline standards for scintigraphy and suggested that grading the severity of gastric emptying delay was relevant to clinical research, but did not establish how that grading would affect decisions about patients.[21] We will address this issue by looking for data on how treatment decisions differ between testing methods. Another controversy was the lack of information regarding whether or not scintigraphy or wireless motility capsule testing could offer any guidance in assessing response to treatment or whether they would remain purely diagnostic tools. We will address this issue by looking for

data on treatment response in terms of patient-reported outcomes. It is also unclear at this time which populations would benefit most from the wireless motility capsule or which order of testing is best to diagnose patients. Currently, clinicians recommend wireless motility capsule testing as an alternative test instead of scintigraphy. However, in cases that are still suspected but indeterminate, it is controversial whether it can replace or should supersede other testing methods.

Constipation

Definition and Prevalence

Constipation is a common symptom, reportedly occurring in 10 to 20 percent of the U.S. population.[22,23] Multiple professional societies (with few variations) define constipation as fewer than two bowel movements per week or a decrease in a person's normal frequency of stools that is accompanied by straining, difficulty passing stool, or passage of hard solid stools.[17] Patients who have fewer than two bowel movements per week should have a physician assess their medical history and perform a physical examination to exclude malignant or organic causes of constipation. A careful history should be able to elicit warning signs such as new onset of symptoms, obstructive symptoms, rectal bleeding, unintentional weight loss, or family history of early colon cancer. A rectal examination can further delineate rectal function and tone, and it can help to exclude a low rectal cancer. A colonoscopy is warranted if fecal occult blood, iron deficiency anemia, or any other warning signs are present, or if the patient with constipation is 50 years of age and has never received a screening colonoscopy.[24] However, the yield of colonoscopy is low in patients with constipation and warning signs. Once an examination excludes organic causes of constipation, a physician can diagnose functional constipation. For individuals who are less than 50 years of age without "red flag" symptoms, no testing is necessary for a diagnosis of constipation, assuming the patient meets the Rome III criteria.

The Rome III criteria define functional constipation as follows:

1. Two or more of the following symptoms
    a. Straining during at least 25 percent of defecations
    b. Lumpy or hard stools in at least 25 percent of defecations
    c. Sensation of incomplete evacuation for at least 25 percent of defecations
    d. Sensation of anorectal obstruction/blockage for at least 25 percent of defecations
    e. Manual maneuvers to facilitate at least 25 percent of defecations (e.g., digital evacuation, support of the pelvic floor)
    f. Fewer than three defecations per week
2. Loose stools rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

Two or more of the above criteria must be present for the last 3 months, and symptoms must have first appeared at least 6 months prior to diagnosis.[25]

Basic Management

Physicians should recommend lifestyle changes and medical management for all patients with symptoms of constipation. Lifestyle changes include drinking appropriate quantities of liquid; removing all possible offending medications; and eating a sufficient amount of

vegetables, fruit, and fiber as recommended by the U.S. Department of Agriculture. Medical management includes avoiding constipating medications, and initiating bulking agents (e.g., fiber supplements), stool softeners (e.g., docusate, mineral oil), osmotic and stimulant laxatives (e.g., lactulose, milk of magnesia, magnesium citrate, polyethylene glycol [Miralax®], PEG-3350, senna), prokinetics (e.g., bisacodyl), or secretagogues/channel enhancers (e.g., linaclotide [FDA approved], lubiprostone [FDA approved and available in U.S.], prucalopride [not yet FDA-approved, but available in Europe and elsewhere]), as indicated. An initial constipation evaluation does not often involve colonic transit testing.

Evaluation of Possible Slow-Transit Constipation

For certain individuals with suspected slow-transit constipation (defined as persistent symptoms of constipation despite medical management and lifestyle changes) colon transit testing can provide insight into the reason for the constipation. Testing can help physicians identify why a patient failed first-line therapy and help identify patients who require surgery.[17] Transit disorders include slow colonic transit or colonic inertia, a hypomotile disorder of the colon where transit in the proximal colon is slow without evidence of retropulsion of the markers from the left colon and without evidence of anorectal dysfunction. Defecatory dysfunction (or functional outlet dysfunction) is the presence of uncoordinated motion of the anorectum muscles causing ineffective or weak expulsion of stool. Idiopathic megacolon (primary or secondary), a pathological enlargement of the colon, can also be present and may occur in conjunction with longstanding neurological diseases or Hirschsprung's disease (a failure of the development of the nerve cells within the colon wall).[26] The main diagnostic methods used to test for colonic motility are radiopaque marker examination, colonic scintigraphy, colonic and anorectal manometry, and wireless motility capsule testing.[27,28] The nonreference standard is radiopaque markers (ROM); however, scintigraphy is a comparable measure of colonic transit. Other investigatory tools that can provide complementary information are imaging tests such as defacography with barium or magnetic resonance imaging, barium enema, endorectal ultrasound, and magnetic resonance imaging of the pelvis.

ROM

Experts use the nonreference standard of ROM testing (commonly known as Sitz Markers) to define slow-transit constipation.[27,28] Different institutions employ varied protocols for ROM testing and major GI societies do not presently endorse one standard protocol. In its simplest form, such testing consists of a patient ingesting the ROMs on day zero and then taking x-rays at day 5; these x-rays use overpenetrated films (110 kiloelectron volts) in order to reduce radiation exposure. Gastroenterologists no longer focus on the areas of colon that have the greatest delays, since studies have shown that this does not predict pathophysiology or treatment. The only exception to this statement is the patient who accumulates markers in the rectum and does not pass them; this would strongly suggest a defecation disorder. Marker retention helps physicians identify patients with slow transit. Some centers also use other testing methods, such as the Metcalf method.[15,17] One disadvantage to ROM is x-ray exposure. Another disadvantage of ROMs is that they primarily assess oro-cecal transit and are not necessarily specific to the colon, since the test requires that patients swallow the markers and pass them out the anus. Any transit delay in the stomach or small bowel, or an anorectal outlet obstruction would also show up as a positive ROM test with retained markers, but there is no simple way to differentiate between

these disorders without further testing. However, the test is valid and in practice since the late 1960s.[15]

Colonic Scintigraphy

Some physicians also perform colon scintigraphy but it is rarely available outside of highly-specialized motility research centers. This procedure requires that patients ingest a radiolabeled meal or radiolabeled tracer so physicians can follow the sequence of transit from the upper to lower GI tract. Research has validated this treatment, and several drug trials have used it to study treatment response. Two protocols exist. One from Temple University uses a seven-region analysis in which a numeric value represents overall colon transit and emptying of the ascending colon; the protocol summarizes the analysis in terms of the half-life of the radiolabeled substance. A second protocol, from the Mayo Clinic, combines the results of a five-region analysis. A disadvantage of colonic scintigraphy is that testing requires several days and requires radiation exposure. Studies have assessed the validity of colon scintigraphy relative to ROM.[29,30] The ANMS guidelines endorse colon scintigraphy as a potential test for evaluating colon transit.

Total Colonic Manometry

Colonic manometry, a relatively new diagnostic test, is not widely available and only specialized centers offer it. For this test, a physician places a manometry catheter with endoscopic and fluoroscopic guidance after a full bowel preparation. The physician leaves the catheter in place for up to 24 hours, and obtains recordings after sedation (needed to place the catheter) has worn off. One disadvantage of this method is its limited availability, which is due to the specialized technical expertise required to perform and interpret this labor-intensive procedure. It is uncertain how physicians can use this information to guide the management of adults with slow-transit constipation.

WMC

WMC testing involves ingesting a capsule and wearing a receiver to collect data. It can detect specific transit times in the stomach, small bowel, and colon and thus detect both upper and lower GI disorders simultaneously with a single device. The pill itself is a large object, which remains large as it passes out of the stomach and into the small intestine. This differs slightly from the regular digestion process, in that the body usually moves food to the small intestine when the stomach has reduced the particles to a size no larger than 3 mm. Physicians can determine the capsule has exited from the stomach when gastric baseline pH rises rapidly (by 3 or more pH units) to a pH greater than 4. Cecal entry occurs when there is a sustained drop in pH of greater than 1 unit, more than 30 minutes after gastric emptying.[31] We measure colonic transit time by calculating the time between cecal entry and rectal exit; rectal exit produces a large temperature reduction.[17] One disadvantage is that in 5 percent of patients undergoing capsule testing, physicians don't collect cecal entry-time data, this reduces the diagnostic potential of the capsule.[15] Camilleri has reported a way to use a combination of small bowel and colon transit times to better interpret these tests which do not report cecal entry.[32] Other disadvantages are: physicians must use radiographic imaging to confirm elimination of the capsule when it fails to pass spontaneously, studies have indicated a 3 percent failure rate for the device, and physicians need to perform another motility testing to confirm whether prolonged colon transit time might be related to defecatory dysfunction. One advantage of capsule testing is the collection of data for the whole gut with one test. For patients with both colonic and gastric emptying delay, a

wireless motility capsule can detect both disorders. Without the capsule, physicians would need two tests to make these assessments--gastric emptying scintigraphy and radioopaque markers. Other advantages include the lack of radiation exposure when the capsule is passed spontaneously and safely, and the fact that physicians can perform capsule testing in the outpatient setting, thereby providing accurate information about real-life conditions. Physicians cannot perform capsule testing in any patient who might have stricture or stenosis. Patients might need additional testing to ensure that narrowing is not present. Another advantage of capsule testing is that it provides a more complete picture of colonic transit (like whole-bowel scintigraphy might if it were more widely available); whereas, ROM testing only offers static imaging. One disadvantage is that there is only a single point of detection during the wireless motility capsule study (data gathering can only occur where the capsule in located) and there is no way to find out the specific location of the capsule, beyond knowing if it has exited an area (stomach, small intestine, or colon). Furthermore, it is uncertain whether all the extra data provided by this modality will be useful to change outcomes in any way.

Use of Colon Transit Testing To Guide Treatment

Most patients with chronic constipation see symptom improvement with medical therapy and/or lifestyle changes. For some patients, all measures fail and physicians must use colon transit testing to better understand the motility disorders. However, a single test may not reflect the full complexity of a patient's motility disturbances since colon transit disorders can be complex to sort out. For example, anorectal dysfunction can impact colonic transit, but physicians detect it using anorectal manometry, separate from other transit testing. When anorectal manometry or balloon expulsion testing identifies anorectal or outlet dysfunction, physicians can treat using biofeedback therapy. Physicians can treat Hirschsprung's disease using surgical segmental resection. Megacolon may require medical therapy tailored to reducing gas formation, and reduction of fiber intake may paradoxically relieve symptoms. If these conservative measures fail, then megacolon may warrant segmental or total colectomy. If testing confirms the presence of slow-transit constipation (colonic inertia) without laxatives, then the next step in evaluation (at some centers) is transit testing with laxatives. A motility expert consensus states that physicians should consider surgery only after confirming colonic inertia.[33] Clinicians can recommend colectomy when there is severe total or segmental slow-transit constipation; however, most clinicians reserve colectomy for patients with the most untreatable conditions. Sometimes an individual may have features of both outlet dysfunction and inertia; in these cases, guidelines suggest that physicians treat the outlet dysfunction before making decisions about slow transit. If outlet dysfunction does not improve with biofeedback therapy, then surgical options may be limited to ileostomy rather than primary anastomosis. Some patients with delayed colonic transit may have evidence of a more diffuse GI disorder, such as gastric or small bowel transit delay.[12,34] It is important to detect the accompanying disorder, since patients with colonic inertia and gastric emptying delay have poorer outcomes from total colectomy. Therefore, an accurate diagnosis is essential to properly manage slow-transit motility disorders.

Outcomes

An important outcome of interest to clinicians is the ability to diagnose slow-transit constipation. Other important clinical outcomes include the ability of testing to influence treatment decisions (e.g., medications, nutrition) or to affect patient-centered outcomes (e.g.,

symptom improvement, need for surgery, quality of life, patient satisfaction). It is also important to consider potential harms such as capsule retention, radiation exposure, and mortality. Clinicians and policymakers may also be interested in the effects on resource utilization such as the need for additional tests, physician services, and hospitalizations.

Controversy

The 2011 ANMS conference addressed controversy regarding the role of capsule testing in the diagnostic evaluation of constipation. Experts debated the timing of wireless motility capsule in the evaluation of patients with suspected motility disorders, especially concerning the pending FDA approval for some of the newer prokinetic/secretagogue medications.

Scope and Key Questions

Our objective is to summarize the evidence on how useful current testing modalities for colonic and gastric motility are for diagnosing disease. Additionally, we seek to determine whether wireless motility capsule testing is useful in conjunction with or instead of other testing modalities for diagnosing and managing delayed gastric emptying or slow-transit constipation. Our goal is to define the populations that would benefit most from motility testing, including wireless motility capsule testing.

Key Questions

We finalized our Key Questions (KQs) below, and graphically depicted them in Figure 1:

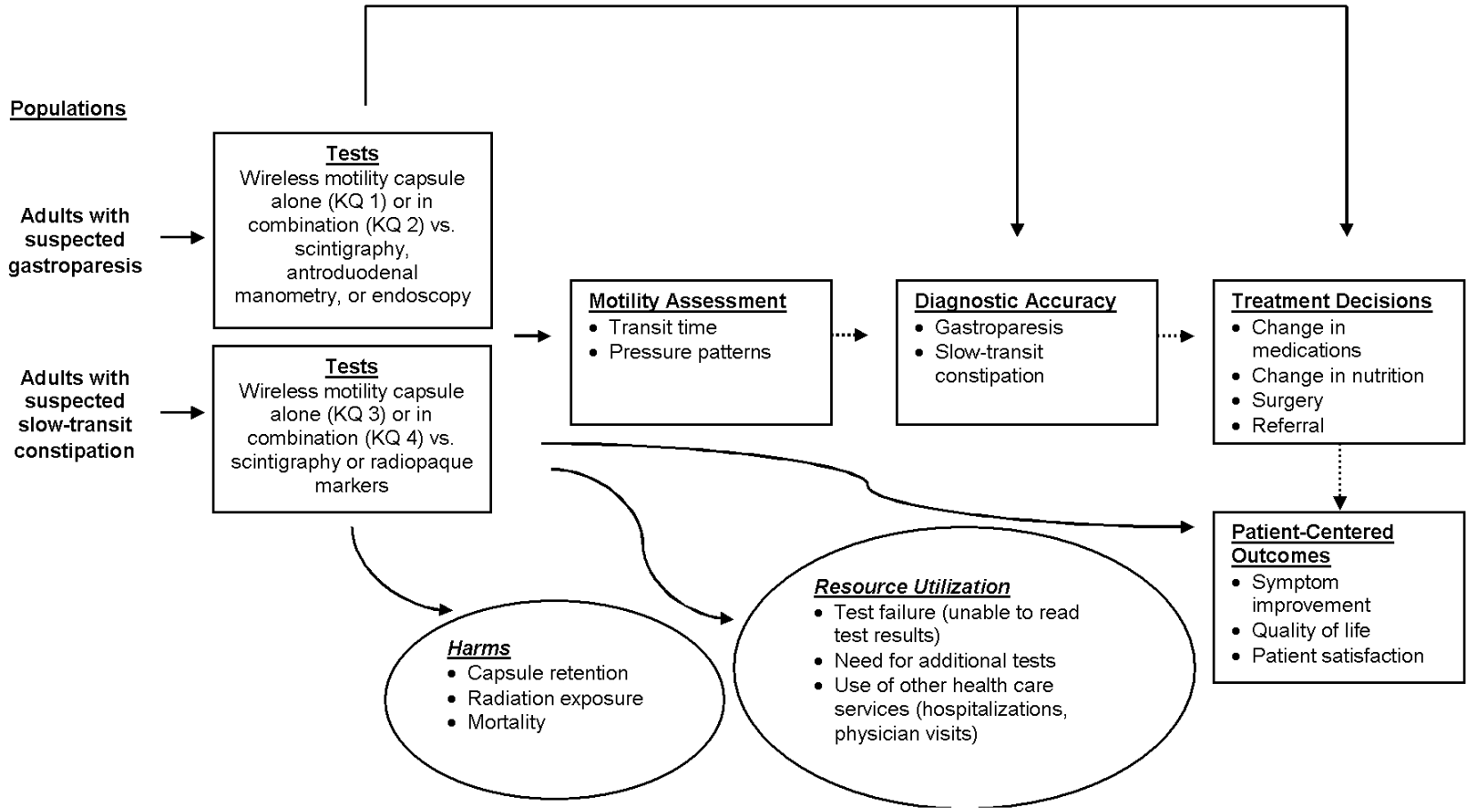
KQ 1. In the evaluation of gastric dysmotility, how does the wireless motility capsule alone compare with gastric scintigraphy, antroduodenal manometry, and endoscopy in terms of diagnostic accuracy of gastric emptying delay, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

KQ 2. When gastric scintigraphy, antroduodenal manometry, or endoscopy is used in the evaluation of gastric dysmotility, what is the incremental value of also using the wireless motility capsule in terms of diagnostic accuracy of gastric emptying delay, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

KQ 3. In the evaluation of colonic dysmotility, how does the wireless motility capsule alone compare with ROM and scintigraphy in terms of diagnostic accuracy of slow-transit constipation, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

KQ 4. When an ROM or scintigraphy is used in the evaluation of colonic dysmotility, what is the incremental value of also using the wireless motility capsule in terms of diagnostic accuracy of slow-transit constipation, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

Figure 1. Analytic framework for research on the comparative effectiveness of diagnostic technologies for evaluating gastroparesis and constipation



KQ = Key Question

Methods

This topic was nominated via the Agency for Healthcare Research and Quality's (AHRQ) Web site. Our Evidence-based Practice Center (EPC) established a team and a work plan to develop the evidence report. The project involved formulating and refining the questions, developing a protocol with input from selected technical experts, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Refinement

We recruited a panel of Key Informants to provide input on the selection and refinement of the questions to be examined. The Key Informants included three gastroenterologists who specialize in motility disorders, a representative from a patient advocacy group, and a representative from a payer organization. We posted our draft Key Questions (KQs) on AHRQ's website in December 2011 for public comment.

We developed the KQs that we presented in the scope and KQ sections of the introduction with input from the Key Informants, representatives of AHRQ, and public comments. The KQs focus on the diagnostic accuracy of the wireless motility capsule alone or in combination with other diagnostic tests in the evaluation of gastroparesis and slow-transit constipation.

Technical Expert Panel

We recruited a Technical Expert Panel (TEP) to review a draft of the protocol for preparing this evidence report. The TEP included five gastroenterologists with expertise in motility disorders, a patient representative, and an expert in diagnostic accuracy. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the KQs. With the feedback from the TEP and AHRQ representatives, we finalized the protocol and posted it on AHRQ's website.

Search Strategy

We searched the following databases for original studies for the periods in parentheses: MEDLINE® (1966 to July 1, 2012) and Embase® (1974 to July 1, 2012). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings terms and text words of key articles we identified a priori (Appendix A). Additionally, we reviewed the reference lists of included articles and any relevant review articles. We also reviewed the conference proceedings for Digestive Disease Week for 2012.

We downloaded the results of the searches and imported them into ProCite® version 5 (ISI ResearchSoft, Carlsbad, Calif.). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in ProCite®. We uploaded the articles from ProCite to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. We used this database to track the search results at the levels of title review, abstract review, and article inclusion/exclusion.

To identify additional studies, the EPC's Scientific Resource Center submitted a request to the manufacturer of the motility capsule, the SmartPill® Corporation, for any published or unpublished randomized controlled trials or observational studies that evaluated the wireless

motility capsule. The SmartPill® Corporation submitted comments on the draft report, but did not submit any new materials. We searched ClinicalTrials.gov to identify any relevant trials.

Study Selection

Two independent reviewers scanned each title from the literature search. In order to eliminate it at this level, both reviewers had to indicate that the title was obviously ineligible. If they disagreed, they promoted the article to the next level of review (Appendix B, Title Review Form). We designed the title review to capture as many studies as possible that reported on the diagnostic accuracy of the wireless motility capsule.

Two investigators reviewed abstracts independently, and excluded an article if both investigators agreed it met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 1 and the Abstract Review Form in Appendix B). The team resolved differences between investigators regarding abstract eligibility through consensus adjudication.

Two reviewers performed another independent parallel full-text review of articles promoted on the basis of abstract review to determine if we should include these articles for data abstraction (Appendix B, Article Review Form). We resolved differences regarding article inclusion through consensus adjudication.

