Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease - Update*

Draft review available for public comment from March 18, 2010 to April 15, 2010.

Research Review Citation: Ip S, Chung M, Moorthy D, Yu WW, Lee J, Chan JA, Bonis PA, Lau J. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update. Comparative Effectiveness Review No. 29. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 11-EHC049-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Executive Summary	Convey quality and SOE better in ES text. For example the surgical vs endoscopic treatments specifically describes result of one study, but doesn't convey whether this evidence should be relied upon. (I interpret it as insufficient or at best very low, but it is not clear to the average reader)	The body of the executive summary has been edited to include a synopsis of the methods and discussion sections. The strength of evidence has been added to the text of the results section, and it is also retained in the table. The SOE refers to the overall body of evidence. This has been explicitly stated in the ES text.
Peer Reviewer #6	Executive Summary	Better description of applicability of evidence in the executive summary. Particular striking in the medical versus surgical treatments section. Was this a population of patients that had more "severe" or chronic GERD symptoms? Were they patients who had been on med mgt for some time? Had they been controlled on meds or not responding?	Summary of available data on patient characteristics and response to prior medical treatment have been added to the executive summary for the medical versus surgical section.
Peer Reviewer #6	Executive Summary	Results of comparing OTC PPIs vs other PPIs is somewhat surprising. Did you look for evidence of publication bias (for this or any of the comparisons?)	Both the grey literature (including the scientific information packets from the pharmaceutical companies) and the published literature were scanned, and non-overlapping studies were included in the database.
Peer Reviewer #6	Executive Summary	Table A. EPC terminology is "Strength of evidence"	Changes were made to Table A. Strength of Evidence is used consistently.
Peer Reviewer #6	Executive Summary	Table A. Make it clear what conclusion the SOE supports. In some cases (last section on p ES8) there is moderate evidence with more than one conclusion. Are each of these conclusions supported by moderate evidence? How many studies for each of them? Or is there a general overarching conclusion that is supported by moderate evidence and each of these bullets are sub-conclusions? Same for first section of ES9, comparisons between different PPIs. There are 2 different contradicting conclusions. Which is supported by "moderate" SOE? Be consistent in describing number of studies for each (2nd section on pES9 – comparisons between different dosages and dosing regimens of PPIs)	Changes were made to Table A. As stated, the SOE is determined by all the evidence available. The SOE pertains to the general overarching conclusion, and each of the bullets are sub-conclusions that provide a foundation to make the overarching conclusion. An overarching conclusion has been added to each section, and when the conclusion is derived from individual study results, it is highlighted.
Peer Reviewer #6	Executive Summary	Table A. Be consistent in describing number of studies for each (2nd section on pES9 – comparisons between different dosages and dosing regimens of PPIs)	Changes were made to Table A. The number of studies has been outlined in all the sections.
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	This report contains information on uses, doses and formulations not approved by the FDA. We urge AHRQ to clearly communicate to the reader when a particular use, dose or formulation is not approved by FDA consistent with other AHRQ systematic reviews. The executive summary lacks conclusions based on objective outcomes. The	Thank you for your comments. Drugs that are not approved by the FDA have been removed. It has been explicitly stated in the methods that only FDA approved drugs are included (Page 6). When reported, the

Commentator & Affiliation	Section	Comment	Response
		objective outcomes noted in question 1 include healing of erosive esophagitis (EE), ambulatory pH, and other indicators of reflux. However, the summary section only discusses comparisons in terms of symptoms, a subjective outcome. We urge including information from the many comparative RCTs on healing of EE and other objective parameters noted in the question. The subjective parameters should also include Patient Reported Outcomes (PROs) as appropriate instruments for symptom evaluation. The points discussed in the executive summary should mirror the input into the questions. We recommend referencing throughout the executive summary to allow the reader to locate the various studies in the relevant sections of the report. The executive summary is the most used portion of report and helps to guide the reader to the various report sections. When discussing multiple studies in the same context and grouping them together, consider and note where appropriate that there are varying scales for classifying esophagitis and varying methodologies to define healing.	objective outcomes were extracted and included. This has been highlighted in the executive summary.
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	Suggest providing greater context for the reader by describing the framework for the grading of the studies within the body of the report, particularly as AHRQ is now using the USPSTF grading system in newly commissioned reports. Although this review focuses on adult studies, the document would be more complete if it mentioned that PPIs are approved for short term treatment of GERD in children 1-17 years of age. In addition, it is not clear whether this report is intended for "older Americans" the group specifically mentioned on line 2 of the executive summary. ES-1, Paragraph 4- "Also notable was the publication of a new consensus definition of GERD in 2006." Suggest including other relevant documents by adding the following –"..and the AGA Institute Technical Review on the management of GERD (Gastro 2008;135:1392–1413) and the AGA medical position statement on the management of GERD (Gastro 2008;135:1383–1391.)" ES-2, Medical versus surgical treatments, Paragraph 1 - Consider including a statement regarding the variability of surgery outcomes based on setting and other parameters. Please see the following references: Vakil N, Shaw M, Kirby R. Clinical effectiveness of laparoscopic fundoplication in a U.S. community. Am J Med 2003;114:1–5. Rantanen TK, Halme TV, Luostarinen ME, et al. The long term results of open antireflux surgery in a community-based health care center. Am J Gastroenterol 1999;94:1777–1781.	Thank you for your comments. This report is targeted at adults only, children 1 to 17 years old are excluded in this review. The report did not specifically address the group "older Americans". Reviewing position statements and other technical treatises are outside the purview of this report.
Kathleen Gans-Brangs, PhD;	Executive Summary	ES-3 and ES-4 "Comparisons between different PPIs" The objective outcomes noted in the key question include healing of erosive	Thank you. This has been added.