Data Abstraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created and pilot tested standardized spreadsheets for data extraction. By creating standardized spreadsheets for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

The study investigators performed double data abstraction on each article. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs that included personnel with both clinical and methodological expertise. We did not hide from the reviewers the identity of the authors of the articles, their respective institutions, or the names of the journals that published the articles.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, country, location of recruitment, start year of recruitment, multi-center versus single center, length of followup, and length of time in between diagnostic tests), study participants (e.g., condition, age, gender, race, weight, prior diagnostic tests, blood sugar, smoking status, diabetes status, defacatory dysfunction status, and the use of prokinetics, narcotics, antidepressants, proton pump inhibitors, and laxatives), eligibility criteria, characteristics of the wireless motility capsule testing (e.g., was the pill swallowed or placed, did patients eat a standardized meal, did they drink Ensure® shakes[b]), comparisons, outcome measures, definitions, and the results of each outcome (including measures of variability). For endoscopy, we would capture the number of hours that participants did not receive anything by mouth before the procedure and the method of sedation. For gastric scintigraphy, we would collect data on duration of testing (e.g., 4 hours) and if the study used liquid or solid components. For antroduodenal manometry, we would collect data on the choice and placement of the catheter. For ROM, we would collect data on the type of ROMs, the timing of dosing of markers

[b]Ensure® is a commercial nutritional drink that is given to subjects in some centers as part of the wireless motility capsule protocol.

and the surveillance x rays, and if the study recorded counts in each segment of the colon, or if it used a total count, or both. For colon scintigraphy, we would collect data on the type of protocol, and the duration of testing. For each of the diagnostic tests, we would collect information on the criteria the study used to make a diagnosis of gastroparesis and slow-transit constipation, and whether it instructed patients on the use of tobacco, prokinetics, narcotics, antidepressants, proton pump inhibitors, or laxatives at the time of the test.

The individual completing the review entered all information from the article review process into a Microsoft Excel (Microsoft, Redmond, WA) spreadsheet. Reviewers entered comments into the system whenever applicable.

Table 1. Inclusion and exclusion criteria

Population and Condition of Interest	• We included studies that evaluated patients with suspected gastroparesis and/or slow-transit constipation. • We included only adult human subjects.
Diagnostic Test of Interest	• We included all studies that evaluated WMC alone or in combination with other tests.
Comparisons of Interest	• For KQs 1 and 2, we included studies that compared WMC with other conventional diagnostic tests for suspected gastroparesis, including scintigraphy, antroduodenal manometry, and endoscopy. • For KQs 3 and 4, we included studies that compared WMC with other conventional diagnostic tests for suspected slow-transit constipation, including scintigraphy and ROM.
Outcomes	• We included studies that reported on at least one of the following outcomes: o Diagnostic accuracy ▪ Gastroparesis: The reference standard is a 4-hour gastric emptying study. ▪ Slow-transit constipation: There is no consensus on a standard, so we examined this outcome relative to each existing standard (ROM and colonic scintigraphy). o Motility assessment ▪ Transit time ▪ Pressure patterns o Treatment decisions ▪ Change in medications ▪ Change in nutrition ▪ Need for surgery ▪ Need for a referral o Patient-centered outcomes ▪ Symptom improvement ▪ Quality of life ▪ Patient satisfaction o Resource utilization ▪ Test failure (unable to read test results) ▪ Need for additional tests because of continued uncertainty about diagnosis ▪ Utilization of other health care services such as hospitalizations and physician visits o Harms, such as capsule retention, radiation exposure, and mortality
Type of Study	• We excluded articles with no original data (e.g., editorials, commentaries, reviews). • We included all types of studies with a comparison group that evaluated WMC.
Timing and Setting	• We included all clinical settings in developed countries. • We included all durations of followup, but our desired length of followup for symptom improvement, quality of life, and need for additional tests was at least 3 months.

KQ = Key Question; ROM = radiopaque markers

Quality Assessment

Two reviewers independently assessed article quality. We selected and modified the questions from the QUADAS-2 quality assessment tool.[35] We supplemented this tool with additional quality-assessment questions (e.g., to assess spectrum bias) based on recommendations in the Methods Guide for Medical Test Review.[36] Our quality assessment included items on: (1) whether the study excluded healthy subjects from the diagnostic accuracy comparison, (2) whether the study excluded severely affected patients, (3) whether the study enrolled a random sample of patients, (4) whether all patients received the same reference standard, (5) whether the study included all patients in the analysis, (6) whether the study interpreted results of the test independently, (7) whether the time period between tests was reasonably short (within 3 months) to ensure the condition did not change, (8) whether the study established cut-off values for test positivity before the study started, (9) whether a stated aim of the study was to compare diagnostic accuracy between wireless motility capsule testing and other diagnostic tests, (10) whether the study reported on conflicts of interest, (11) whether a commercial source related to motility testing funded the study, and (12) whether a commercial source related to motility testing employed or gave funding or fees to any of the authors.

When multiple publications reported on the same study and the assessments of study quality differed, we did not change the unclear responses to a yes or no based on reporting in a different publication. We assessed study quality for each individual publication because the analyses often differed even though it was conducted among the same patient population.

The two reviewers resolved differences in quality assessment.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population (e.g., age, etiology, comorbidities, prior surgery or gastric pacer), diagnostic tests (e.g., use of opiates during testing, use of bowel motility-altering agents, such as laxatives or prokinetic agents), outcomes, and settings (e.g., referral center) are typical for the treatment of individuals with suspected gastroparesis or slow-transit constipation.

Data Analysis and Synthesis

We had planned to conduct meta-analyses when there was sufficient data (e.g., at least five studies for hierarchical summary receiver operator characteristic curves for diagnostic accuracy and at least three studies for other outcomes) and studies were sufficiently homogenous with respect to key variables (e.g., population characteristics, study duration, and diagnostic tests). We qualitatively summarized studies not amenable to pooling.

We considered gastric scintigraphy and clinical symptoms to be reference standards and ROM to be a nonreference standard. For measures of diagnostic accuracy when there was a reference standard, we summarized the results in terms of sensitivity, specificity, and test concordance. For measures of diagnostic accuracy when there was a nonreference standard, we summarized the results in terms of positive percent agreement, negative test agreement, and test concordance.[37] We can describe the results of any given study in terms of the number of positive and negative tests detected by the index test and the reference standard or nonreference standard (see Figures 2 and 3). We report the diagnostic test accuracy results separately for studies that included known patients and nondiseased controls and for studies that included patients suspected of having the condition.

Figure 2. Calculation for sensitivity, specificity, and test concordance when there is a reference standard

	Reference standard – positive result	Reference standard – negative result
Index test – positive test result	a	b
Index test – negative test result	c	d

Sensitivity = (a / (a + c)) * 100%

Specificity = (d / (b + d)) * 100%

Test concordance = ((a + d) / (a + b + c + d)) * 100%

Figure 3. Calculation for positive and negative percent agreement and test concordance when there is a nonreference standard

	Nonreference standard – positive result	Nonreference standard – negative result
Index test – positive test result	a	b
Index test – negative test result	c	d

Percent positive agreement = (a / (a+c)) * 100%

Percent negative agreement = (d / (b + d)) * 100%

Test concordance = ((a + d) / (a + b + c + d)) * 100%

We conducted a sensitivity analysis where we included data that were only reported in a conference abstract.

When the reference standard was a clinical diagnosis, we chose a 10 percent difference between tests in sensitivity or specificity as a potentially important difference because researchers powered key studies to detect a 10 percent difference.[32] When the reference/nonreference standard was another diagnostic test, we considered it similar if the wireless motility capsule had test concordance of at least 80 percent.

Data Entry and Quality Control

A second reviewer checked the data that we entered into the Excel spreadsheets. Second reviewers were generally more experienced members of the research team. We discussed any problems with a reviewer's data abstraction at a meeting with the reviewers. In addition, a third team member audited 10 percent of the included studies. We found a few discrepancies. For that reason, the lead investigators re-checked the outcome data as they prepared the text of the results on each KQ.

Rating the Body of Evidence

At the completion of our review, we graded the strength of the best available evidence addressing KQs 1 through 4 by adapting an evidence grading scheme listed in both the Methods Guide for Medical Test Review[36] and the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[38,39] Both of these evidence grading schemes use the recommendations of GRADE Working Group.[40] We applied evidence grades to the bodies of evidence about each diagnostic test comparison for each outcome. We assessed the strength of the best available evidence by assessing the risk of bias, consistency, directness, and precision.

To evaluate the risk of bias, we considered: (1) if researchers published the study as an abstract only or as a peer-reviewed manuscript, (2) whether researchers interpreted the results of the wireless motility capsule independently from the results of other diagnostic tests, and (3) if there were other major quality issues. We contacted the authors regarding blinding of diagnostic test results if it was unclear in the manuscript. We did not evaluate abstracts on blinding. We considered spectrum bias (i.e., the extent to which disease severity affects the test results) as part of the assessment of risk of bias. We rated the body of evidence as "low risk of bias" if the study interpreted the diagnostic test results independently and there were no other major quality issues (see above list of items included in the quality assessment). We rated the body of evidence as "medium risk of bias" if the study interpreted the diagnostic test results independently and there was one major quality issue, or the study did not interpret the results of the diagnostic test results independently and there were no other major quality issues. We rated the body of evidence as "high risk of bias" if the study interpreted the diagnostic test results independently and there was more than one major quality issues, or the study did not interpret the results of the diagnostic test results independently and there were at least one major quality issue.

We rated the body of evidence as "consistent" if most of the studies showed the same direction of effect. We rated the consistency of a single study as "not applicable." We rated the body of the evidence as "direct" if most of the studies directly addressed the KQs. We based our rating of precision on the width of the confidence intervals for sensitivity, specificity, and positive and negative predictive values. If the width of the confidence interval was less than or equal to 10 percent, then we considered the body of evidence to be "precise."

We classified evidence pertaining to the KQs into four basic categories: (1) "high" SOE (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" SOE (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" SOE (evidence is unavailable or does not permit a conclusion).[40]

Peer Review and Public Commentary

Experts in gastroenterology and gastrointestinal motility disorders and individuals representing stakeholder and user communities were invited to provide external peer review of this comparative effectiveness review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in

a “disposition of comments report” that will be made available 3 months after AHRQ posts the final comparative effectiveness review on the AHRQ Web site.

Results

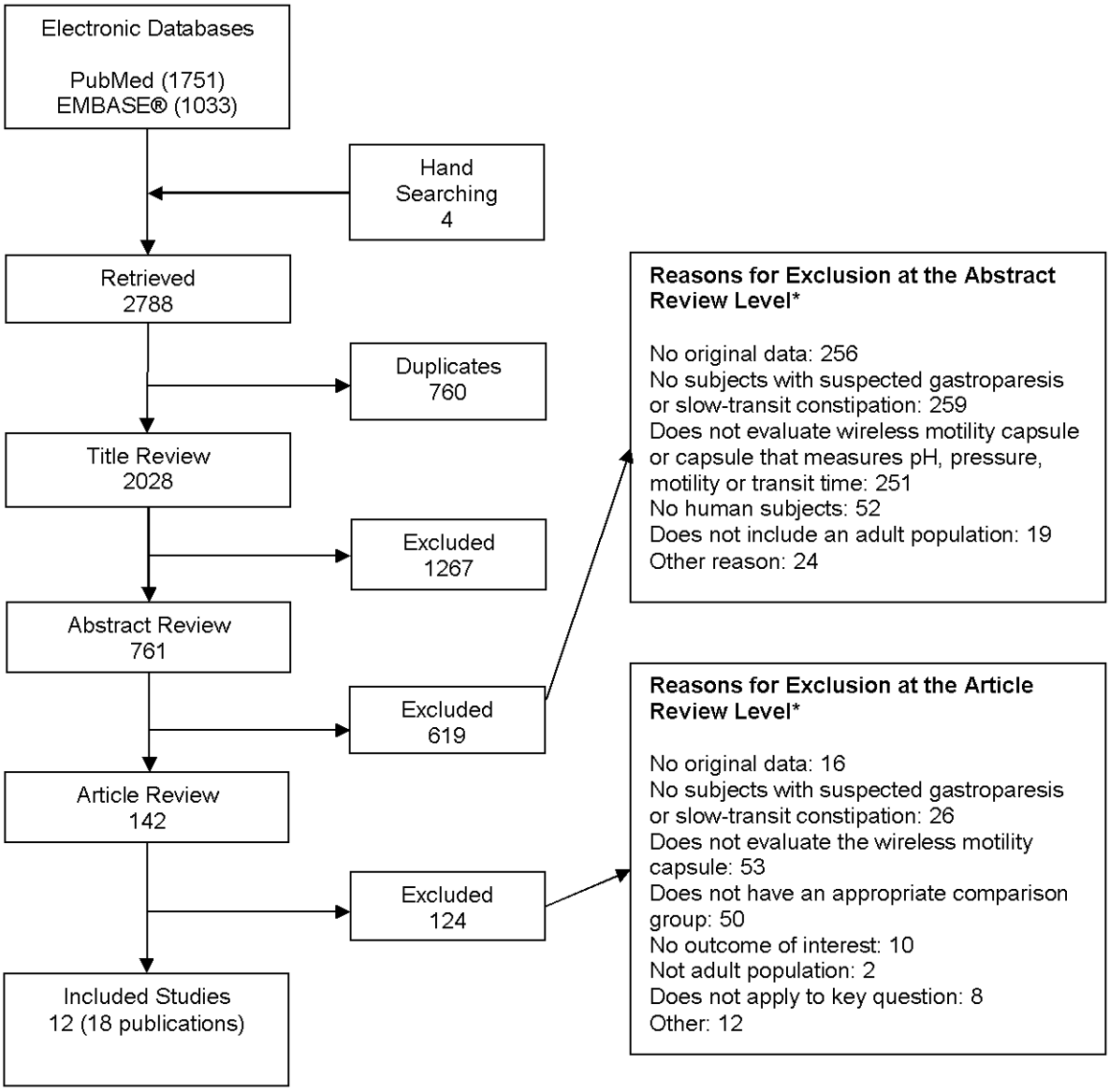
Search Results

Figure 4 summarizes the results of our literature search. Our search retrieved 2,028 unique records. After reviewing the titles and abstracts, we considered 142 articles as potentially relevant and we reviewed the full text of each article for eligibility (see Appendix C for a list of the excluded articles). We included a total of 12 studies (in 18 publications) in this review.[12,17,32,34,41-48] One manuscript[45] conducted additional analyses among the subjects included in another manuscript by Kuo et al.[16] Two manuscripts[49,50] conducted additional analyses among the subjects included in the manuscript by Rao et al.[17] Two abstracts[46,51] reported on the same patient population. One manuscript[34] previously appeared in two abstracts.[52,53]

Seven studies (10 publications) evaluated the wireless motility capsule test among patients with gastroparesis,[12,16,34,41-45,52,53] and nine studies (14 publications) evaluated the wireless motility capsule test among patients with slow-transit constipation.[12,17,32,34,42,44,46-53]

We identified four protocols from our search of ClinicalTrials.gov. We were able to match one protocol to a published manuscript using the NCT number[32,54] and matched two others based on the study descriptions.[16,17,55,56] We were unable to match the fourth protocol to any published study and the ClinicalTrials.gov website did not post results.[57] This study compares the gastric emptying time as measured by the wireless motility capsule with that measured by gastric scintigraphy in patients over age 64 years.

Figure 4. Summary of literature search, with numbers of articles involved in each search step



*Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

Study Design Characteristics

We included a total of 12 studies from 18 publications (see Appendix D, Evidence Table 1).[12,16,17,32,34,41-53] Seven studies were prospective,[16,17,32,41,43,47,48] Four studies were retrospective,[12,34,42,44] and one did not specify a study design.[46] Five of the prospective studies occurred at multiple study centers,[16,17,32,43,47] one occurred at a single center,[48] and the other prospective studies did not report the number of study locations. All prospective studies applied the tests concurrently. One of the retrospective studies involved chart review from multiple centers[12] with the remainder using information from single centers.[34,42,44] Six studies were in meeting abstracts,[41-44,46,47] the remainder were in peer-reviewed publications.

All studies that reported the study location occurred in the United States (U.S.).[12,16,17,32,34,41,43,44] One study took place in multiple countries including the U.S.[32] All studies that reported the location of recruitment occurred in tertiary centers.[12,17,34,41-44,48]

Three studies reported the start year of recruitment.[12,16,34] One began recruitment in 2005[16] with the other two starting recruitment in 2007.[12,34] Length of followup for the prospective studies and those with unspecified designs included the day of the testing only,[41,43,44,46,51] 3 days,[16] 5 days,[47,48] 14 days,[32] and 21 days.[17]

Prospective studies included patients with known gastroparesis[16,41,43] or constipation.[17,32,48] Four retrospective studies included patients with suspected gastroparesis or constipation[12,34,42,44] and one included patients with known constipation exclusively.[46] Six of the prospective studies also included patients without gastroparesis or constipation,[16,17,41,43,47,48] whereas one study included only patients with known constipation.[32] Three studies that included patients with constipation used the Rome III criteria as inclusion criteria.[17,32,48] Two studies reported age restrictions. One allowed patients 18 to 80 years of age[32] and two others included patients older than 65 years of age.[47,48]

Study Population Characteristics

No gender restrictions were made in the inclusion criteria, although the majority of participants with gastroparesis or constipation were female (Appendix D, Evidence Table 2). The mean age was 40 or greater in all studies that reported an average.[12,17,32,34,46-48] Three studies reported on race or ethnicity.[16,32,34] Greater than 80 percent of the participants were white in these studies. No study reported a measure of weight, blood sugar, or smoking status at baseline. Two studies reported on the percent of patients with diabetes.[12,45] Fifteen and 37 percent had diabetes. Two studies reported on defecatory dysfunction.[12,46] Twenty of 32 subjects had defecatory dysfunction in one study[46] and in another study 64 percent of patients with had defecatory dysfunction.[12] Studies rarely reported use of medications such as prokinetics, opiates, antidepressants, proton pump inhibitors, and laxatives, prior to and during the studies. Diagnostic testing prior to the study included scintigraphy[12,16,34,43] and ROM.[12,34]

Characteristics of Diagnostic Tests

In Tables 2, 3, and 4, we summarized the characteristics of the tests the studies used, taking into consideration how the evaluation of gastrointestinal motility is dependent on multiple factors, including not only the type of test but also the specific protocol employed (Appendix D, Evidence Table 3). The specific protocols these studies employed were often not standardized. We detailed the characteristics of the gastric scintigraphy tests in Table 2. We detailed the characteristics of wireless motility capsule testing for gastroparesis in Table 3. We detailed the characteristics of ROM testing in Table 4. Only two abstracts reported on antroduodenal manometry testing, and both provided limited information regarding study characteristics. No included studies reported on colonic manometry.

Table 2. Characteristics of gastric scintigraphy testing in studies of patients with symptoms of possible gastroparesis

Author, Year	Duration of Test	Tougas Protocol*	Patients Off Tobacco at Time of Test	Patients Off Prokinetics at Time of Test	Patients Off Opiates at Time of Test	Patients Off Antidepressants at Time of Test
Rao, 2011[34]	NR	NR	NR	NR	NR	NR
Kuo, 2008[16]	4 hours	Yes	Yes	Yes	Yes	No
Brun, 2011[41] [abstract]	4 hours	Yes	NR	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	NR	NR	NR	NR	NR	NR
Lee, 2010[42] [abstract]	4 hours	Yes	NR	NR	NR	NR
Reddymasu, 2010[43] [abstract]	4 hours	Yes	NR	NR	NR	NR
Lee, 2012[45]	4 hours	Yes	NR	Yes	Yes	NR

NR = not reported

*The Tougas protocol refers to a 4-hour solid state gastric scintigraphy protocol agreed upon by consensus of the American Neurogastroenterology and Motility Society and the Nuclear Medicine Society.[21]

Table 3. Characteristics of WMC testing in studies of patients with symptoms of possible gastroparesis or slow-transit constipation

Author, Year	Criteria for Abnormal	Standardized Meal	Type of Meal	Ensure® Challenge	Off Tobacco at Time of Test	Off Prokinetics at Time of Test	Off Opiates at Time of Test	Off Anti-Depressants at Time of Test	Off PPIs at Time of Test	Was Another Study Referenced in Lieu of Providing Details Within Current Study?
Kuo, 2011[12]	5 hours	NR	NR	NR	NR	NR	Yes	No	Yes	Yes[16,17]
Rao, 2011[34]	5 hours	Yes	Bar	NR	NR	NR	Yes	No	Yes	Yes[16,17,32]
Camilleri, 2010[32]	5 hours	Yes	Egg Beaters®	Yes	NR	Yes	Yes	Yes	Yes	Yes[17]
Saad, 2010[50] [Sub-analysis of data[17]]	NR	Yes	Bar	Yes	NR	Yes	NR	No	Yes	Yes[17]
Hasler, 2009[49] [Sub-analysis of data[17]]	NR	Yes	Bar	Yes	NR	Yes	Yes	No	Yes	No
Rao, 2009[17]	NR	Yes	Bar	Yes	NR	Yes	NR	No	Yes	No
Kuo, 2008[16]	NR*	Yes	Egg Beaters®	Yes	Yes	Yes	Yes	No	Yes	No
Brun, 2011[41] [abstract]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee, 2010[42] [abstract]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reddymasu, 2010[43] [abstract]	Gastric cph < 73	NR	NR	NR	NR	NR	NR	NR	NR	NR
Paulson, 2009[51]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee, 2009[44] [abstract]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rao, 2009[46] [abstract]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rao, 2009[47] [abstract]	NR	Yes	Bar	Yes	NR	NR	NR	NR	NR	NR
Lee, 2012[45]	5 hours	Yes	Egg Beaters®	Yes	NR	Yes	Yes	NR	Yes	Yes[16]
Rao, 2012[48]	5 hours	Yes	Bar	NR	NR	Yes	NR	NR	Yes	No

cph = contractions per hour; NR = not reported; PPI = proton pump inhibitor

*Reference article that came up with 5 hour criteria.

Table 4. Characteristics of ROM testing in studies of patients with symptoms of slow-transit constipation

Author, Year	Markers Swallowed	Type of Markers Were Used	Timing of Ingestion	Days Imaging Studies Were Taken	Method of Analysis	Considered Prolonged Colon Transit	Was Another Study Referenced in Lieu of Providing Details?
Kuo, 2011[12]	Historically by chart review	ROM	NR	NR	NR	NR	Not referenced
Rao, 2011[34]	NR	ROM	NR	NR	NR	Retention of ≥6 ROM at 120 hrs was defined as abnormal colonic transit	Yes[17,58]
Camilleri, 2010[32]	Yes	ROM	Ingestion of 24 ROM on 3 consecutive days	Abdominal x rays taken on day 4 and day 7 (144 hours after ingestion of first markers)	Metcalf method= Count number and distribution of markers. Sum the number of markers visualized on day 4 and day 7 x rays and equating 1 marker to 1 hr of colonic transit time	Colonic transit time greater than 67 hrs is considered delayed	Yes[59]
Saad, 2010[50] Sub-analysis of data[17]	Yes	ROM	Ingestion of 24 ROM	Abdominal x-rays taken on day 2 and day 5 after ingestion of first markers	See reference	Retention of > 20% of ROM after 5 days	Yes[60]
Hasler, 2009[49] Subset of study[17]	Yes	ROM*	Ingestion of 24 ROM (one capsule)	NR	NR	NR	Yes[17]
Rao, 2009[17]	Yes	ROM*	Ingestion of 24 ROM (one capsule)	Abdominal x ray 48 hrs and 5 days (120 hrs) after ingestion	Radiographs were reviewed at each location. All radiographs were reviewed by 2 independent blinded investigators.	Retention of > 5 markers at day 5 was considered abnormal	Yes[58,60]
Mysore, 2010[53] [abstract]	Yes	NR	NR	NR	NR	NR	Not referenced
Rao, 2009[46] [abstract]	Yes	NR	NR	NR	NR	NR	Not referenced
Rao, 2012[48]	Yes	ROM*	Ingestion of 24 ROM (one capsule)	Day 5	Radiographs on day 5 were reviewed	Retention of > 5 markers at day 5 was considered abnormal	Yes[58]

NR = not reported; ROM = radiopaque markers

*Sitzmarks®, Konsyl Pharmaceuticals; Fort Worth, TX.

KQ 1. Evaluation of Gastric Dysmotility: WMC Alone Versus Other Diagnostic Tests

Key Points

- The diagnostic accuracy of WMC is similar to scintigraphy. The sensitivity of WMC compared with the reference standard of a clinical diagnosis of gastroparesis ranged from 65 to 68 percent and the specificity ranged from 82 to 87 percent. The sensitivity of gastric scintigraphy compared with a clinical diagnosis of gastroparesis ranged from 34 to 44 percent and the specificity ranged from 93 to 94 percent. Sensitivity of the wireless motility capsule compared with gastric scintigraphy ranged from 59 to 86 percent and specificity ranged from 64 to 81 percent. (Strength of evidence [SOE]: Low)
- Transit data obtained via WMC correlate well with scintigraphic gastric emptying data. (SOE: Low)
- Pressure profiles obtained via WMC add to the diagnostic accuracy. Scintigraphy does not measure pressure patterns. (SOE: Low)
- Information derived from WMC testing alters management in patients with suspected gastroparesis (50 to 69 percent change in management for medicine, diet, or surgery). (SOE: Low)
- WMC testing may reduce the need for other testing, but this conclusion was based on one study with a high risk of bias. WMC testing may not reduce the need for anorectal manometry. (SOE: Low)
- Harms associated with WMC were minimal. While studies did not report any major safety issues, conclusions about harms will likely change with new evidence. (SOE: Low)
- The SOE was insufficient regarding the effect of WMC testing on patient-centered outcomes, as no studies addressed this type of outcome.
- The SOE was insufficient for the comparison of WMC with antroduodenal manometry in patients with suspected gastroparesis, as we did not find any studies evaluating this comparison.
- The SOE was insufficient for the comparison of WMC with endoscopy in patients with suspected gastroparesis, as we did not find any studies evaluating this comparison.

WMC Versus Gastric Scintigraphy

Diagnostic Accuracy

We found seven studies with 560 total patients that examined this outcome for this comparison (Tables 5 and 6 and Figure 5).[12,16,34,41,43-45] Three of these studies appeared as abstracts only.[41,43,44] These studies defined diagnostic accuracy in various ways. Two studies, one of which appeared as an abstract only,[43] included subjects with and without gastroparesis and evaluated the sensitivity and specificity of the wireless motility capsule and gastric scintigraphy compared with clinical gastroparesis. The sensitivity of wireless motility capsule ranged from 65 to 68 percent and the specificity ranged from 82 to 87 percent. The sensitivity of gastric scintigraphy compared with clinical gastroparesis ranged from 34 to 46 percent and the specificity ranged from 93 to 94 percent.

All studies, including one abstract,[44] looked at diagnostic agreement between the modalities. Diagnostic agreement between wireless motility capsule and gastric scintigraphy ranged from 59

to 86 percent positive test agreement and from 64 to 81 percent for negative test agreement. We estimated the concordance between the two tests to range between 35 and 81 percent. The range reflects the heterogeneity of the studies, which used different definitions of gastroparesis as determined by wireless motility capsule, as well as different study inclusion criteria. The results from the abstract do not change these conclusions.

One study[16] examined the specific outcome of diagnostic reclassification for this comparison. The authors recalculated diagnostic accuracy of the wireless motility capsule after reclassifying subjects as gastroparetic or normal based on their 4-hour scintigraphic study results. The receiver operating characteristic area under the curve for gastric emptying time was 0.94, the sensitivity was 87 percent, and the specificity was 92 percent.

One study[45] estimated the diagnostic accuracy, which they termed "diagnostic gain," of wireless motility capsule compared with gastric emptying scintigraphy (Table 7), using various combinations of gastric emptying time, wireless motility parameters, and gastric scintigraphy. The study defined diagnostic gain as abnormal motility detected by wireless motility capsule, deducting the number of subjects with abnormal gastric scintigraphy but normal wireless motility studies, over the total number of subjects, expressed as a percentage. In patients with confirmed gastroparesis (based on symptoms and prior scintigraphy within 2 years), gastric scintigraphy alone was abnormal in 51 percent of patients whereas 70 percent of patients had an abnormal wireless motility capsule study using a combination of gastric emptying time and motility parameters. The overall diagnostic gain of wireless motility capsule compared with gastric scintigraphy was 19 percent ($P = 0.04$).

One study[41] compared the coefficient of variation (COV) for various measures obtained by gastric scintigraphy and gastric emptying time via wireless motility capsule. This abstract evaluated the relationship between gastric emptying time of the wireless motility capsule and different parameters obtained via 4-hour gastric scintigraphy: namely retention at 2 hours, retention at 4 hours, time of 50 percent emptying, or time of 90 percent emptying. Both tests were obtained simultaneously and they reported that the time of 90 percent emptying by scintigraphy had the COV most similar to that of gastric emptying time by wireless motility capsule (Table 8).

Table 5. Diagnostic accuracy of WMC compared with gastric scintigraphy in the evaluation of gastroparesis comparing patients with known gastroparesis with known non-diseased controls

Author, Year	Definition for GP – WMC	Definition for GP - GES	Total N	Sensitivity of WMC Compared With Clinical GP	Specificity of WMC Compared With Clinical GP	Sensitivity of GES Compared With Clinical GP	Specificity of GES Compared With Clinical GP	Correlation Between WMC and GES, (95% CI)	AUC, (95% CI)
Kuo, 2008[16]	Threshold NR; abrupt pH rise (usually >3 pH units) from gastric baseline to a pH >4 as determined by software and 2 reviewers	>10% of meal retained after 4 hr	61 patients with GP 87 subjects without GI dysmotility	65%*	87%*	34% (2-hr), 44% (4-hr)*	93%*	0.63 (0.50-0.75) (2-hr) 0.73 (0.61-0.82) (4-hr)	0.83 (0.74–0.90) (WMC) 0.79 (0.71–0.88) (GES, 2-hr) 0.82 (0.77–0.91) (GES, 4-hr)
Reddymasu, 2010[43] [abstract]	Motility criteria: gastric cph < 73 or frequency of gastric contractions > 100 mm Hg being less than 2/hr	>10% of meal retained after 4 hr	41 patients with GP 66 subjects without GI dysmotility	68% (motility criteria: 88%)*	82% (motility criteria: 30%)*	46%*	94%*	NR	NR

AUC = area under the curve; CI = confidence interval; cph = contractions per hour; GES = gastric scintigraphy; GI = gastrointestinal; GP = gastroparesis; hr = hours; mm Hg = millimeters mercury; NR = not reported; WMC = wireless motility capsule
*Numerator and denominator not available.

Table 6. Diagnostic accuracy of WMC compared with gastric scintigraphy in the evaluation of gastroparesis including only patients with known or suspected gastroparesis

Author, Year	Definition for GP – WMC	Definition for GP- GES	N Analyzed With GP	Sensitivity of WMC Compared With Symptoms	Specificity of WMC Compared With Symptoms	Sensitivity of GES Compared With Symptoms	Sensitivity of WMC Compared With GES	Specificity of WMC Compared With GES	Concordance of WMC and GES
Kuo, 2011[12]	Emptying time > 5 hr	Based on result of prior testing	83 with suspected GI dysmotility	24/52 (46%)	19/28 (68%)	17/44 (39%)	10/17 (59%)	18/28 (64%)	17/45 (35%)
Rao, 2011[34]	NR	>10% of meal retained after 4 hr	36 suspected	24/36 (66%)	NR	15/36 (42%)	12/15 (80%)	17/21 (81%)	29/36 (81%)
Lee, 2009[44] [abstract]	NR	NR	32 suspected GI dysmotility	NR	NR	NR	9/14 (64%)	8/10 (80%)	NR
Lee, 2012[45]	WMC emptying time > 5 hr	>10% of meal retained after 4 hr	43 suspected	26/43 (60%)	NR	22/43 (51%)	86%*	66%*	77%*

GES = gastric scintigraphy; GI = gastrointestinal; GP = gastroparesis; hr = hours; NR = not reported; WMC = wireless motility capsule
*Numerator and denominator not available.

Figure 5. Summary of the sensitivity and specificity of WMC compared with gastric scintigraphy in patients with known or suspected gastroparesis

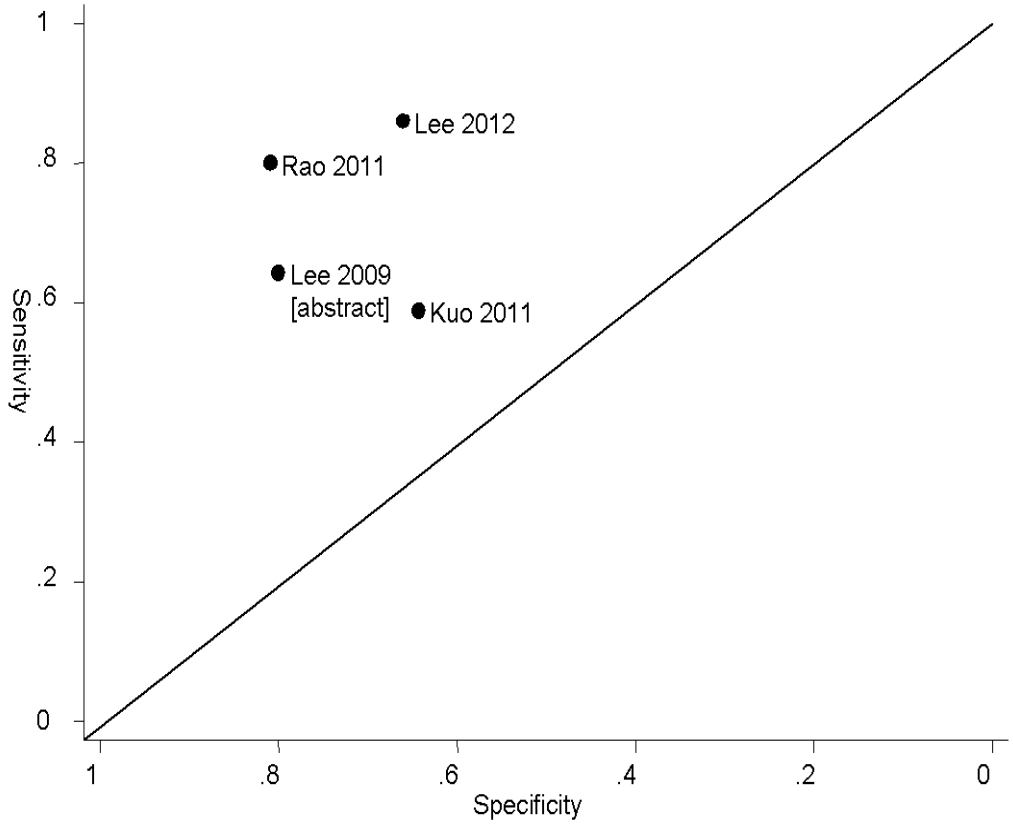


Table 7. Diagnostic gain of WMC compared with gastric scintigraphy in the evaluation of gastroparesis

Author, Year	Definition for Gastroparesis	Total N	GES	GES + GET	GES + G/SB PM	GES + GET + G PM	GET + G/SB PM	GES + GET + SB PM	GES + GET + G/SB PM
Lee, 2012[45]	5 hours	43	51%	67%	65%	67%	70%	75%	74%

GES = gastric emptying scintigraphy; GET = gastric emptying time; G/SB PM = gastric/small bowel pressure measurements; G PM = gastric pressure measurements; SB PM = small bowel pressure measurements

Table 8. Coefficient of variation* of gastric emptying among patients with gastroparesis using gastric scintigraphy and WMC

Author, Year	Definition for Gastroparesis	2h % Retention - GES	4h % Retention - GES	2h % Emptying - GES	4h % Emptying – GES	T50 - GES	T90 - GES	GET - WMC
Brun, 2011[41] [abstract]	Not reported	41%	129%	44%	24%	49%	30%	34%

GES = gastric emptying scintigraphy; GET = gastric emptying time; T50 = time of 50% emptying; T90 = time of 90% emptying; WMC = wireless motility capsule
*The coefficient of variation is a measure of dispersion of a probability distribution, defined as the ratio of the standard deviation of values to the mean of the values in a distribution. The coefficient of variation by itself doesn't tell us which test is better. It only provides a measure of how precisely the test can measure the value of interest, in this case, percent retention or percent emptying.

Motility Assessment

Transit Times

Five studies, including two abstracts,[41,43] evaluated wireless motility capsule-derived transit times in comparison with gastric scintigraphy alone for patients with gastroparesis.

Kuo et al.[16] evaluated 87 healthy subjects and 61 patients with gastroparesis via simultaneous gastric scintigraphy and wireless motility capsule. They compared gastric emptying via scintigraphy at 2 hours (GES-2h) and 4 hours (GES-4h) using wireless motility capsule to obtain gastric emptying time. Normative data for gastric scintigraphy at 2- and 4-hour time points came from the Tougas protocol. The study reported that the correlation coefficient between gastric emptying time via wireless motility capsule and GES-4h was 0.73 and the correlation coefficient between gastric emptying time via wireless motility capsule and GES-2h was 0.63. The study calculated receiver operating characteristic curves to evaluate the clinical utility of the diagnostic tests for gastric emptying time via the wireless motility capsule and GES-2h and GES-4h cut-offs compared with clinical diagnosis. They reported the area under the receiver operating characteristic curve and the sensitivity and specificity of the three diagnostic tests. The study did not observe any statistically significant difference between the areas under the curve for gastric emptying time via the wireless motility capsule and GES-4h. The authors then compared gastric emptying time via the wireless motility capsule with GES-4h. Using these data, the authors concluded that the area under the curve for gastric emptying time via the wireless motility capsule was 0.94, sensitivity was 87 percent, and specificity was 92 percent.

In a subsequent abstract,[41] the investigators reported on variability using additional scintigraphically-derived parameters (T50 or the time of 50 percent emptying of the meal, and T90 or the time of 90 percent emptying of the meal) and reported that gastric emptying time via the wireless motility capsule correlated more closely with T90 than with GES-2h or GES-4h; however, data provided in this abstract were limited.

Lee et al.[45] enrolled 48 subjects with symptoms of gastroparesis and a prior abnormal gastric emptying study. These patients then underwent simultaneous gastric scintigraphy and wireless motility capsule testing. Data from 43 subjects were available for analysis. Looking at transit alone, the study calculated overall device agreement at 77 percent (positive agreement 86 percent, negative agreement 66 percent). Seven subjects had a delayed wireless motility capsule with normal scintigraphy, whereas three subjects had a delayed scintigraphy but normal transit time on wireless motility capsule.

Rao et al.[34] evaluated 86 patients referred for motility evaluation in a retrospective fashion, comparing the wireless motility capsule with conventional motility testing. Of these patients, 36 had upper gastrointestinal symptoms and also underwent 4-hour gastric scintigraphy. The investigators reported that when they compared wireless motility capsule and gastric scintigraphy results in these patients using transit data alone, both studies were abnormal in 12 of 15 (80 percent) subjects and both tests were normal in 17 of 21 (81 percent) subjects. The study reported an overall device agreement of 81 percent using transit alone. There was diagnostic discrepancy in five of the 36 subjects (14 percent).

Reddymasu et al.[43] evaluated 66 healthy subjects and 41 patients with gastroparesis using simultaneous wireless motility capsule testing and scintigraphy. It defined gastroparetic patients as having symptoms consistent with gastroparesis and a prior abnormal gastric scintigraphy. When the study looked at wireless motility capsule-derived transit data isolated from pressure

parameters and compared it with clinical symptoms and a prior abnormal gastric scintigraphy test, the study reported the sensitivity of the wireless motility capsule at 68 percent and specificity at 82 percent. The study reported a current gastric scintigraphy to have a sensitivity of 46 percent and specificity of 94 percent.

Pressure Patterns

Two studies, including one that was published as an abstract only,[43] evaluated wireless motility capsule-derived pressure patterns in comparison with gastric scintigraphy alone for patients with gastroparesis. Lee et al.[45] evaluated 43 subjects with symptoms of gastroparesis and a previously-abnormal gastric scintigraphy within 2 years of enrollment. The authors reported that 47 percent of subjects had abnormal gastric or small bowel pressure measurements using the wireless motility capsule. However, the study did not perform a direct comparison between pressure parameters derived by wireless motility capsule (in the absence of transit data) and scintigraphic data alone. The authors did, however, evaluate the additional diagnostic gain achieved by using a combination of transit and pressure parameters. Specifically, 10 of 21 subjects with a normal gastric emptying scintigraphy had pressure abnormalities identified by wireless motility capsule. When compared with gastric scintigraphy alone, this study found a statistically significant improvement in diagnostic gain using a combination of gastric scintigraphy and wireless motility study ($P = 0.002$).

Reddymasu and colleagues[43] evaluated 66 healthy and 41 gastroparetic patients with simultaneous wireless motility capsule testing and scintigraphy. The study defined gastroparetic patients as having symptoms consistent with gastroparesis and a prior abnormal gastric scintigraphy. When the study looked at gastric pressure patterns in isolation from transit data and compared them with a clinical diagnosis of gastroparesis based on symptoms and a prior scintigraphy, the sensitivity of the wireless motility capsule was 88 percent and specificity was 30 percent. This was in comparison with gastric scintigraphy, which had a sensitivity of 46 percent and specificity of 94 percent. This abstract did not report data evaluating the combination of wireless motility capsule-derived transit and pressure data in comparison with scintigraphy.