Commentator & Affiliation	Section	Comment	Response
AstraZeneca		esophagitis (EE), ambulatory pH, other indicators of reflux, etc. However, the summary section only discusses comparisons in terms of symptoms, a subjective outcome. Consider including information from the many comparative RCTs on healing of EE and other objective parameters noted in the question so that the points discussed in the summary mirror the input into the questions.	
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	ES-4, Paragraph 1 – Some of the doses noted for PPIs are not approved for use in the United States. Please provide details or a table that provides information on the FDA approved doses and indications.	Thank you for your comments. Drugs that are not approved by the FDA have been removed. It has been explicitly stated in the methods that only FDA approved drugs are included (Page 6).
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	ES-4, Last paragraph – "Pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis at 8 weeks compared with omeprazole 20 mg." - No reference was provided for this statement in the executive summary section, however, the same sentence appears in the body of the report and is cited using the following reference: "Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World Journal of Gastroenterology 13(33):4467 -72 , 2007." The conclusion for this paper limits its findings to "elderly" patients, however, this report does not make that specification. We recommend the last paragraph be revised to read: A single paper, "Pantoprazole 40 mg and rabeprazole 20 mg provided significantly better symptom relief and healing of esophagitis at 8 weeks compared with omeprazole 20 mg in elderly patients. (Population studied, per the publication, is > 65 years of age)." ES-7. "An increased risk of bone fracture is now added to this list, although the strength of association is uncertain." Please note that all PPIs now have a warning in prescribing information regarding the risk of osteoporosis-related bone fractures within their prescribing information. Consider including in the report.	Thank you. This has been added.
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	ES-8, Table A – As noted in the general comments above, referencing is needed for the Executive Summary section. For example, in Table A where specific studies are cited, referencing would allow the reader to more fully explore the concepts being discussed throughout the body of the report. ES-9, Table A No studies are cited to support the statement, "There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over	Thank you for your comments. The first statement refers to an overarching conclusion, while the following statements provide study data points that might be useful for clinicians.