Treatment Decisions

Three studies, including one abstract,[44] addressed this outcome for this comparison (Table 9). Kuo et al. found that examination with wireless motility capsule changed management in 52 of 83 (63 percent) patients.[12] Rao et al.[34] found that physicians made changes in management owing to wireless motility capsule testing in 18 of 36 (50 percent) of patients. However, the numbers of patients for whom physicians made particular categories of management changes were not available in the report. Lee et al. found that, physicians made management changes in multiple areas in patients who underwent examination by wireless motility capsule, compared with "another modality," for a total of 22 of 32 (69 percent) patients.[44]

Table 9. Change in treatment decisions due to examination by WMC compared with gastric scintigraphy in the evaluation of gastroparesis

Author, Year	Study Design	Total N	Total Change in Management	Changes in Medication	Changes in Diet	Changes in Procedure (G-tube Placement, J-tube Placement, or Surgery)
Kuo, 2011[12]	Retrospective chart review	83	52/83 (63%)	39/83 (47%)	9/83 (11%)	4/83 (5%)
Rao, 2011[34]	Retrospective chart review	36	18/36 (50%)	NR	NR	NR
Lee, 2009[44] [abstract]	Retrospective cohort	32	22/32 (69%)	18/22 (82%)	6/22 (27%)	4/22 (18%)

G-tube = gastronomy tube; J-tube = jejunostomy tube; NR = not reported

Resource Utilization

One study addressed resource utilization as an outcome.[12] Kuo et al. reviewed outpatient records of patients who had undergone wireless motility capsule testing to determine if capsule testing eliminated the need for additional tests. They assumed that patients who were undergoing evaluation for presumptive gastroparesis would undergo scintigraphy, that patients who were undergoing evaluation for presumptive small intestinal dysmotility would undergo barium studies, that patients with presumed slow-transit constipation would undergo ROM studies, and that WMC eliminated the need for these tests if these tests were not performed for patients with the aforementioned symptoms. They found there was no need for additional testing via gastric scintigraphy in nine of 52 patients (17.3 percent) patients, no need for additional testing via small bowel barium transit in seven of 13 (53.8 percent) patients, and no need for additional testing via radiopaque colon marker tests in 41 of 60 (68 percent) patients.

Patient-Centered Outcomes

No studies addressed patient-centered outcomes for this comparison.

Harms

The studies had limited data on potential harms of wireless capsule testing. Kuo et al.[16] evaluated 148 patients and reported that 46 percent required an abdominal x-ray to verify passage of the capsule because they did not return the capsule. Five subjects required a second x-ray to ensure passage; however, the capsule did pass in all subjects. The study reported 10 adverse events; six were unrelated to the wireless motility capsule and three were probably not related. The one event that the study felt to be associated with capsule use was capsule retention in the stomach due to entrapment with a fiber supplement; however, the capsule did pass in this case after administration of intravenous erythromycin. The study did not report any serious adverse events.

Rao et al.[34] reported on 86 patients who underwent wireless motility capsule testing in addition to conventional motility testing. The study did not report any serious adverse events and all subjects successfully expelled the capsule.

No other studies reported on this outcome.

WMC Versus Antroduodenal Manometry

No included studies addressed this comparison.

WMC Versus Endoscopy

No included studies addressed this comparison.

SOE

For most of the outcomes included in this Key Question, the SOE was low or insufficient. We included seven studies for diagnostic accuracy; however, four of the seven were felt to have a high risk of bias and only two of the seven were felt to be precise studies—both of which were felt to have high risk of bias. With regards to motility assessment, we also felt the strength of evidence was low, primarily due to risk of bias. Similar issues were present with the subquestions for treatment decisions, resource utilization, and harms. Please see Table 10 for more details.

Table 10. Numbers of studies and subjects, SOE domains, and SOE among studies comparing WMC testing with gastric scintigraphy

Outcome	Number of Studies/ Abstracts	Domains Pertaining to SOE				SOE
		Risk of Bias	Consistency	Directness	Precision	
Diagnostic accuracy	7[12, 16, 34, 41, 43-45] / 3	Medium	Consistent	Direct	Imprecise	Low
Motility assessment	5[16,34,41,43,45] / 2	Medium	Consistent	Direct	Imprecise	Low
Treatment decisions	3[12,34,44] / 1	High	Consistent	Direct	Imprecise	Low
Harms	2[16,34] / 0	Medium	Consistent	Direct	Imprecise	Low
Patient-centered outcomes	0	N/A	N/A	N/A	N/A	Insufficient
Resource utilization	1[12] / 0	High	Unknown	Direct	Imprecise	Low

N/A = not applicable; SOE = strength of evidence; WMC = wireless motility capsule

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

KQ 2. Evaluation of Gastric Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

Key Points

- Adding wireless motility capsule testing to conventional motility testing improves diagnostic accuracy in patients with suspected gastroparesis (sensitivity of scintigraphy compared with symptoms ranged from 42 to 51 percent; sensitivity of wireless motility capsule ranged from 60 to 66 percent). (SOE: Low)

- Adding wireless motility capsule testing to conventional motility testing improves assessment of motility parameters in patient with suspected gastroparesis. Scintigraphy does not measure pressure patterns. (SOE: Low)
- The strength of evidence was insufficient for treatment decisions, harms, patient-centered outcomes, and resource utilization. We did not find any studies addressing these outcomes.
- The strength of evidence was insufficient that the addition of wireless motility capsule testing to antroduodenal manometry or endoscopy affects diagnostic accuracy, motility assessment, treatment decisions, harms, patient-centered outcomes, or resource utilization. We did not find any studies addressing these comparisons.

WMC Plus Gastric Scintigraphy Versus Gastric Scintigraphy Alone

Diagnostic Accuracy

Two studies addressed this question with a total of 79 applicable patients.[34,45] Rao et al. evaluated 86 patients with symptoms of dysmotility and normal baseline endoscopic and radiographic evaluations.[34] Of those 86 patients, 36 had predominant upper gastrointestinal symptoms and underwent evaluation with 4-hour gastric scintigraphy and wireless motility capsule testing. On testing, gastric scintigraphy confirmed clinical suspicion for gastroparesis in 42 percent of patients whereas the wireless motility capsule confirmed suspicion for gastroparesis in 66 percent of patients. The two studies were abnormal in 12 of 15 patients (80 percent) and both were normal in 17 of 21 patients (81 percent) with an overall device agreement of 81 percent. There was diagnostic discrepancy in 5 of 36 (14 percent) subjects, representing at least some degree of diagnostic gain from the two modalities in combination. The studies did not calculate the statistical significance of this increased diagnostic yield.

Lee et al. evaluated 43 patients with symptoms of gastroparesis and previous abnormal gastric scintigraphy.[45] All patients underwent simultaneous gastric scintigraphy and wireless motility capsule study. Twenty-two of 43 patients (51 percent) had abnormal gastric scintigraphy, whereas 26 of 43 patients (60 percent) had abnormal gastric transit on wireless motility capsule. The study calculated overall device agreement for transit time at 77 percent (positive agreement 86 percent, negative agreement 66 percent). Seven of 43 patients had delayed gastric transit on wireless motility capsule and normal gastric scintigraphy. Three of 43 patients had delayed gastric scintigraphy with normal gastric transit on wireless motility capsule. In addition, this study evaluated gastric pressure parameters and found additional gain using those parameters. Ten of 21 subjects with a normal GES had pressure abnormalities identified by wireless motility capsule. When compared with gastric scintigraphy alone, this study found a statistically significant improvement in diagnostic gain using a combination of gastric scintigraphy and wireless motility study ($P = 0.002$).

Motility Assessment

Transit Times

The article by Rao et al. looked only at transit times and did not include pressure patterns in their analysis.[34] Thus, the findings above represent only transit time assessment. The study by Lee et al. looked at both transit times and pressure patterns. However, even when looking at transit times alone and disregarding pressure patterns entirely, there was a statistically significant

improvement in diagnostic gain discovered by scintigraphy plus wireless motility capsule transit time as compared with scintigraphy alone ($P = 0.02$).

Pressure Patterns

The only article to evaluate the role of gastric scintigraphy in combination with wireless motility capsule pressure patterns as compared with scintigraphy alone was that of Lee et al.[45] As stated above, they found that the addition of pressure profile analysis to scintigraphy data significantly increased diagnostic yield. They looked at multiple pressure pattern parameters, including contractile frequency and a calculated motility index. When taken together, the data obtained with scintigraphy plus wireless motility capsule-derived pressure patterns increased diagnostic yield over scintigraphy alone.

Treatment Decisions

We did not find any studies meeting our eligibility criteria that reported on the effect of testing on treatment decisions.

Resource Utilization

No included studies addressed this outcome for this comparison.

Patient-Centered Outcomes

No included studies addressed this outcome for this comparison.

Harms

The article by Rao[34] found no harms from either modality of testing. The article by Lee[45] did not report on harms; however, these numbers are small and insufficient to address this issue.

WMC Plus Antroduodenal Manometry Versus Antroduodenal Manometry Alone

No studies addressed this comparison.

WMC Plus Endoscopy Versus Endoscopy Alone

No studies addressed this comparison.

SOE

We graded the SOE for this KQ as low. While few studies addressed this question specifically, the ones that did were among the better studies in terms of quality, and demonstrated independent review of the wireless motility capsule and scintigraphy. Both were peer-reviewed full manuscripts. We did not include any abstracts in this analysis. We assessed risk of bias as medium and rated these studies as consistent and direct. We rated precision as low but this is difficult to gauge for this question. Table 11 summarizes our grading of the SOE.

Table 11. Numbers of studies and subjects, SOE domains, and SOE among studies comparing WMC testing plus gastric scintigraphy compared with gastric scintigraphy alone

Outcome	Number of Studies / Abstracts	Domains Pertaining to SOE				SOE
		Risk of Bias	Consistency	Directness	Precision	
Diagnostic accuracy	2[34,45] / 0	Medium	Consistent	Direct	Imprecise	Low
Motility assessment	2[34,45] / 0	Medium	Consistent	Direct	Imprecise	Low
Treatment decisions	0	N/A	N/A	N/A	N/A	Insufficient
Harms	0	N/A	N/A	N/A	N/A	Insufficient
Patient-centered outcomes	0	N/A	N/A	N/A	N/A	Insufficient
Resource utilization	0	N/A	N/A	N/A	N/A	Insufficient

N/A = not applicable; SOE = strength of evidence; WMC = wireless motility capsule
SOE was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

KQ 3. Evaluation of Colonic Dysmotility: WMC Alone Versus Other Diagnostic Tests

Key Points

- The SOE comparing WMC with colonic or whole-gut scintigraphy was insufficient because no articles or abstracts formally evaluated this comparison.
- The diagnostic accuracy of WMC is similar to ROM. Concordance between ROM and WMC was approximately 80 percent in three larger studies. The sensitivity for wireless motility capsule compared with clinical suspicion ranged from 32 to 46 percent and the specificity ranged from 95 to 100 percent. The sensitivity of day-5 ROM ranged from 28 to 37 percent and the specificity ranged from 95 to 100 percent. (SOE: Low)
- WMC was comparable with ROM in their ability to detect colonic transit time and identify slow-transit constipation. (SOE: Low)
- WMC testing affects treatment decisions based on ROM testing. Very small numbers made comparison difficult for treatment decisions. Studies reported a 7 percent change in nutrition, a 21 percent referral to surgery, and a 4 percent change in nutritional and behavioral therapies with WMC. (SOE: Low)
- WMC testing can affect resource utilization. (SOE: Low)
- Studies infrequently reported harms and adverse events for WMC or ROM. (SOE: Low)
- The SOE was insufficient regarding patient-centered outcomes. We did not identify any studies that met our inclusion criteria and evaluated this outcome.

WMC Versus Colonic Scintigraphy

We did not include any studies that addressed this comparison.

WMC Versus ROM

Nine studies reported in 14 publications compared the WMC with ROM in colon dysmotility patients.[17,32,48-50,53] One study had three publications,[17,49,50] but we only describe one publication below.[17] The additional studies compared an unclear subset of patients' results to the Bristol stool test[50] and studied how irritable bowel syndrome may alter pressure results measured by the wireless motility capsule among moderate and severe constipation without reporting the corresponding ROM results.[49] Another full-text publication[34] updated an abstract,[53] so we only reported on the full-text publication.

One study included patients with suspected slow-transit constipation, gastroparesis, or intestinal dysmotility.[12] Only the diagnostic accuracy results contribute because the study did not distinguish between the clinical management changes for patients with suspected slow-transit constipation or changes from other patients, or because it reported results based on the final diagnosis, not the suspected diagnosis. Two abstracts[42,44] included patients with suspected gastrointestinal dysmotility disorders, but did not report results separately for slow-transit constipation. We presented the results from this study under KQ 1. All other studies enrolled patients who received a previous diagnosis of chronic or slow-transit constipation according to Rome criteria.

Diagnostic Accuracy

Tables 12 and 13 and Figure 6 summarize data reported on diagnostic accuracy, sensitivity, and specificity within the included studies.[12,17,32,34,48]

Two studies[17,48] evaluated the sensitivity and specificity of colon transit time measured by WMC compared with clinical suspicion. The sensitivity for WMC ranged from 32 to 46 percent and the specificity ranged from 95 to 100 percent. The sensitivity of day-5 ROMs ranged from 28 to 37 percent and the specificity ranged from 95 to 100 percent.

Five studies compared the diagnostic accuracy of WMC testing with ROM among patients with known or suspected constipation.[12,17,32,34,48] The positive percent agreement ranged from 43 to 87 percent and the negative percent agreement ranged from 67 to 91 percent. As three larger studies determined the concordance between ROM and WMC to be approximately 80 percent,[32,34,48] we found the tests to be considered similar based on criteria set out in the methods. One study,[12] which found a lower concordance rate, had a different population focus and much smaller sample size. Another study[17] reported the Spearmen correlation coefficient between colonic transit times recorded by the wireless motility capsule and day-2 and day-5 ROM counts. The correlation among constipated subjects was 0.74 on day 2 and 0.69 on day 5.

Table 12. Diagnostic accuracy and test concordance of WMC and ROM in the evaluation of constipation comparing patients with known constipation with known non-diseased controls

Author, Year	Definition for Slow-Transit Constipation CTT WMC	Definition for Slow-Transit Constipation ROM	Total N	Sensitivity of CTT WMC Compared With Clinical Constipation	Specificity of CTT WMC Compared With Clinical Constipation	Sensitivity of ROM Compared With Clinical Constipation	Specificity of ROM Compared With Clinical Constipation	Concordance of CTT WMC and ROM
Rao, 2009[17]	44 hours for men and 59 hours for women	Day 2: NR Day 5 ROM sensitivity was based on cut off of 5 or more markers retained	67 with known constipation 81 without gastrointestinal disease	46%*	95%*	Day 5: 22/67 (37%)	Day 5: 95%*	Day 2: 0.78† (0.70-0.84) Day 5: 0.59 (0.46-0.69)
Rao, 2012[48]	59 hours	> 5 markers retained on Day 5	25 with known constipation 11 without gastrointestinal disease	8/25 (32%)	11/11 (100%)	7/25 (28%)	11/11 (100%)	Among constipated subjects: 0.71 Among controls: 0.28

CTT = colonic transit time; NR = not reported; ROM = radiopaque markers; WMC = wireless motility capsule

*Numerator and denominator not reported.

†Spearman correlation coefficient.

Table 13. Diagnostic accuracy and test concordance of WMC compared with ROM markers in the evaluation of constipation including only patients with known or suspected constipation

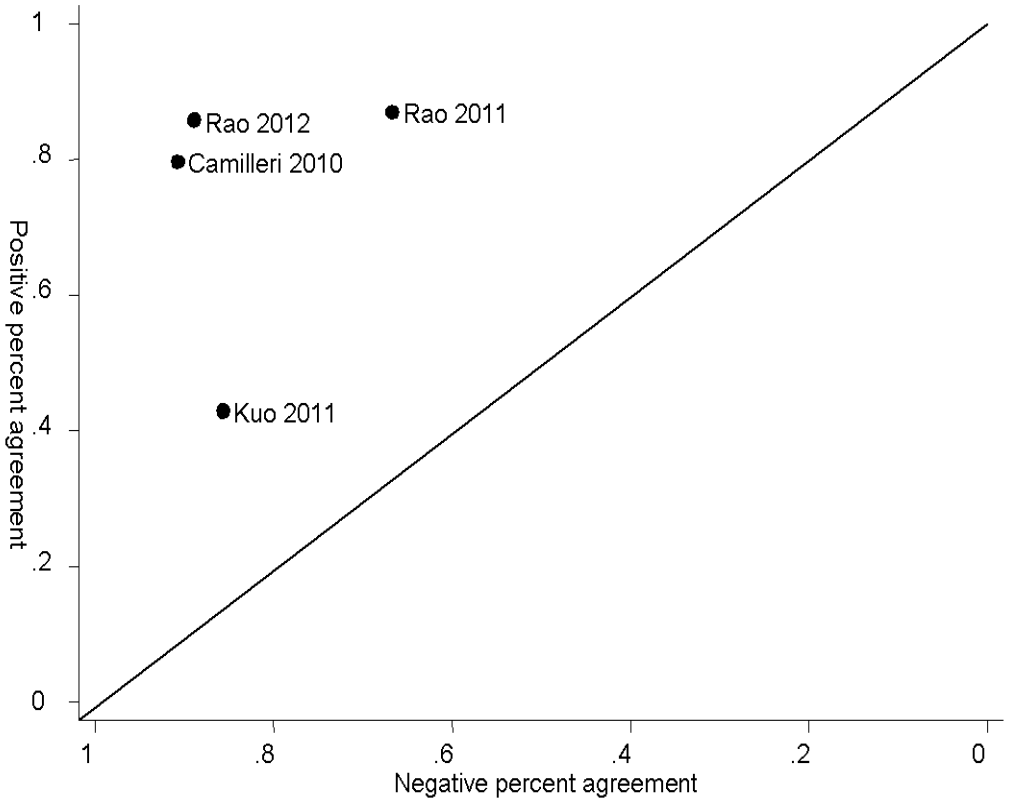
Author, Year	Definition for Slow-Transit Constipation WMC	Definition for Slow-Transit Constipation	N Analyzed With Constipation	Positive Percent Agreement of CTT WMC Compared With ROM	Negative Percent Disagreement of CTT WMC Compared With ROM	AUC, CTT WMC Compared With ROM	Concordance of CTT WMC and ROM
Rao, 2009[17,50]	CTT 44 hours for men and 59 hours for women	Day 5 ROM sensitivity was based on cut off of 5 or more markers retained	67 known	Day 5: 19/23=83%*	NR	NR	Day 2: 0.74† Day 5: 0.69
Camilleri, 2010[32]	59 hours	Delayed on days 4 and 7	157 known	47/59 (80%; CI, 67 to 98%)	89/98 (91%; CI, 83 to 92%)	NR	136/157 (87%)
Kuo, 2011[12]	59 hours	NR	7 with information on colonic transit time from both ROM and WMC	3/7 (43%)	6/7 (86%)	NR	9/14 (64%)
Rao, 2011[34]	NR	6 or more ROM at 120 hours	50 suspected	20/23 (87%)	18/27 (67%)	NR	38/50 (76%)
Rao, 2012[48]	59 hours	> 5 markers retained on Day 5	25 known	6/7 (86%)	16/18 (89%)	NR	22/25 (88%)

AUC = receiver operating characteristic area under curve; CI = 95 percent confidence interval; CTT = colonic transit time; NR = not reported; ROM = radiopaque markers; WMC = wireless motility capsule

*This study also reported that 31 subjects had a colonic transit time greater than 59 hours measured by wireless motility capsule testing, and 21 of these subjects were also delayed based on day-5 ROM count.

†Spearman correlation coefficient.

Figure 6. Summary of the positive and negative percent agreement of WMC compared with ROM in patients with known or suspected constipation



Motility Assessment

Transit Time

Three studies reported data on transit times measured by WMC and ROM (Table 14). One study reported significantly different colonic transit times as measured by WMC (median 43.5 hours) compared with ROM (median 55 hours; $P < 0.001$). Transit times do differ between testing modalities as ROM testing includes gastric and small bowel transit time, whereas WMC does not.[32] However, the correlation coefficient between these numbers was 0.71. Two other studies[17,48] reported correlation coefficients between colonic transit time by WMC and day-5 ROM count ranging from 0.69 to 0.71.

Table 14. Transit times recorded by WMC and ROM in the evaluation of constipation

Author, Year	Study Design	Total N Constipated	WMC Transit Time	ROM Transit Time*	Spearman Correlation Coefficient
Camilleri, 2010[32]	Prospective cohort	157	CTT median (25-75 percentiles) 43.5 h (21.7-70.3)	Median (25-75 percentiles) 55.0 h (31.0-85.0)	0.71 ($P < 0.001$)
Rao, 2009[17]	Prospective cohort	67	Median (25-75 percentiles), hours GET 3.5 (3.0-4.2) CTT 46.7 (24.0-91.9)	Median (25-75 percentiles), Day 5 ROM count 1 (0-17)	0.69
Rao, 2012[48]	Prospective cohort	25	CTT median (25-75 percentiles) 45 h (37-60)†	Median (25-75 percentiles), Day 5 ROM count, 6 (1-6)	0.71 ($P = 0.0001$)

CTT = colonic transit time; GET = gastric emptying time; NR = not reported; ROM = radiopaque markers; SBTT = small bowel transit time; SD = standard deviation; WGTT = whole gut transit time; WMC = wireless motility capsule
*In an ROM test, transit delay is measured by counting the number of markers remaining at a certain time interval after the capsule is ingested. There are 24 markers at the start.
†Data abstracted from figures.

Pressure Patterns

No study compared WMC with ROM and reported on pressure patterns. A sub-study reported on pressure patterns[49] but we excluded it because the publication did not report ROM results. Similarly, an abstract reporting on pressure patterns mentioned that testing with ROM occurred, but did not report on ROM results.

Treatment Decisions

Change in Medications

Only two studies offered information regarding how WMC informed changes in medications, compared with ROM.[12,34] Both these studies reported data gleaned from retrospective chart reviews and no studies prospectively assessed whether change in medication was appropriate based on diagnostic testing (Table 15). Of these two included studies, one study reported an overall change in medications of 71 percent[12] and another reported a 40 percent change.[34]

Table 15. Change in medications following a WMC for the evaluation of slow-transit constipation

Author, Year	Study Design	% Changed Medications After WMC	% Changed Medications After ROM
Rao, 2011[34]	Prospective cohort	40% overall change, but not specified for LGI or UGI symptoms Treatment Prokinetic agents 6% Prescription laxatives 20% Antidepressants 12% Withdrawal of opioids 6% Antiemetics 6%	Not reported (all patients had previously had ROM)
Kuo, 2011[12]	Retrospective cohort	71% changed medications	Not reported

LGI = lower gastrointestinal; ROM = radiopaque makers; UGI = upper gastrointestinal; WMC = wireless motility capsule

Change in Management: Referral, Referral to Surgery, or Change in Nutrition

Only two studies offered information about change in care management for WMC compared with use of ROM.[12,34] Both studies reported data gleaned from retrospective chart reviews and no studies prospectively assessed whether change in medication was appropriate based on diagnostic testing (Table 16). One study reported a person changing their nutritional intake and three people being referred to surgery.[12] The other study reported that 28 percent of the patients were referred for anorectal manometry and 16 percent for breath testing based on the WMC capsule results. Four percent received new nutritional or behavioral therapies.[34]

Table 16. Change in other management following WMC and ROM for evaluation of slow-transit constipation

Author, Year	Study Design	WMC Change in Nutrition	WMC Referral to Surgery	ROM
Rao, 2011[34]	Prospective cohort	Nutritional and behavioral therapies 4%	Not specifically reported	NR
Kuo, 2011[12]	Retrospective cohort	Change in nutritional program, 7%	Referred to surgery, 21%	NR

NR = not reported; ROM = radiopaque markers; WMC = wireless motility capsule

Resource Utilization and Patient-Centered Outcomes

Table 17 summarizes the changes in resource utilization based on WMC or ROM testing in the evaluation of slow-transit constipation. Three studies reported on unreadable results from the WMC test and problems with followup for the radiopaque marker testing.[17,32,48] Unreadable results from the WMC ranged from 4 to 8 percent, and problems with ROM followup ranged from zero percent to 7 percent. Another study reported patients being referred for anorectal manometry (28 percent) and breath testing (16 percent).[34] This study also reported that 26 out of 50 patients (53 percent) received new information on their diagnosis based on the WMC test.

Table 17. Change in resource utilization following WMC and ROM testing for evaluation of slow-transit constipation

Author, Year	Study Design	WMC Subsequent Tests	ROM Subsequent Tests	WMC New Diagnoses	ROM New Diagnoses	Unreadable Results From WMC (For Resource Utilization Section)	Failure to Attend Followup ROM Radiographs or Read on Wrong Day (For Resource Utilization)
Camilleri, 2010[32]	Prospective	NR	NR	NR	NR	8/180 (4%)	5/180 (3%)
Rao, 2011[34]	Prospective	Anorectal manometry, 28%* Breath testing for bacterial overgrowth or carbohydrate intolerance, 16%*	NR	Prolonged gastric emptying, 14/50 (28%) Rapid gastric emptying, 2/50 (4%) Prolonged small bowel transit, 7/50 (14%) Prolonged colon transit, 3/50 (6%)	NR	N/A (based on chart review of completed tests; had to have readable result to be included)	N/A (based on chart review of completed tests)
Rao, 2009[17]	Prospective	NR	NR	NR	NR	14/165 (8%)	12/165 (7%)
Rao, 2012[48]	Prospective	NR	NR	Delayed small bowel transit time, 1/25 (4%) Delayed gastric emptying time, 3/25 (12%)	NR	3/39 (8%)	0/39 (0%)

N/A = not applicable; NR = not reported; ROM = radiopaque markers; WMC = wireless motility capsule
*Numerators and denominators not reported.

Harms

The articles reporting on the comparison of WMC testing and use of ROM reported very few harms (Table 18).

The types of harms the articles most frequently mentioned were inability to swallow the capsule, technical failure or data loss, and failure to pass the capsule within the time frame of initial testing.[17,32,48] Patients required x-rays at day 21 to exclude capsule retention in some cases, but this was based on simultaneous ROM testing during the study (and a day-5 x-ray showing retention of the capsule). No studies reported deaths from exposure to the WMCs or ROMs. The Rao et al. article[17] reported a technical failure rate of 3.4 percent in the literature, and a technical failure rate of 10 percent in the study. No studies that reported on harms reported serious adverse events.[17,32,46,48] The only reported adverse events were from Camilleri et al.[32] with two patients suffering dysphagia with ingestion attempts for the WMC, and one patient suffering abdominal pain after ingestion of the capsule. The authors determined these were "definitely related" to the capsule itself.

In comparison of harms, although the articles discussed the radiation exposure risk between WMC and ROM, they did not report the difference in actual exposure in any unit of measure for comparison on a person-by-person basis. The research protocols in the studies we included used between one and three sequential x-rays to assess ROM transit. Study protocols mandated that if the patient does not observe passage of the WMCs, then x-rays at days 7 or 21 were necessary to detect retention. This x-ray exposure was necessary in four patients at day 7[32] and in 14 patients at day 21.[17] In clinical practice beyond the study setting, x-rays would be required only if the patient was symptomatic. The studies rarely reported any symptoms from WMC ingestion.

Table 18. Summary of the adverse events from WMC testing in the evaluation of slow-transit constipation

Author, Year	Serious Adverse Events	Other Adverse Events	Retained Capsule	Retained Capsule Requiring Intervention	Radiation Exposure	Mortality
Rao, 2009[17]	None	NR	0 non-constipation 14/67 constipated	11/67	NR	NR, presumably 0
Camilleri, 2010[32]	None	31 adverse events (could have more than 1 per person)	NR	0/180	At least 1 person	NR, presumably 0
Rao, 2011[34]	None	NR	0	0	NR	NR, presumably 0
Rao, 2009[46]* [abstract]	None	None	0	0	NR	NR
Rao, 2012[48]	None	NR	1/39	NR	NR	NR

NR = not reported; WMC = wireless motility capsule

*Results were not reported for radiopaque marker testing.

SOE

Although relatively few articles compared the diagnostic accuracy of the WMC with the use of ROM for evaluating slow-transit constipation, Table 19 shows that the strength of evidence was low in support of the diagnostic accuracy of WMC in evaluating slow-transit constipation. The risk of bias in these studies was low, but the total amount of evidence was sparse. The strength of evidence also was low regarding the accuracy of the WMC in assessing motility times in patients with possible slow transit constipation, and regarding the low risk of harm associated with use of the device. The strength of evidence was low or insufficient regarding other outcomes associated with use of the device.

Table 19. Numbers of studies and subjects, SOE domains, and SOE among studies comparing WMC with ROM

Outcome	Number of Studies (Participants) / Number of Abstracts	Domains Pertaining to SOE				SOE
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	
Diagnostic accuracy of slow-transit constipation	5 (306)[12,17,32,34,48] / 0	Medium	Consistent	Direct	Precise	Low
Motility time assessment	3 (249)[17,32,48] / 0	Medium	Consistent	Direct	Precise	Low
Treatment decisions	2 on medications & referrals (169)[12,34] / 0	Medium	Consistent	Direct	Imprecise	Low
Harms	5 (388)[17,32,34,46,48] / 1	Medium	Consistent	Direct	Imprecise	Low
Patient-centered outcomes	0	N/A	N/A	N/A	N/A	Insufficient
Resource utilization	4 (299)[17,32,34,48] / 0	Medium	Consistent	Direct	Imprecise	Low

N/A = not applicable; SOE = strength of evidence
SOE was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable or does not permit a conclusion.

KQ 4. Evaluation of Colonic Dysmotility: WMC in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

Key Points

- Strength of evidence was insufficient because no studies directly addressed the outcomes for this comparison.

Summary

We reviewed nine studies (14 publications) that looked at the comparison of WMC with scintigraphy or ROM in the evaluation of colonic dysmotility.[12,17,32,34,42,44,46-53] However, no studies specifically looked at the incremental value of WMC testing in addition to ROM or scintigraphy in terms of diagnostic accuracy of slow-transit constipation. Additionally, no studies looked at the incremental value of also using the WMC in addition to ROM or scintigraphy in terms of motility, treatment decisions, patient-centered outcomes, harms, and resource utilization. One study[34] attempted to answer this question by comparing the WMC with conventional motility tests, including both scintigraphy and ROM. However, the data were incomplete and did not directly answer the KQ regarding incremental value specifically. Thus, the evidence was insufficient to determine the incremental value of using WMC in combination with other conventional tests of colonic motility.

Study Quality (For All KQs)

We reported study quality separately for full-length publications and abstracts because the abstracts had limited information about study methods (Appendix D, Evidence Table 4). The overall study quality was fair.

Of the 11 full-length publications,[12,16,17,32,34,45,48-50,52,53] six stated that a goal was to compare the diagnostic accuracy of WMC with a reference/nonreference standard.[12,17,32,34,45,49] Five publications excluded healthy controls from the diagnostic accuracy analyses,[12,34,45,52,53] with the remainder including both healthy controls in the comparison of diagnostic tests. Two publications excluded severely ill patients,[16,34] one publication[49] included these patients and the remainder had unclear reporting. Five publications used the same reference standard for all patients,[16,17,32,49,50] one publication allowed different reference standards,[45] and four publications did not report on the reference standard with enough detail to determine if the studies used the same reference standard for all participants. No publication analyzed all patients. Seven of the studies performed the WMC and reference standard within three months of each other,[16,17,32,34,45,50,52] often with concurrent testing. Six publications reported a threshold for disease positivity or cited that they used a threshold from a previous publication.[17,32,34,45,49,50] Only three publications interpreted the WMC results independently from the reference standard.[17,32,34] One of these publications was a retrospective chart review.[34] Four publications explicitly stated that they did not interpret the test results independently.[12,16,45,49,50] For the two publications with unclear reporting[52,53] and those publications that did not interpret results without knowledge of the other test results, we contacted the authors to obtain information on

independent assessment of the tests. We were able to confirm from the authors that they interpreted the results independently in three publications that did not report blinding.[16,45,50]

Nine full-length studies reported on conflicts of interest.[12,16,17,32,34,45,48-50] A commercial source related to motility testing funded six of the studies and one study was independent of commercial funding.[34] Of two studies with unclear commercial funding,[12,45] a related publication[16] reported that one study[45] had commercial funding. All of the studies that reported on conflict of interest included an author employed by industry or an author who received funding or fees from at least one commercial source related to motility testing.

The seven abstracts did not provide sufficient details to evaluate all domains of study quality. One abstract excluded healthy controls from the analyses,[44] five abstracts included healthy controls,[41,43,46,47,51] and one had unclear inclusion.[42] Two abstracts reported that all patients received the same reference standard,[41,43] with the remainder having unclear consistency of a reference standard. No abstract stated that they interpreted results of WMC independently of the reference standard. Two studies reported that the WMC assessment and reference standard occurred within three months.[41,43] One study stated in the abstract a threshold for disease based on the WMC.[43] Three studies stated the aim was to compare the diagnostic accuracy of the WMC with a reference standard.[42-44]

No abstract reported on conflict of interest. However, many of the abstract authors were authors of the full-length publications we reviewed, and some of those publications reported potential conflicts as noted above.

Discussion

Potential Niche for WMC

WMC could improve how clinicians test for gastroparesis or slow-transit constipation because the capsule is small and can be transported to patients wherever they live. Also, the capsule does not involve any radioactive material or x-ray exposure, and can record information about pressure, transit, and location simultaneously. The manufacturer states that the device presents little risk to patients, with less than 0.1 percent or six cases out of 6,000 patients reporting capsule retention.[61] Other testing modalities for gastric emptying and colonic motility assessment do not share the same characteristics as the wireless motility capsule. A number of academic centers use scintigraphy to assess gastric transit abnormalities and whole-gut motility; however, this involves radiation exposure, significant patient time requirements, and significant cost. Antroduodenal manometry assesses gastric pressure parameters but it has limited availability and is more invasive than other testing modalities; thus, clinicians more commonly use it as an investigative tool than as a clinical test. Radiopaque markers are portable and small, but require radiation exposure, access to fluoroscopy, and radiology interpretation. One of the major limitations of other modalities for testing gastric or colonic motility is they can't evaluate both transit and pressure—yet both are involved in disease pathogenesis. The wireless motility capsule has the potential to evaluate both transit and pressure simultaneously, which could allow more optimal assessment of motility than evaluation of either parameter independently. Likewise, by recording both parameters, the wireless motility capsule could potentially provide a more accurate diagnosis with less testing which would use fewer resources and enhance patient convenience. In our review of the literature, clinicians employed a wide variety of methods when using scintigraphy and radiopaque marker testing. In contrast, studies report only a single method for using the wireless motility capsule. In addition, clinicians can perform the procedure in any office with a nurse, while one needs experts at an academic center with specialized equipment and large investments of time to perform antroduodenal manometry or colonic or whole-gut scintigraphy. In this way, the wireless motility capsule may prove to be more reproducible and more standardized than some of the other testing modalities. Note that there are few prospective randomized studies of gastric scintigraphy or radiopaque markers and multiple methods of practice of these tests. Currently, clinicians only use one type of software to analyze wireless motility capsule, which may make testing more comparable between centers as well. No studies directly assessed using capsule internationally or in a community-based environment to measure this effect.

In light of this potential niche, the wireless motility capsule is becoming much more readily available in both academic and community centers. However, questions remain about the position of the wireless motility capsule in the diagnostic algorithm for suspected motility disorders such as gastroparesis and slow-transit constipation. Since patients may have more than one of these disorders causing their symptoms, identifying the co-existent disorder is an important component for better understanding and treating a patient's disease.

Some questions to consider are: Is a test with the ability to detect more than one disorder like wireless motility capsule better than existing modalities that focus in only one region? Is the wireless motility capsule equivalent to conventional testing? Is it superior? Is it more likely to establish a concrete diagnosis or guide medical therapy than conventional motility testing? Should it be used as a stand-alone test? What should be done when wireless motility capsule is normal but clinical suspicion remains?

Recommendations from the American Neurogastroenterology and Motility Society (ANMS) practice guidelines suggest that physicians can use wireless motility capsule to diagnose patients with suspected gastroparesis and slow-transit constipation, as well as more generalized motility disorders, but these are consensus guidelines. There was no specific information about when or how physicians should use wireless motility capsule. Thus, the current literature has not clearly answered these important questions.

We must also consider the potential limitations of the wireless motility capsule. The manufacturer does not recommend using the capsule for patients with severe gastroparesis because there is a possibility of capsule retention. In addition, the wireless motility capsule evaluates motility at only a single point, as opposed to antroduodenal manometry, which has multiple recording points, or scintigraphy, which looks at transit of an entire meal. One assumes that the single point of measurement is representative of motility parameters as a whole; however, this is an assumption only and not clearly established in the literature. In assessing constipation, one cannot separate patients with slow-transit constipation from defecatory dysfunction based on only colonic transit time, so one needs further motility testing like balloon expulsion or anorectal manometry, and clinical judgment to evaluate defecation. Finally, parameters of motility for a non-digestible solid are different than those for either liquids or a meal, implying that patients can have abnormalities with one modality that would not be seen with another. In short, while the potential of wireless motility capsule testing is exciting, many questions remain as to whether it is equivalent or superior to other modalities. And its appropriate place in the diagnostic algorithm is still unclear.

Key Findings and Implications

Few studies met our criteria for evaluation. The paucity of full-length articles with independent data limited our ability to answer the Key Questions definitively.

Key Question 1. Evaluation of Gastric Dysmotility: WMC Alone Versus Other Diagnostic Tests

WMC Versus Scintigraphy

We found low strength of evidence from seven studies[12,16,34,41,43-45] to support that wireless motility capsule is comparable with gastric scintigraphy in diagnostic accuracy. The sensitivity was moderately greater in some studies, but they reported slightly lower specificity. The test agreement and diagnostic gain were moderate. Diagnostic agreement between wireless motility capsule and gastric scintigraphy ranged from 58 to 86 percent for positive test agreement and from 64 to 81 percent for negative test agreement.

We found low strength of evidence from five studies[16,34,41,43,45] that transit data obtained via wireless motility capsule testing correlate well with scintigraphic gastric emptying. The reporting of the results in these studies was heterogeneous. One study reported a correlation coefficient of 0.73 between gastric emptying time measured by the wireless motility capsule and 4-hour gastric emptying measured by gastric scintigraphy.[16] When comparing wireless motility capsule with gastric scintigraphy, one should keep in mind that wireless motility capsule measures emptying of an indigestible object after the emptying of a meal, while gastric scintigraphy measures emptying of a meal. In a sense, then, wireless motility capsule indirectly measures what gastric scintigraphy measures. Good correlation between the two tests indicates that delayed meal

emptying generally translates into delayed indigestible object emptying. Other studies reported sensitivity, specificity, and device agreement between wireless motility capsule transit data and gastric scintigraphy.[34,43,45] All three studies examining transit time showed similar sensitivity and specificity for wireless motility capsule and scintigraphy, and some studies reported increased diagnostic gain of sensitivity with wireless motility capsule.

Low strength of evidence from two studies supports the utility of wireless motility capsule versus scintigraphy in measuring pressure profiles.[43,45] Wireless motility capsule reports pressure patterns, but scintigraphy can not detect pressure patterns. It does appear, however, that abnormalities are more likely to be seen with wireless motility capsule than scintigraphy, especially if one adds assessing pressure patterns to the equation. However, based on the literature, there remain questions as to whether increased diagnostic detection has clinical implications.

Low strength of evidence supports how testing with wireless motility capsule versus scintigraphy might change treatment. Three studies identified change in treatment.[12,34,44] Wireless motility capsule was associated with a change in management ranging between 50 and 69 percent of patients, change in medication in 47 to 82 percent of patients, and change in diet in 11 to 27 percent of patients. Since scintigraphy is the reference standard, physicians would likely make all decisions based on clinical symptoms and scintigraphy testing. There was low quality evidence suggesting that wireless motility capsule is comparable with scintigraphy in informing a change in management. Although Kuo et al.[12] reported that a large percentage of patients in their study avoided testing, they accepted the results of the individual test as definitive and elected not to pursue additional testing. The authors suggested that the best way to study the comparative effectiveness of these diagnostic modalities would be to randomize subjects to receive care guided by either wireless motility capsule or reference standard testing (which could be uniformly applied), and then assess outcomes (including the need for additional tests) using blinded reviewers.

There is low strength of evidence regarding harms from wireless motility capsule as compared with scintigraphy. Many articles mentioned harms, but overall the articles did not report any serious adverse events, deaths, bowel obstructions, or rehospitalizations in patients using the wireless motility capsule or gastric scintigraphy. A measurable portion of the study participants who received the wireless motility capsule reported minor symptoms such as nausea, abdominal discomfort, or bloating. Studies noted loss of data capture or device failure; however this does not seem to qualify as a true harm.

Overall, we had graded the strength of evidence for many outcomes addressing Key Question (KQ) 1 to be low because we considered the evidence to have medium risk of bias, consistent reporting, direct nature of the data, and imprecise findings. The main limitation weighting the risk of bias was that the studies did not prespecify enrollment of patients or enroll them randomly; in fact many studies did not report how they selected patients for testing and study. Another limitation was the lack of advance prespecification of criteria and values of positivity of the tests being used. The final major limitation was that few studies mentioned whether they selected a person without conflict of interest to manage the data collected. Most studies had limited followup duration, which hampers our ability to draw conclusions about some of the outcomes that are really important to patients. A major strength of the full-length articles was that there was independent review of the results in the analysis.

We could not conduct a meta-analysis because of the heterogeneity of the data and patient populations in the studies. Our ability to compare studies was limited by lack of consistency in

how the studies defined reference standards. The reference standard the studies commonly used was community based gastric scintigraphy testing performed within 2 years of enrollment into a study. Local standards for scintigraphy vary greatly, and this introduced heterogeneity into the patient populations under investigation. Many studies had different definitions for key outcomes such as diagnostic agreement, sensitivity, and specificity, as well as different diagnoses based on similar test results. We can explain this latter discrepancy by the fact that cut off values for detecting gastroparesis with wireless motility capsule have changed over time. It is uncertain if the available examinations of motility testing captured the full spectrum of patients, as academic referral centers were the primary recruitment site for studies. Overall, seven studies with 560 patients addressed the question of diagnostic accuracy.[12,34,41-45] For a rare illness, the large number of patients included for evaluation reflects the great length that researchers have taken to assess the quality of this modality. Several studies suggested there was some diagnostic gain with wireless motility capsule as compared with scintigraphy, assuming all additional cases identified were correct and not false positives.[12,16,34,43,45] Employing simultaneous scintigraphy and wireless motility capsule at the time of assessment, the investigators attempted to minimize the impact of having a heterogeneous population. Sensitivity and specificity for both scintigraphy and wireless motility capsule compared with symptoms in these studies is expectedly low given the issues above and the fact that the denominator may not have truly reflected entirely gastroparetic patients. Device agreement is a more useful parameter to measure in these papers than sensitivity and specificity.[36] However, agreement is likely to be imperfect because these two modalities look at different mechanisms of transit.

Regarding treatment decisions, we did find that, in three studies, wireless motility capsule testing altered the management of patients with suspected gastroparesis (50 to 69 percent change in management for medicine, diet, or surgery). However, the strength of evidence was low (i.e., likely to be changed by future evidence).

The evidence was insufficient to draw conclusions regarding the differences or similarities between gastric scintigraphy and wireless motility capsule with regards to patient-centered outcomes or resource utilization. Very little research examined resource utilization, and no studies specifically examined this outcome with any rigor.

The findings reported in the literature are consistent with what would be expected based on the pathophysiology of gastroparesis and the comparative methods of wireless motility capsule and gastric scintigraphy. Comparing scintigraphy with wireless motility capsule is fundamentally a challenging endeavor. Both modalities evaluate different parameters. Scintigraphy looks at transit of a test meal and does not assess pressure. When the stomach processes a meal, fundic accommodation is followed by antral contractions that break up the food into small particles that are then propelled from the antrum to the duodenum. In comparison, the wireless motility capsule is not digested and is believed to exit the stomach when the gastric motility patterns change from a fed to fasting state and migratory motility complexes resume. As such, these two technologies are evaluating different parameters and a direct comparison may be challenging if one looks at transit alone.

WMC Versus Antroduodenal Manometry or Endoscopy

No head-to-head comparison of antroduodenal manometry (which can record pressure patterns) and wireless motility capsule was found in patients with suspected gastroparesis in our review. This makes it difficult to make a more definitive assessment of the ability of wireless motility capsule to detect abnormalities in pressure patterns in our defined populations.

Similarly, we did not find any studies that compared wireless motility capsule testing with endoscopy among patients with suspect gastroparesis.

Key Question 2. Evaluation of Gastric Dysmotility: Wireless Motility Capsule in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

Wireless Motility Capsule Plus Gastric Scintigraphy Versus Gastric Scintigraphy Alone

Two studies[34,45] assessed the incremental value of using the wireless motility capsule with gastric scintigraphy. We found low strength of evidence to suggest that wireless motility capsule is associated with modest improvement in diagnostic accuracy over use of scintigraphy alone for patients with suspected gastroparesis. We also found low strength of evidence to support the incremental benefit of wireless motility capsule in evaluating transit times and pressure patterns. The two studies that did attempt to address this question had a method of data collection that may not have allowed for full understanding of diagnostic discrepancy. Discrepancy is when one test shows disease and the other test does not show disease. The authors assumed that a discrepancy with results (when wireless motility capsule was positive but scintigraphy was not) was always a diagnostic gain in a population of patients with gastroparesis.[34] This assumption is difficult to confirm without having an independent gold standard for establishing the diagnosis.

While few studies addressed this question specifically, the ones that did were among the better studies in terms of quality, and demonstrated independent review of the wireless motility capsule and scintigraphy. We assessed risk of bias as medium and we felt these studies were consistent and direct. We felt precision was low but this is difficult to gauge for this question. The overall strength of evidence was low for this Key Question. It is very hard to prove an incremental benefit of the test when clinicians use it in addition to other testing modalities because it is hard to determine how studies performed clinical decisionmaking. It may be unclear which test the clinician used to form an opinion of the case, and it may be unclear how much the incremental information contributed to the decisionmaking process. The retrospective nature of studies also limited the strength of evidence.

In addition, understanding the incremental benefit of wireless motility capsule when added to gastric scintigraphy should take into account the fact that eligibility criteria for these studies required a previous positive test for gastric emptying scintigraphy and documented gastroparetic symptoms. Therefore, the addition of wireless motility capsule testing showed incremental sensitivity over scintigraphy testing alone in this population, which one should take into account when judging these results' clinical applicability.

The incremental benefit for wireless motility capsule when assessing suspected gastroparesis is consistent with the nature of the disorder and the tests, since the wireless motility capsule offers pressure data and motility data which are not discernible by scintigraphy alone, as well as lower gastrointestinal motility data which can help explain symptoms in patients with combinations of motility disorders. Additional reported information in combination with scintigraphy can add measurable benefit, especially with regard to identifying a more diffuse motility disorder. The evidence was limited and there was no information to guide any conclusions regarding treatment decisions, utilization, patient-centered outcomes, or harms when evaluating the incremental value of also using wireless motility capsule testing.

Incremental Value of Wireless Motility Capsule Compared with Antroduodenal Manometry Alone or Endoscopy Alone

We did not find any studies that evaluated the incremental value of adding the wireless motility capsule test to either antroduodenal manometry or endoscopy in patients with suspected gastroparesis.

Key Question 3. Evaluation of Colonic Dysmotility: Wireless Motility Capsule Alone Versus Other Diagnostic Tests

Wireless Motility Capsule Versus Radiopaque Markers

The strength of evidence was low from five studies containing 306 patients comparing wireless motility capsule with radiopaque markers in terms of their accuracy in diagnosing slow-transit constipation.[12,17,32,34,48] The diagnostic accuracy of the wireless motility capsule was similar to radiopaque markers (concordance was about 80 percent in three of the larger studies). Sensitivity and specificity were 46 and 95 percent for wireless motility capsule compared with clinical constipation, and 37 and 95 percent for radiopaque markers.[17] The wireless motility capsule was comparable with radiopaque markers in assessing diagnostic accuracy, and matched the sensitivity in different target populations in a reliable way.

The strength of evidence was low to suggest a strong correlation between the colonic transit time estimated by wireless motility capsule versus radiopaque markers. The correlation coefficients between these two measures ranged from 0.69 to 0.71.

The strength of evidence was low regarding the effect of wireless motility capsule testing on treatment decisions based on radiopaque marker testing. We graded the strength of evidence as low because only two retrospective chart reviews offered information about change in management for the wireless motility capsule compared with use of radiopaque markers.[12,34] These two studies differed in the patient populations and the reporting of the outcomes. One of the studies reported few events, providing imprecise results. The data were further limited because not all patients underwent both diagnostic tests of interest. We found low strength of evidence that wireless motility capsule can affect resource utilization.

The strength of evidence was low in the five studies reporting on harms relevant to wireless motility capsule or radiopaque markers.[17,32,34,46,48] Studies infrequently reported harms and adverse events for the wireless motility capsule or radiopaque markers. The wireless motility capsule is comparable to radiopaque markers with regard to low frequency of harms, as studies did not report any serious adverse events or mortality. Radiopaque marker testing involves exposure to at least one x-ray. A small proportion of patients who received wireless motility capsule required day 21 x-ray (by protocol) if the capsule had not spontaneously passed; in practice, patients might not require x-ray assuming they witness capsule passage or are asymptomatic. Studies reported technical failures in prototype devices with rates between 3 and 10 percent, depending on the study.[17,48] Other harms or adverse events reported included dysphagia, abdominal discomfort, bloating, or nausea, which happened infrequently. These all resolved spontaneously.[32]

The strength of evidence was insufficient to make any conclusions about patient-centered outcomes like symptom improvement, quality of life, and patient satisfaction. No included studies addressed these outcomes of interest. These are difficult outcomes to assess without using dedicated symptom scores or mining large sources of data on hospital and physician visits. We

will also need longer duration studies to address questions about change in quality of life or symptoms, which requires assessment along multiple time points.

Many factors contributed to our giving an overall grading of low strength of evidence for comparing the diagnostic accuracy of wireless motility capsule versus radiopaque markers in assessing slow-transit constipation (KQ 3). We felt the evidence had a moderate risk of bias because many of the studies were small, prospective, cohort studies that lacked randomized patient selection, did not report if there was blinding of assessment, and often did not apply the same reference standard to all the patients. Furthermore, many studies recruited patients from academic referral centers and it is uncertain if they captured the full spectrum of patients. Most studies had limited followup duration, which hampered our ability to draw conclusions about some of the outcomes that are important to patients, such as patient satisfaction or change in symptom scores. We had only imprecise estimates of the effects on treatment decisions and harms. The way studies defined non-reference standards limited our conclusions. In several of the studies the non-reference standard test was a community based radiopaque marker study of varying protocol. The multiple protocols had different assessment methods, which could have influenced the results. We could not conduct a meta-analysis because of the heterogeneity of reported data and patient populations in the studies. Although the strength of evidence was low, it is impressive how well these devices correlated, given the studies' limitations.

Much like the comparison between scintigraphy and wireless motility capsule, radiopaque markers and wireless motility capsule assess different components of transit. Some of the points of assessment coincide and provide comparable data, but the additional pressure and transit data offered by the wireless motility capsule make it a different modality. With the high level of diagnostic agreement between radiopaque markers (the non-reference standard) and wireless motility capsule for diagnosing slow-transit constipation, one may be able to use wireless motility capsule instead of radiopaque markers. More evidence will help to strengthen the support for this type of use and define which populations would gain the most benefit from one test versus another. Overall, the studies showed diagnostic agreement between wireless motility capsule and radiopaque markers for assessing and diagnosing slow-transit constipation.

Wireless Motility Capsule Versus Colonic Scintigraphy

We found no evidence to evaluate the wireless motility capsule in comparison with colonic scintigraphy in patients with suspected slow-transit constipation. We excluded studies on scintigraphy from our analysis because they compared testing in healthy subjects separately from those with constipation or slow-transit constipation and thus were not eligible for inclusion.

Key Question 4. Evaluation of Colonic Dysmotility: Wireless Motility Capsule in Combination With Other Diagnostic Tests Versus Other Diagnostic Tests Alone

No studies directly addressed any outcomes of interest related to KQ 4. The main clinical use of wireless motility capsule was determined by consensus to be a replacement test. However, there are also patients with indeterminate test results for whom physicians will recommend wireless motility capsule. Is the combination of tests more definitive than one test alone? What is the added benefit of the detection of other gut motility abnormalities when assessing colonic transit? If wireless motility capsule also finds gastric emptying delay, should we consider this a diagnostic gain? Many of the studies counted these additional diagnoses as a diagnostic gain,

since wireless motility capsule is also comparable to gastric scintigraphy in detecting gastric emptying delay. While there is evidence of concordance between tests, there is little data about the timing of these tests in a diagnostic workup. The design of the studies was to define the role of wireless motility capsule as a possible replacement for other tests, and not to show its use in combination with other tests. The little data that were available from small trials about these outcomes were heterogeneous and did not specify the nature of the patient populations of interest, therefore it was impossible to generalize based on these data. One could assess the incremental value of a new technology by diagnostic gain. However, when trying to judge whether a new test can be a replacement or adjunct to an old test, it is difficult to get a clear picture of which test was most helpful in making a diagnosis without a blinded comparison or without follow up that can assess the validity of the diagnosis and/or treatment effects over time. There are statistical techniques that one can use to do this type of analysis, but the studies did not report the data in sufficient detail to perform the calculations.

Applicability (For All Key Questions)

The applicability of the literature is limited since all studies took place in referral centers and there was no prospective testing of the wireless motility capsule as a diagnostic tool in patients with suspected disease (all included studies involved patients with known disease). When a study used a comparison group without constipation or gastroparesis, it included "healthy" controls, instead of patients who may have similar presenting symptoms who do not have constipation or gastroparesis. These controls tended to be college-aged men, compared with middle-aged females with suspected disease. Additionally, it is unclear how previous treatments or comorbidity, including diabetes, affect test performance or how the test results ultimately affect management.

Limitations and Strengths of our Review Process

Our review had three major limitations:

1. No standards exist in the field of motility assessment for determining the minimum improvement of diagnostic accuracy that will identify one test as superior to another test. There are also no standards to establish the equivalence of motility tests. We arbitrarily chose a 10 percent difference in sensitivity or specificity as a potentially important difference between tests.[32] We felt this threshold was a conservative minimum improvement over a reference standard with moderate diagnostic accuracy (between 50 and 80 percent). If the reference standard had a larger diagnostic accuracy (90 percent or greater), a 10 percent absolute difference is too large to expect.
2. We excluded studies that only enrolled non-diseased participants as our review focused on studies that compared the diagnostic accuracy of the tests for patients with gastroparesis or slow-transit constipation. We recognize that many of the most commonly cited studies in the field included non-diseased participants.[18,19,62-75] Thus, we excluded a number of studies that evaluated characteristics of the wireless motility capsule.
3. Experts in the field believe that scintigraphy and radiopaque markers have imperfect diagnostic accuracy. There are several options to account for the imperfection of the reference standard.[76] We chose to incorporate two of these in our review. (1) We presented the results as if the reference standard had no measurement error and acknowledged this imperfection. (2) We present concordance of the test results when available. We did not attempt to adjust the results to correct for the measurement error.

This adjustment would have required assumptions that we did not have sufficient data to justify. Another option is to examine patient outcomes according to the wireless motility capsule. We had included patient outcomes (e.g., need for medications, additional tests) in our review. Unfortunately, we found few studies evaluating these outcomes.

The major strength of our review process was its comprehensiveness. We included abstracts, contacted industry for unpublished studies, and contacted study authors for missing data.

Limitations of the Identified Literature

Our aim was to compare the wireless motility capsule versus other testing modalities in terms of accuracy in diagnosing and managing gastroparesis and slow-transit constipation. The literature limited our ability to answer our Key Questions for several reasons:

1. No study directly addressed the incremental value of using the wireless motility capsule in addition to using a radiopaque marker or scintigraphy in the evaluation of colonic dysmotility (KQ 4). Only limited data addressed the incremental value of using the wireless motility capsule in addition to using gastric scintigraphy, antroduodenal manometry, or endoscopy in the evaluation of gastric dysmotility (KQ 2).
2. All study sites were referral centers that tend to have patients with more severe disease. The study results have limited generalizability to primary care clinics or general gastroenterology centers, which both see a greater spectrum of disease severity. The sensitivity and specificity of the wireless motility capsule may be different in referral center settings than in other settings, and the positive and negative predictive values will be different when the prevalence of disease is different.
3. Many studies included non-diseased patients in the comparison of the diagnostic accuracy of the wireless motility capsule versus other tests, using a clinical diagnosis of disease as the reference standard rather than the results of the other diagnostic tests.
4. The non-diseased participants had very different demographic characteristics than the gastroparesis and slow-transit constipation patients. For example, the majority of the non-diseased participants were college-aged males whereas the gastroparesis and slow-transit constipation patients were middle-aged women. Using clinical diagnosis as the reference standard, it is difficult to determine if the wireless motility capsule and other tests are distinguishing disease from non-disease or measuring differences in motility by demographic differences such as age and sex.
5. Variability in the administration of the motility tests and outcome assessments may explain some of the heterogeneity in the study results. Many studies used similar protocols to perform the wireless motility capsule testing and other tests, but with slight modifications, such as in the contents of the meal. Frequently, the timing of the motility assessment differed for the wireless motility capsule and the alternative test within and between studies, which may explain differences in the test results and the diagnostic accuracy differences between studies.
6. The abstracts we included did not report enough data to fully understand the study population, answer our Key Questions, or assess the quality of the studies.
7. We were unable to compare the results of studies with and without industry or investigator conflicts of interest because the company that manufactures the wireless motility capsule sponsored most of the studies. The other studies did not report on conflicts of interest. No study stated that it was performed independent of industry

sponsorship with authors who had no previous or current financial relationships with the manufacturer of the wireless motility capsule.

8. Many studies included patients with gastroparesis defined by clinical symptoms and a prior abnormal gastric scintigraphy via local standards; however, symptoms of gastroparesis can be non-specific and many local facilities do not follow a standardized gastric scintigraphy protocol. As such, it is difficult, based on the data, to separate patients with gastroparesis from those with functional dyspepsia or other functional gastrointestinal disorders. This may have, to some degree, affected data with regards to sensitivity, specificity, and device correlation.
9. We attempted to assess publication bias by contacting the manufacturer of the wireless motility capsule and requested any unpublished data, but received no response.
10. Not all studies reported sufficient numbers to describe all the combinations of test results; some only provided means or medians. This hampered our ability to perform analyses, especially when analyzing combinations of tests.
11. Very few studies reported on patient-centered outcomes, limiting our abilities to draw conclusions on these outcomes.

Future Research Needs

Future research should ideally emphasize a cure to these diseases that is nontoxic, cheap, easily available, and safe without major surgery or implanted devices. As far as diagnostic testing, the goal is always to find accurate, effective, inexpensive tools to diagnose or exclude cases and qualify their severity in a reproducible way, especially when treatment is expensive, unavailable, or accompanied by great risks. Studies that compare the diagnostic modalities should have blinded interpretation of the results and make every attempt to classify patients by identical criteria and standardized protocols that other centers can repeat and verify. In terms of study design, we may need multi-center trials in order to enroll patients in sufficient quantity to be meaningful. Preferably, investigators independent from the corporation that makes wireless motility capsule would lead these trials. We recommend that research focus more on prospectively studied patients in larger numbers with an appropriate spectrum of symptoms and adequate followup to determine whether the diagnosis was accurate over time. Due to the difficulty enrolling patients, carefully crafted retrospective analyses should also be considered.

We need further research to evaluate how clinicians should use wireless motility capsule in combination with or instead of other testing modalities when evaluating slow-transit constipation. The studies we reviewed used alternative measures to assess anorectal function, such as anorectal manometry, since wireless motility capsule does not capture data about this region reliably. Thus, clinicians will likely use wireless motility capsule in combination with this test.

Eventually, we need outcomes studies to see if testing helps to improve quality of life or symptom control. It is unclear at present whether a more sensitive diagnostic test might just provide lead-time bias for diagnosis but not actually change the outcomes or management steps overall for the patient. As we identify other targeted therapies, we will need to reassess the value of testing. We are aware that a new therapy is in Stage II trials for patients with diabetes and gastric emptying delay, which may increase the need for research into this area if it becomes available for use.[77] Currently, most patients with nausea- and vomiting-predominant symptoms of gastroparesis receive similar first-line treatment with antiemetics or prokinetics. As treatment options for gastroparesis expand (some at great expense), then more accurate detection of disease

prior to initiation of therapy may play a more prominent role in disease management. The literature did not report on resource utilization with and without using the wireless motility capsule; we will need more studies evaluating these measures.

Few data are available regarding the optimal timing of wireless motility capsule testing when diagnosing and treating patients with symptoms of possible gastroparesis or slow-transit constipation. We need to do further work to classify the types of patients within subgroups of gastroparesis or slow-transit constipation to identify severe cases that may need more urgent evaluation. Finally, little is known about whether testing should be used to assess the effectiveness of treatment or if subsequent testing would offer any benefit in long-term management of patients. Currently, symptoms and symptom resolution guide therapeutic decisions, but these require careful interpretation.

Conclusions

Based on the current literature, the wireless motility capsule appears to be accurate in detection of gastroparesis and slow-transit constipation and may provide increased diagnostic gain as compared with standard motility testing. The literature indicates that it is accessible, reproducible, standardized, emits no radiation, and is available in locations remote from academic centers (qualities which are in stark contrast to the limited availability and utility of other testing modalities in current practice). While the strength of evidence is low, the data were relatively consistent and suggested that this modality is no less sensitive than conventional testing. The evidence is insufficient to determine whether use of the wireless motility capsule will improve outcomes of care. Although we found limited evidence on the impact of WMC testing on patient outcomes, we should acknowledge that it is also true that little evidence exists on the impact of conventional motility testing.

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Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
AHRQ	Agency for Healthcare Research and Quality
ANMS	American Neurogastroenterology and Motility Society
AUC	area under the curve
CI	confidence interval
COV	coefficient of variance
cph	contractions per hour
CTT	colonic transit time
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
G PM	gastric pressure measurements
G/SB PM	gastric/small bowel pressure measurements
GES	gastric emptying scintigraphy
GES-2hr	gastric emptying via scintigraphy at 2 hours
GES-4hr	gastric emptying via scintigraphy at 4 hours
GET	gastric emptying time
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment Development and Evaluation
hr	hours
KQ	key question
min	minutes
mmHg	millimeters of mercury
NA or N/A	not applicable
NR	not reported
PPI	proton pump inhibitor
ROC	receiver operating characteristic
ROM	radiopaque markers
SB	small bowel
SB PM	small bowel pressure measurements
SBTT	small bowel transit time
SD	standard deviation
T50	time of 50% emptying
T90	time of 90% emptying
U.S.	United States
WGTT	whole gut transit time
WMC	wireless motility capsule

Appendix A. Detailed Electronic Database Search Strategies

PubMed Strategy

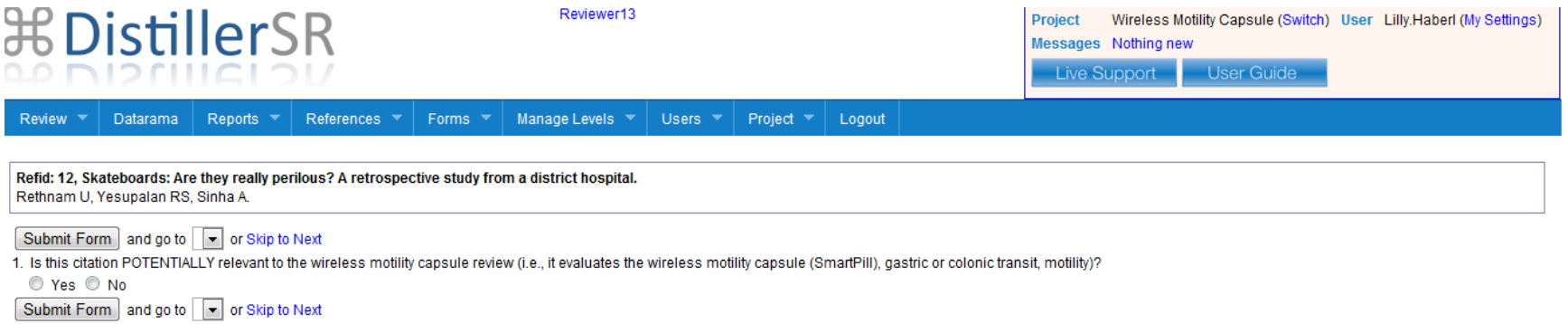
Search #	Search String	# Hits
#1	"Capsule Endoscopy"[mh]	1316
#2	(Wireless[tiab] OR radiotelemetr*[tiab]) AND (motility[tiab] OR capsule*[tiab])	708
#3	Smartpill*[tiab]	13
#4	#1 OR #2 OR #3	1800
#5	(animal[mh] NOT human [mh])	3685271
#6	#4 NOT #5	1751

EMBASE Strategy

Search #	Search String	# Hits
#1	(Wireless:ti,ab OR radiotelemetr*:ti,ab) AND (motility:ti,ab OR capsule*:ti,ab)	1090
#2	Smartpill:ti,ab	74
#3	#1 OR #2	1106
#4	([animals]/lim NOT [humans]/lim)	4640790
#5	#3 NOT #4	1033

Appendix B. Forms

Title Review Form



Abstract Review Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Wireless Motility Capsule vs. Other Diagnostic Technologies for Evaluating Gastroparesis and Slow-Transit Constipation: A Comparative Effectiveness Review
Abstract Review Form

1. Exclude article if: **(Check the first response that applies)**

- ☐ No original data (e.g., review article, commentary, editorial)
- ☐ No subjects with suspected gastroparesis or slow-transit constipation
- ☐ Does not evaluate the wireless motility capsule or a capsule that measures pH, pressure, motility, or transit time
- ☐ No human subjects
- ☐ Does not include an **adult population**
- ☐ Other reason for exclusion (specify:)

2. Unclear

- ☐ Unclear - pull article for review

3. Include

- ☐ Include article for review
- ☐ Mark if case report

4. Handsearch

- ☐ Exclude article from review, but pull for handsearching (i.e., systematic review published since 2005)

Tests for the evaluation of gastroparesis	Tests for the evaluation of slow-transit constipation
• Gastric scintigraphy • Antroduodenal manometry • Endoscopy	• Radiopaque markers • Scintigraphy

5. Comments **(Please limit to 250 characters)**

Submit Form and go to or Skip to Next

Article Review Form

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Wireless Motility Capsule vs. Other Diagnostic Technologies for Evaluating Gastroparesis and Slow-Transit Constipation: A Comparative Effectiveness Review
Article Review

1. Exclude article if: (Check the first response that applies)

- ☐ No original data (e.g. review article, commentary, editorial)
- ☐ No subjects with suspected gastroparesis or slow-transit constipation unless evaluates the wireless motility capsule
- ☐ Does not evaluate the wireless motility capsule (exclude Given, Bravo, Heidelberg capsule, video capsule endoscopy, OMOM, M2A, and patency capsules)
- ☐ Does not have an appropriate comparison group (see below) AND does not report on harms of the wireless motility capsule
- ☐ Does not report on an outcome of interest
- ☐ No human subjects
- ☐ Does not include an adult population
- ☐ Does not apply to key question
- ☐ Other reason for exclusion (specify):

2. Include

- ☐ Include article for gastroparesis
- ☐ Include article for slow-transit constipation
- ☐ Include article for harms

3. Handsearch

- ☐ Exclude article from review, but pull for handsearching (i.e., systematic review published since 2005)

Tests for the evaluation of gastroparesis	Tests for the evaluation of slow-transit constipation
• Gastric scintigraphy • Antroduodenal manometry • Endoscopy	• Radiopaque markers • Scintigraphy

4. Comments (limit 250 characters):

Data Abstraction Forms

Table 1. Study Design data abstraction form

Refid	Author, year	Study design	Other study design	Country - Select if US	Country - Specify other	Location of recruitment	Other location of recruitment	Start year of recruitment	Multi vs. Single center
		• RCT • Retrospective cohort • Prospective cohort • Prospective cohort with historical comparison • Other study design		• US • Multi including US • Multi not including US • Other • Not reported		• General public • Tertiary center • Other • Not reported			• Multi-center • Single center • Not reported

Length of followup reported as	Length of followup	Unit for length of followup	Length of time between tests reported as	Enter the length of time in between tests	Unit for length of time in between tests	Type of patients included - gastroparesis	Type of patients included - constipation	Were normal people included	Inclusion criteria
• Mean • Median • Range		• None • Days • Weeks • Months • Years • Not reported	• Mean • Median • Range		• None • Days • Weeks • Months • Years • Not reported	• Known • Suspected • Not applicable	• Known • Suspected • Not applicable	• Yes • No	

Table 2. Population characteristics data abstraction form

Refid	Author, year	Sample size at baseline	Population	Age-Select measure	Age	Gender not reported	Gender, N male	Gender, % male	Race not reported	Race, N White	Race, % White
				• Mean • Median • Range • Not reported					• Not reported		

Race, N African American	Race, % African American	Race, N Asian	Race, % Asian	Race, N Hispanic	Race, % Hispanic	Race, specify other race	Race, N other	Race, % other	Weight-Select measure	Weight (kg)	Prior testing, specify prior test
									• Mean • Median • Range • Not reported		

Prior testing, N	Prior testing, %	Blood sugar-Select measure	Blood sugar	Smoking status, define smoker	Smoker, n	Smoker, %	Specify type of diabetes	Diabetes, N	Diabetes, %	Defecatory dysfunction, N	Defecatory dysfunction, %
		• Mean • Median • Range • Not reported					• Type 1 • Type 2 • Both • Not specified • Not reported				

Prior use of prokinetics, N	Prior use of prokinetics, %	Prior use of narcotics, N	Prior use of narcotics, %	Prior use of antidepressants, N	Prior use of antidepressants, %	Prior use of PPIs, N	Prior use of PPIs, %	Prior use of laxatives, N	Prior use of laxatives, %

Use of prokinetics at time of test, N	Use of prokinetics at time of test, %	Use of narcotics at time of test, N	Use of narcotics at time of test, %	Use of antidepressants at time of test, N	Use of antidepressants at time of test, %	Use of PPIs at time of test, N	Use of PPIs at time of test, %	Use of laxatives at time of test, N	Use of laxatives at time of test, %

Table 3. Diagnostic test data abstraction form

Refid	Author, year	Diagnostic test	Criteria used for diagnosis of gastroparesis	Criteria used for diagnosis of slow-transit constipation	Were patients off tobacco at time of test?	Were patients off prokinetics at time of test?	Were patients off of narcotics at time of test?
		• Wireless motility capsule • Gastric scintigraphy • Antroduodenal manometry • Endoscopy • Colonic scintigraphy • Radiopaque			• Yes • No • Not reported	• Yes • No • Not reported	• Yes • No • Not reported

Were patients off antidepressants at time of test?	Were patients off of PPIs at time of test?	Were patients off laxatives at time of test?	If wireless motility capsule, was the pill swallowed or placed?	If wireless motility capsule, was a standardized meal used?	If wireless motility capsule, enter standardized meal
• Yes • No • Not reported	• Yes • No • Not reported	• Yes • No • Not reported	• Swallowed • Placed	• Yes • No • Not reported	

If wireless motility capsule, were patients given Ensure?	Record number of hours after test Ensure was given	If gastric scintigraphy, what was the duration of testing?	If gastric scintigraphy, were liquid or solid components used?	If manometry, which catheter was used?	If manometry, how was the catheter placed?
• Yes • No • Not reported		• 1.5-hour • 2-hour • 3-hour • 4-hour/Tougas • Other • Not reported	• Liquid • Solid • Both • Not reported		• Endoscopy • Fluoroscopy • Blind passage • Other • Not reported

If endoscopy, enter the number of hours without food (NPO)	If endoscopy, indicate the method of sedation	If colonic scintigraphy, enter the protocol used	If colonic scintigraphy, enter the duration of testing	If ROM, enter the type of markers used	If ROM, enter the timing of markers
• 6 hours • Other • Not reported	• Conscious sedation • General • Other • Not reported	• Temple • Mayo • Other • Not reported		• Circles • Other • Not reported	

Table 4. Outcomes data abstraction form

Refid	Author, year	What outcome of interest did you find?	Other outcome (please describe):	If diagnostic accuracy, what are the comparisons?	1st reviewer: where is the outcome found in paper:	2nd reviewer: abstracted or not?	2nd reviewer: if not abstracted, please document why
		• Diagnostic accuracy- gastroparesis • Diagnostic accuracy- constipation Transit time • Pressure patterns • Change in medications • Change in nutrition • Surgery • Need for referral • Symptom improvement • Quality of life • Patient satisfaction • Test failure (unable to read test results) • Need for additional tests because of continued uncertainty about diagnosis • Utilization of other health care services • Capsule retention • Radiation exposure • Mortality • Other				• Outcome abstracted • Outcome not abstracted	

Table 5. Study quality data abstraction form

Refid	Author, year	Were "healthy" and "normal" patients excluded from the diagnostic accuracy comparison?	Were severely affected patients excluded?	Was a random sample of patients enrolled (as opposed to consecutive)?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
		• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear

Did the study specifically state that the results (reference standard and SmartPill) were interpreted without knowledge of the results of the other tests?	Is the time period between reference standard and SmartPill test short enough to be reasonably sure that the target condition did not change between the two tests (within 3 months)?	Were cut-off values of tests positivity for the reference standard and SmartPill established before the study was started (in the methods section)?	Was a stated aim of the study to compare the diagnostic accuracy of SmartPill compared to scintigraphy, manometry, radiopaque markers, or endoscopy among patients with symptoms of or with gastroparesis or constipation?	Did the study report on conflicts of interest ("none declared" and "no conflicts reported" counts as a yes)?	If conflicts of interest reported, was the study itself funded by a commercial source related to motility testing?	If yes (funded by commercial source related to motility testing), were any of the authors employed by a commercial source or receive funding or fees from a commercial source related to motility testing?
• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear	• Yes • No • Unclear

Appendix C. List of Excluded Articles

Adler, D. G., Chand, B., Conway, J. D., Diehl, D. L., Kantsevoy, S. V., Kwon, R. S., Mamula, P., Rodriguez, S. A., Shah, R. J., Song, L. M., and Tierney, W. M. Capsule endoscopy of the colon. Gastrointest Endosc. 2008; 68 (4): 621-3. **No original data**

Ahmad, N. A., Iqbal, N., and Joyce, A. Clinical impact of capsule endoscopy on management of gastrointestinal disorders. Clin Gastroenterol Hepatol. 2008; 6 (4): 433-7. **Not wireless motility capsule**; **does not apply to key question**

Amano, Y., Yuki, T., Kusunoki, R., and Kinoshita, Y. Gastric screening examination using PillCam ESO 2: a pilot study. Dig Liver Dis. 2011; 43 (7): 580-1. **Not wireless motility capsule**

Aparicio, J. R., Martinez, J., and Casellas, J. A. Right lateral position does not affect gastric transit times of video capsule endoscopy: a prospective study. Gastrointest Endosc. 2009; 69 (1): 34-7. **No subjects with gastroparesis or constipation**

Apostolopoulos, P., Kalantzis, C., Gralnek, I. M., Liatsos, C., Tsironis, C., and Kalantzis, N. Clinical trial: effectiveness of chewing-gum in accelerating capsule endoscopy transit time--a prospective randomized, controlled pilot study. Aliment Pharmacol Ther. 2008; 28 (4): 405-11. **No subjects with gastroparesis or constipation; not wireless motility capsule**

Atia, A., Rammohan, M., Ahn, C., Hebuterne, X., Girard-Pipau, F., and Buchman, A. L. Pectin supplementation increases colonic short chain fatty acid production(SCFA) in patients with short bowel syndrome(SBS). Gastroenterology. 2009; 136 (5): A140. **No subjects with gastroparesis or constipation; no appropriate comparison**

Attaluri, A., Valestin, J., and Rao, S. S. C. Is small bowel and colonic motility altered in constipated patients with methanogenic flora?. Neurogastroenterol. Motil.. 2010; 22 79. **No appropriate comparison**

Bai, Y., Gao, J., Song, B., Zhou, Y. Q., Zou, D. W., and Li, Z. S. Surgical intervention for capsule endoscope retained at ileal stricture. Endoscopy. 2007; 39 Suppl 1 E268-9. **Not wireless motility capsule**

Baichi, M. M., Arifuddin, R. M., and Mantry, P. S. What we have learned from 5 cases of permanent capsule retention. Gastrointest Endosc. 2006; 64 (2): 283-7. **Not wireless motility capsule**

Baker, J., Hasler, W. L., Camilleri, M., Rao, S., Thorne, N. K., Ringel, Y., Kuo, B., Esfandyari, T., Gupta, A. D., Scott, S. M., McCallum, R., Parkman, H. P., Soffer, E. E., and Di Baise, J. K. Impairment of overall and regional high amplitude colon contractions in severe slow transit constipation measured by wireless motility capsules. Gastroenterology. 2011; 140 (5): S531. **No appropriate comparison**

Banerjee, R. and Reddy, D. N. Endoscopy-assisted wireless intragastric pH monitoring. Gastrointest Endosc. 2007; 65 (1): 182. **No original data**; **not wireless motility capsule**

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Willis, H. J., Thomas, W., Willis, D. J., and Slavin, J. L. Feasibility of measuring gastric emptying time, with a wireless motility device, after subjects consume fiber-matched liquid and solid breakfasts. Appetite. 2011; 57 (1): 38-44. **Does not apply to key question**; **other exclusion**

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Appendix D. Evidence Tables

Table 1. Study design characteristics of studies evaluating the wireless motility capsule

Author, Year	Study design	Country	Start year of recruitment Location of recruitment Multi or single center	Length of followup (days) Length of time between tests	Type of patients included Normal/healthy patients included?	Inclusion criteria
Kuo, 2011[12]	Retrospective cohort, chart review	US	2007 Tertiary center Multi-center	Followup NR Simultaneous tests	Suspected constipation Suspected gastroparesis No	Patients undergoing WMC testing to exclude delayed gastric, small intestinal or colonic transit.
Rao, 2011[34]	Retrospective cohort, chart review	US	2007 Tertiary center Single center	Followup NR Simultaneous	Suspected constipation Suspected gastroparesis No	Reported symptoms suggestive of GI dysmotility for at least 6 mo and had normal upper endoscopy and/or colonoscopy, normal hematology and metabolic profiles, and normal abdominal ultrasound CAT scan evaluations. Patients with a history of appendectomy, cholecystectomy or cesarean section, or hysterectomy. No history of severe dysphagia, bezoars, GI obstruction, inflammatory bowel disease, and earlier gastrectomy or colectomy or other abdominal/pelvic surgeries.
Camilleri, 2010[32]	Prospective cohort	Multi including US	Start year NR Multi-center	2 Simultaneous	Known constipation No	18 to 80 years old, symptoms of chronic functional constipation for at least one year; self-reported hard stool at least 25% of the time w/ at least one of 6+ symptoms of functional constipation by Rome III criteria

Author, Year	Study design	Country	Start year of recruitment Location of recruitment Multi or single center	Length of followup (days) Length of time between tests	Type of patients included Normal/healthy patients included?	Inclusion criteria
Saad, 2010[50] [Sub-analysis of data[17]]	Prospective cohort, post hoc analysis[17]	US	Start year NR Tertiary center Multi-center	5 Simultaneous	Known constipation Yes	18+ years old, healthy people, chronically constipated with 2+ symptoms in past 12 months of: straining at defecation, lump/hard stools, sensation of incomplete evacuation all in at least quarter of the time, and/or three of fewer bowel movements per week. Healthy included no previous GI surgery other than uncomplicated appendectomy, cholecystectomy, or cesarean section
Hasler, 2009[49] [Subset of study[17]]	Prospective cohort	US	Start year NR Tertiary center Multi-center	Followup NR Simultaneous	Known constipation Yes	Self-reported constipated by Rome II Criteria for chronic functional constipation; at least 2/6 symptoms of constipation for at least 3 months; no patients with functional outlet obstruction with balloon expulsion time >60 s; no prior GI surgery other than appendectomy, cholecystectomy, or c-section; healthy patients had no GI symptoms on Mayo screening, not morbidly obese (BMI >35 kg/m^2), not on medications known to affect gut transit, no cardiovascular, endocrine, renal, or hepatic disease.
Rao, 2009[17]	Prospective cohort	US	Start year NR Tertiary center Multi-center	21 Simultaneous	Known constipation Yes	Constipated: fulfilled Rome II criteria for chronic functional constpiation and at least 2/6 symptoms of constipation, no previous abdominal surgery other than uncomplicated cholecystectomy or c-section; Healthy patients inclusion: screening with Mayo GI Disease questionnaire.

Author, Year	Study design	Country	Start year of recruitment Location of recruitment Multi or single center	Length of followup (days) Length of time between tests	Type of patients included Normal/healthy patients included?	Inclusion criteria
Kuo, 2008[16]	Prospective cohort	US	2005 Location NR Multi-center	3 Simultaneous	Known gastroparesis Yes	No patients with previous GI surgery except those with uncomplicated appendectomy and/or laparoscopic cholecystectomy. No patients with prescriptions for drugs such as birth control, antidepressants, antilipids that had changed in past 6 months, not pregnant. Healthy: between 18-65 with no GI disease according to the Mayo GI Disease Screening Questionnaire and no cardiovascular, endocrine, renal and chronic disease, have average bowel movement frequency of at least one per 48 h, no pregnancy, no surgery within the past 3 months, no clinical evidence of diverticulitis as evidenced by the absence of chronic or acute abdominal pain, no medications or over-the-counter agents that could influence GI motility, no tobacco use within 8 h before and after capsule ingestion, no alcohol use 24 h before capsule ingestion and during the monitoring period and a body mass index <35. Gastroparesis patients were Males and females between ages 18 and 65 years with history of nausea and vomiting, early satiety, epigastric pain or discomfort for at least 6 months and documented abnormal scintigraphy as defined by local medical centre standards within 2 years. Gastroparetics with excessively delayed GET (>90% of a standard egg meal retained after 2 h), average bowel movement frequencies exceeding 72 h, evidence of gastric bezoar within the last 3 years, stricture, peptic ulcer, severe dysphagia to solid food and pills, severe vomiting, severe abdominal pain, severe weight loss (>4.5 kg in last 2 months), or diabetes with a hemoglobin A1C >10 were excluded.

Author, Year	Study design	Country	Start year of recruitment Location of recruitment Multi or single center	Length of followup (days) Length of time between tests	Type of patients included Normal/healthy patients included?	Inclusion criteria
Brun, 2011[41]	Prospective cohort	US	Start year NR Tertiary center Center NR	Followup NR Simultaneous	Known gastroparesis Yes	NFS
Mysore, 2010[52]	Prospective cohort[34]	NR	Start year NR Tertiary center Center NR	5 Time between NR	Suspected constipation Suspected gastroparesis No	Symptoms of dysmotility
Mysore, 2010[53] [earlier version of study[34]]	Prospective cohort[34]	NR	Start year NR Tertiary center Center NR	5 Time between NR	Suspected constipation Suspected gastroparesis No	Symptoms of dysmotility
Lee, 2010[42]	Retrospective cohort	NR	Start year NR Tertiary center Single center	Followup NR Time between NR	Suspected constipation Suspected gastroparesis No	Not further specified
Reddymasu, 2010[43]	Prospective cohort	US	Start year NR Tertiary center Multi-center	Followup NR Simultaneous	Known gastroparesis Yes	Previously healthy; gastroparetic (defined as presence of abdominal pain, nausea, and vomiting with a previously documented delayed GES

Author, Year	Study design	Country	Start year of recruitment Location of recruitment Multi or single center	Length of followup (days) Length of time between tests	Type of patients included Normal/healthy patients included?	Inclusion criteria
Paulson, 2009[51]	Not specified	NR	NR	1 Time between NR	Known constipation Yes	Not further specified
Lee, 2009[44]	Retrospective cohort	US	Start year NR Tertiary center Single center	NR	Suspected constipation Suspected gastroparesis No	Patients who presented to single tertiary center for evaluation of potential GI dysmotilities
Rao, 2009[46]	Not specified	NR	NR	1 Time between NR	Known constipation Yes	Not further specified
Rao, 2009[47]	Prospective cohort, matched prospective cohort	NR	Start year NR Location NR Multi-center	1 Time between NA	Known constipation Yes	Over the age of 65
Lee, 2012[45]	Prospective cohort	US	2005 Tertiary center Multi-center	2 to 5 Simultaneous	Known gastroparesis No	Males and females between ages 18 and 65 years with history of nausea and vomiting, early satiety, epigastric pain or discomfort for at least 6 months and documented abnormal scintigraphy by local standards within 2 years were enrolled
Rao, 2012[48]	Prospective cohort	NR	Start year NR Location NR Single center		Known constipation Yes	Patients over 65 years of age referred to tertiary care center for evaluation of constipation; negative colonoscopy within past year, normal hematology, biochemistry, and thyroid function test excluding metabolic disorder

Abbreviations: BMI = body mass index; GET = gastric emptying time; GI = gastrointestinal; h = hours; mo = month; NA = not applicable; NFS = not further specified; NR = not reported; s = seconds; US = United States

Table 2. Study population characteristics of studies evaluating the wireless motility capsule

Author, year	Population, N	Males (%), age in years	Race	Prior Testing N (%)	Blood sugar Smoking status Diabetes status Defecatory dysfunction	Prior use of prokinetics, narcotics, antidepressants, PPIs, laxatives
Kuo, 2011[12]	No comparison population, 83	17 (20.5), Mean: 43	NR	GES, 44 ROM, 16 Other, 48	Blood sugar NR Smoking NR Diabetes: 12 (14.6) Defecatory: 27	Prokinetics NR No narcotics 3 to 7 days prior Antidepressants NR No PPIs No laxatives
Rao, 2011[34]	Combined (UGI, LGI), 86	9, Mean: 44.5	W: 77 (89.5) AA: 4 (4.7)	GES: 36 ROM: 50	NR	Prokinetics: 14% UGI, 6% LGI Narcotics: 8% UGI, 6% LGI Antidepressants: 44% UGI, 30% LGI PPIs: 58% UGI, 12% LGI Laxatives: 19% UGI, 44% LGI
Camilleri, 2010[32]	Chronic constipation, 158	20, Mean: 42.5	W: (83) AA: (13) A: (2)	NR	NR	No prokinetics No narcotics No antidepressants No PPIs for 7 days No laxatives
Saad, 2010[50] [Sub-analysis of data[17]]	Chronic constipation, 46	4, Mean: 44	NR	NR	NR	No prokinetics for 48 hours Antidepressants stable dose No PPIs for 48 hours No laxatives for 48 hours

Author, year	Population, N	Males (%), age in years	Race	Prior Testing N (%)	Blood sugar Smoking status Diabetes status Defecatory dysfunction	Prior use of prokinetics, narcotics, antidepressants, PPIs, laxatives
Saad, 2010[50] [Sub-analysis of data[17]]	Healthy, 64	(47), Mean: 38	NR	NR	NR	NR
Hasler, 2009[49] [Subset of study[17]]	Constipation, 36	5, Mean: 47.4	NR	Anal balloon expulsion (100%)	Defecatory dysfunction: 0	No prokinetics for 2 days No narcotics for 7 days Antidepressants if ≥ 6 mo No PPIs for 7 days No laxatives for 2 days
Hasler, 2009[49] [Subset of study[17]]	Healthy, 53	27, Mean: 37.2	NR	NR	NR	No prokinetics for 2 days No narcotics for 7 days Antidepressants if ≥ 6 mo No PPIs for 7 days No laxatives
Rao, 2009[17]	Constipation, 78	9, Mean: 45	NR	NR	NR	No prokinetics for 48 hours Narcotics NR Antidepressants stable dose No PPIs for 48 hours No laxatives for 48 hours

Author, year	Population, N	Males (%), age in years	Race	Prior Testing N (%)	Blood sugar Smoking status Diabetes status Defecatory dysfunction	Prior use of prokinetics, narcotics, antidepressants, PPIs, laxatives
Rao, 2009[17]	Healthy, 87	47, Mean: 39	NR	NR	NR	No prokinetics for 48 hours Narcotics NR Antidepressants stable dose No PPIs for 48 hours No laxatives for 48 hours
Kuo, 2008[16]	Gastroparesis, 61	10, Age NR	W: 50 AA: 7 H: 4	Scintigraphy, 1	NR	NR
Kuo, 2008[16]	Healthy, 87	55, Age NR	W: 69 AA: 7 A: 5 H: 4	NA	NR	NR
Brun, 2011[41]	Gastroparesis, 87	NR	NR	GES (100)	NR	NR
Brun, 2011[41]	Healthy, 61	NR	NR	NR	NR	NR
Mysore, 2010[52]	Total, 86 (UGI: 11, LGI: 45, mixed: 30)	9, Range: 18 to 85	NR	Barium studies: 0.3, barium enema: 0.2	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	Total, 71 (UGI: 6, LGI: 13, mixed: 22)	9, Range: 19 to 85	NR	NR	NR	NR
Lee, 2010[42]	Total, 50	NR	NR	NR	NR	NR
Reddymasu, 2010[43]	Gastroparesis, 41	8, Age NR	NR	NR	NR	NR
Reddymasu, 2010[43]	Healthy, 66	38, Age NR	NR	NR	NR	NR
Paulson, 2009[51]	Constipation, 32	7, Age NR	NR	NR	NR	NR
Paulson, 2009[51]	Healthy, 15	6, Age NR	NR	NR	NR	NR
Lee, 2009[44]	Total, 32	NR	NR	NR	NR	NR
Rao, 2009[46]	Constipation, 32	7, Mean: 49	NR	NR	NR	NR
Rao, 2009[46]	Healthy, 15	6, Mean: 45	NR	NR	NR	NR

Author, year	Population, N	Males (%), age in years	Race	Prior Testing N (%)	Blood sugar Smoking status Diabetes status Defecatory dysfunction	Prior use of prokinetics, narcotics, antidepressants, PPIs, laxatives
Rao, 2009[47]	Constipation, 10	5, Mean: 74	NR	NR	NR	NR
Rao, 2009[47]	Healthy, 12	6, Mean: 70	NR	NR	NR	NR
Lee, 2012[45]	Gastroparesis, 43	8 (18), Mean: 42	NR	GES: 43 (100)	Blood sugar NR Smoking status NR Diabetes: 16 (37.2) Defecatory dysfunction NR	No prokinetics for 3 days No narcotics for 3 days Antideppressants NR No PPIs for 3+ days prior Laxatives NR
Rao, 2012[48]	Constipation, 27	25 Median age women: 71, Median age men: 74	NR	Colonoscopy	NR	No prokinetics for 48 hours No PPIs for 7 days No laxatives for 48 hours
Rao, 2012[48]	Healthy, 12	7 Median age men: 68 years; Median age women: 70	NR	Mayo GI Disease Questionnaire	NR	No prokinetics for 48 hours No PPIs for 7 days No laxatives for 48 hours

Abbreviations: A= Asian; AA = African American; CTT = colon transit time; GES = gastric emptying scintigraphy; GET = gastric emptying time; GI = gastrointestinal; H = Hispanic; h = hours; kg = kilogram; LGI = lower gastrointestinal tract; mo = month; NR = not reported; PPI = proton pump inhibitor; ROM = radiopaque markers; UGI = upper gastrointestinal tract; W = white

Table 3. Diagnostic tests in studies evaluating wireless motility capsule

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Kuo, 2011[12]	Wireless motility capsule	Gastroparesis: Emptying time > 5 hours Constipation: Colonic transit time > 59 hours	Tobacco NR Prokinetics NR No narcotics Antidepressants allowed No PPIs No laxatives	Capsule swallowed Std meal NR Ensure NR
Rao, 2011[34]	Wireless motility capsule	Gastroparesis: They used standard criteria of > 5 hours abnormal (disregard above) Constipation: standard criteria of CTT > 59 hours	Tobacco NR Prokinetics NR No narcotics No antidepressants No PPIs No laxatives	Capsule swallowed Std meal: 255 kcal nutrition bar Ensure NR
Rao, 2011[34]	Gastric scintigraphy	Gastroparesis: greater than 10% retention at 4 hours (delayed gastric emptying)	Tobacco NR Prokinetics NR Narcotics NR Antidepressants NR PPIs NR Laxatives NR	NFS

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Rao, 2011[34]	Colonic scintigraphy	Constipation: Retention of 6 or more radiopaque markers at 120 hours was defined as abnormal colonic transit.	Tobacco NR Prokinetics NR Narcotics NR Antidepressants NR PPIs NR Laxatives NR	NFS
Camilleri, 2010[32]	Wireless motility capsule	Gastroparesis: > 5 hours Constipation: 59 hours	Tobacco NR No prokinetics No narcotics No antidepressants No PPIs No laxatives	Capsule swallowed Std meal: egg beaters Ensure given 6 h after test
Camilleri, 2011[32]	Radiopaque markers	Gastroparesis: > 5 hours Constipation: 67 hours	Tobacco NR No prokinetics No narcotics No antidepressants No PPIs No laxatives	24 ROM on 3 successive days X-ray day 4 (72 h after ingestion of first set) and day 7 (144 h after ingestion of first set) Type of counts: both segment and total colon

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Saad, 2010[50] [Sub-analysis of data[17]]	Wireless motility capsule	Constipation: based on 95th percentile of healthy control population	Tobacco NR No prokinetics Narcotics NR Antidepressants allowed No PPIs No laxatives	Capsule swallowed Std meal: SmartBar Ensure given 6 h after test
Saad, 2010[50] [Sub-analysis of data[17]]	Radiopaque markers	Constipation: delayed whole got transit defined as retention of >20% of ROM after 5 days	Tobacco NR No prokinetics Narcotics NR Antidepressants allowed No PPIs No laxatives	24 ROM in capsule X-ray 48 h after ingestion
Hasler, 2009[49] [Subset of study[17]]	Wireless motility capsule	Constipation: >59 hours transit time	Tobacco NR No prokinetics No narcotics Antidepressants allowed No PPIs No laxatives	Capsule swallowed Std meal: SmartBar Ensure given 6 h after test

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Hasler, 2009[49] [Subset of study[17]]	Radiopaque markers	Constipation: >59 hours transit time	Tobacco NR No prokinetics No narcotics Antidepressants allowed No PPIs No laxatives	24 ROM in capsule X-ray as needed Type of counts NR
Rao, 2009[17]	Wireless motility capsule	Constipation: based on 95th percentile of healthy control population as 59 hours for women and 44 hours for men	Tobacco NR No prokinetics Narcotics NR Antidepressants allowed No PPIs No laxatives	Capsule swallowed Std meal: SmartBar Ensure given 6 h after test
Rao, 2009[17]	Radiopaque markers	Constipation: based on 95th percentile of healthy control population as 59 hours for women and 44 hours for men	Tobacco NR No prokinetics Narcotics NR Antidepressants allowed No PPIs No laxatives	24 ROM in one capsule X-ray 48 h after ingestion and 120 h after ingestion and 21 days after ingestion Type of co unts NR

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Kuo, 2008[16]	Wireless motility capsule	Gastroparesis: Threshold not reported; abrupt pH rise (usually >3 pH units) from gastric baseline to a pH >4 as determined by software and 2 reviewers.	No tobacco for healthy Tobacco NR for gastroparetic No prokinetics No narcotics Antidepressants allowed No PPIs for gastroparetic No laxatives	Capsule swallowed Std meal: scrambled egg substitute, bread, strawberry jam, water Ensure given 6 h after test
Kuo, 2008[16]	Gastric scintigraphy 4h	Gastroparesis: >10% retained at 4h as determined by X-ray	No tobacco for healthy Tobacco NR for gastroparetic No prokinetics No narcotics Antidepressants allowed No PPIs for gastroparetic No laxatives	4-hour/Tougas duration Solid components used

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Kuo, 2008[16]	Gastric scintigraphy 2h	NR	No tobacco for healthy Tobacco NR for gastroparetic No prokinetics No narcotics Antidepressants allowed No PPIs for gastroparetic No laxatives	2-hour duration Solid components used
Brun, 2011[41]	Wireless motility capsule	Gastroparesis: NFS	NR	NR
Brun, 2011[41]	Gastric scintigraphy	Gastroparesis: NFS	NR	Radioactive meal Meal retention assessed at 2 h and 4 h
Mysore, 2010[52]	Wireless motility capsule	NR	NR	NR
Mysore, 2010[52]	Standard testing	NR	NR	NFS
Mysore, 2010[53] [earlier version of study[34]]	Wireless motility capsule	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	Gastric scintigraphy	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	Antroduodenal manometry	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	Colonic scintigraphy	NR	NR	NR
Mysore, 2010[53] [earlier version of study[34]]	Radiopaque markers	NR	NR	NR

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Lee, 2010[42]	Wireless motility capsule	NR	NR	NR
Lee, 2010[42]	Other diagnostic motility tests, including 4-hr gastric scintigraphy	NR	NR	Gastric scintigraphy: 4-hour/Tougas duration ROM: circles
Reddymasu, 2010[43]	Wireless motility capsule	Gastroparesis: (gastric cph <73 or frequency of gastric contractions >100 mmHg being less than 2/hour)	NR	NR
Reddymasu, 2010[43]	Gastric scintigraphy	Gastroparesis: abnormal if >10% of the radio-labeled meal was retained in the stomach at the end of 4 hours.	NR	NR
Paulson, 2009[51]	Wireless motility capsule	NR	NR	NR
Paulson, 2009[51]	Anal manometry	NR	NR	NR
Lee, 2009[44]	Wireless motility capsule	NR	NR	NR
Rao, 2009[46]	Wireless motility capsule	NR	NR	Capsule swallowed
Rao, 2009[46]	Radiopaque markers	NR	NR	NR
Rao, 2009[47]	Wireless motility capsule	NR	NR	Capsule swallowed Std meal: nutrient bar Ensure given 6 h after test

Author, year	Diagnostic test	Criteria used for constipation or gastroparesis	Use of tobacco, prokinetics, narcotics, antidepressants, PPIs, laxatives at test time?	Diagnostic test protocol
Lee, 2012[45]	Wireless motility capsule	Gastroparesis: 5 hours	Tobacco NR No prokinetics No narcotics Antidepressants NR No PPIs Laxatives NR	Capsule swallowed Std meal: 50 mL water Ensure given 6 h after test
Lee, 2012[45]	Gastric scintigraphy	Gastroparesis: <10% gastric retention at 4 h.	Tobacco NR No prokinetics No narcotics Antidepressants NR No PPIs Laxatives NR	Std meal: eggbeaters with markers 4-hour/Tougas duration Solid components given Meal retention assessed at 2 h and 4 h
Rao, 2012[48]	Wireless motility capsule	Constipation: Rome III	No prokinetics for 48 hours No PPIs for 7 days No laxatives for 48 hours	Capsule swallowed Std meal: nutrient bar and 50 mL water
Rao, 2012[48]	Radiopaque markers	Constipation: Rome III	No prokinetics for 48 hours No PPIs for 7 days No laxatives for 48 hours	Single capsule with 24 ROM swallowed directly before WMC

Abbreviations: BMI = body mass index; CTT = colon transit time; GES = gastric emptying scintigraphy; GET = gastric emptying time; GI = gastrointestinal; h = hours; kg = kilogram; LGI = lower gastrointestinal tract; m = meter; mL = milliliter; NA = not applicable; NFS = not further specified; NR = not reported; PPI = proton pump inhibitor; ROM = radiopaque markers; Std = standardized; UGI = upper gastrointestinal tract; US = United States; WMC = wireless motility capsule

Table 4. Study quality of studies evaluating wireless motility capsule

Author, year	Healthy and normal excluded	Severely affected patients excluded	Random sample	Same reference standard	Were all patients included in the analysis	Blinding of investigators	Reasonable time between tests	Pre-established cut-off values	Stated aim diagnostic accuracy	Conflict of interest stated	Commercial/Industry support	Author employees of funder
Kuo, 2011[12]	Yes	Unclear	No	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes
Rao, 2011[34]	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Camilleri, 2010[32]	No	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saad, 2010[50] [Sub-analysis of data[17]]	No	Unclear	No	Yes	No	Yes*	Yes	Yes	No	Yes	Yes	Yes
Hasler, 2009[49] [Subset of study[17]]	No	No	No	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
Rao, 2009[17]	No	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kuo, 2008[16]	No	yes	Unclear	Yes	No	Yes*	No	No	No	Yes	Yes	Yes
Brun, 2011[41]	No	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	No	No	Unclear	Unclear
Mysore, 2010[52]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	Unclear	Unclear
Mysore, 2010[53] [earlier version of study[34]]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear
Lee, 2010[42]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Reddymasu, 2010[43]	No	Unclear	No	Yes	Unclear	No	Yes	Yes	Yes	No	Unclear	Unclear
Paulson, 2009[51]	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	no	No	Unclear	Unclear
Lee, 2009[44]	Yes	Unclear	No	Unclear	Yes	No	Unclear	Unclear	Yes	No	Unclear	Unclear

Author, year	Healthy and normal excluded	Severely affected patients excluded	Random sample	Same reference standard	Were all patients included in the analysis	Blinding of investigators	Reasonable time between tests	Pre-established cut-off values	Stated aim diagnostic accuracy	Conflict of interest stated	Commercial/Industry support	Author employees of funder
Rao, 2009[46]	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear
Rao, 2009[47]	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear
Lee, 2012[45]	Yes	Unclear	Unclear	No	No	Yes*	Yes	Yes	Yes	Yes	Unclear	Yes
Rao, 2012[48]	No	No	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes**

*Article did not indicate blinding, but author was contacted via e-mail and confirmed blinding.
**Author consultant to company not employee