Commentator & Affiliation	Section	Comment	Response
		24 weeks." In fact, the report itself states: "No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months." We suggest deletion of the statement, "There is some evidence that rabeprazole 10 mg may provide better symptom relief than esomeprazole 40 mg at 4 weeks, and also that pantoprazole 20 mg provides better control of heartburn than esomeprazole 40 mg over 24 weeks." We further suggest the report conclude: "No consistent comparative difference in symptom relief was observed between esomeprazole (20 to 40 mg), lansoprazole (15 to 30 mg), pantoprazole (20 to 40 mg), dexlansoprazole (10 mg) or rabeprazole (10 to 20 mg) over a period ranging from 4 weeks to 6 months, "	
Kathleen Gans-Brangs, PhD; AstraZeneca	Executive Summary	ES-9, Table A "Comparisons between PPIs and over-the-counter dosages of PPIs (omeprazole 20 mg, lansoprazole 15 mg)" Please note in the table that over the counter PPIs are not FDA-approved for GERD. They are approved for the symptom of frequent heartburn only up to 2 week courses x 3 in a year." [See the label for Prilosec OTC - http://www.prilosecotc.com/en_US/hcp/Documents/Monograph.pdf Prevacid OTC - http://prevacid24hr.com/now-available.jsp Zegerid OTC - http://www.zegeridotc.com/zegeridotc/help/product-details.jspa ES-10, Table A Domperidone 10 mg is not approved for use by the FDA. Table should note that this drug is not FDA approved. ES-11, Table A "Obesity, presence of baseline typical GERD symptoms, and more severe esophagitis were significantly associated with worse medical treatment	Thank you for your comment. We have included a statement that OTC PPIs are approved for the symptoms of frequent heartburn (ES-17), the Results (page 37, Page 157). Domperidone is not being evaluated; it is listed as a co-intervention.
Bob Jasak; AstraZeneca	Executive Summary	For the most part, the report provides a nice summary of the pros and cons related to various treatments for gastroesophageal reflux disease (GERD). However, we did want to point out that the study appears to neglect a discussion of long-term proton pump inhibitor (PPI) use and its effect on bone weakness, increased risk for certain infections, and poor absorption of certain important nutrients. In addition, in the discussion of surgical complications in the executive summary, the authors only focus on the highest reported rates of any given complication, such as citing dysphagia occurring 23 percent of the time. We would recommend that the authors include the range of reported complications in surgical and endoscopic therapy for GERD into the executive summary to ensure that the complications associated with these procedures are accurately described.	Thank you for your comments. We assessed both long-term and short-term adverse events when reported within the included studies.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Good.	Thank you for your comments.
Peer Reviewer #2	Introduction	GERD treatment has two major troubles: undertreatment and inadequate treatment cause unnecessary loss in QOL, and overtreatment due to inadequate diagnostic testing cause unnecessary loss of healthcare budgets and avoidable long term side effects. Reducing both major problems is the rationale for producing reports like this. Although one of the reasons for this update is mentioned to be the revision of the diagnostic criteria for GERD in 2006, this report mainly handles treatment options. It might further improve by in depth exploration of diagnostic entities, criteria for treatment and criteria for ending treatment: this would address the problem of overtreatment more adequately. By trying to discriminate subgroups that would possibly benefit from specific treatment options a beginning is made with this exploration.	This report addressed only the treatment modalities for GERD. This has been clarified in the executive summary (Page ES-2) and the Introduction (Page 1)
Peer Reviewer #3	Introduction	Excellent	Thank you for your comments.
Peer Reviewer #4	Introduction	This section is adequate.	Thank you for your comments.
Peer Reviewer #5	Introduction	Good	Thank you for your comment
Peer Reviewer #1	Methods	Techniques are similar to those previously used and are good. Have reviewed the appropriate literature.	Thank you for your comments.
Peer Reviewer #2	Methods	Search strategies are justifiable and adequate, definitions for outcome are appropriate, statistical methods sophisticated and OK	Thank you for your comments.
Peer Reviewer #3	Methods	Yes on all counts	Thank you for your comments.
Peer Reviewer #4	Methods	Figure 1: Consider adding quality of life and work productivity as clinical endpoints.	Thank you for your comments. We have added the outcomes to the clinical endpoints.
Peer Reviewer #4	Methods	Also, on intermediate outcomes, on the analytical framework, whether there is any utility for adding esophageal impedance monitoring since it is a relatively new technique that evaluates both acid and nonacid reflux events.1,2	We recognize that importance of the variability in diagnosis of GERD. Data on esophageal impedance monitoring was extracted when available; to incorporate a discussion of the variability in diagnosis of GERD is outside the scope of this report.
Peer Reviewer #4	Methods	The search strategy, in general, is adequate. I do note that their cutoff date was week 2 of 2010, but the Medline search target was extended to July 2010 in order to examine safety issues with long term PPI use. Although the target dates included most of the studies, there are potentially some that were omitted from this review, which is understandable.	Thank you for your comments. The date of the latest update search for this report has been extended to August 2010

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	Innovations are adequate although there is no documentation for a way to address behavioral therapy for GERD in any of the studies. Outcomes of Interest are adequate. Again, whether they considered esophageal impedance monitoring as one of their outcomes is not addressed.	We agree the lifestyle and behavioral modification interventions varied across studies and are usually incompletely reported, and it is difficult to ascertain the specifics of the intervention recommended to the participants. When available, the details of the interventions were included.
Peer Reviewer #4	Methods	It is unfortunate, again, that cost effectiveness and cost benefit outcomes were not included in this review. Study designs of interest are adequate.	A cost analysis is not in the scope of this report.
Peer Reviewer #4	Methods	There are some issues concerning the use of systematic reviews in the management of extraesophageal manifestations of GERD section. The entire dataset was evaluated; however, in this subcategory (which is a very difficult category to evaluate) they only included systematic reviews in their Methods section, although in their Results section they do include randomized controlled trials. Since my expertise is focused on extraesophageal manifestations of GERD, I will address most of my comments in this section of the review. There are two issues that are problematic when utilizing existing systematic reviews for evaluation of outcomes in extraesophageal manifestations of GERD. Although this method may be more efficient, it is not adequate. In extraesophageal manifestations of GERD, such as cough, the symptom may be caused by multiple etiologies, and more than one potential etiology may be present in up to 50% of cough patients. 3 So, omitting or attempting to treat only one etiology may not impact the disease state in question. Evaluating outcomes in extraesophageal reflux manifestations is much more complex than evaluation of esophageal manifestations of GERD such as esophagitis or GERD symptoms that have validated scales or endoscopic findings. Systematic reviews do not allow careful assessment of the study population. Furthermore, the number of high quality studies utilizing appropriate study populations in randomized controlled trials are extremely limited in this field. The number of study subjects with chronic GERD reviewed systematically in PPI utilization studies number in the thousands, whereas only a few hundred subjects exist in subject populations with extraesophageal manifestations of GERD. Furthermore, the number of individual, high quality studies using appropriate study populations in a randomized controlled trial is extremely limited. Most investigators examine medical GERD therapy on the extraesophageal manifestations. For instance, PPIs-	We agree with the comment. We acknowledged the limitations of using data from systematic reviews in the Discussion (Page 152)

Commentator & Affiliation	Section	Comment	Response
		these medications decrease esophageal acid events, but reflux events still occur. Proton pump inhibitors decrease the acidity of refluxate, not the number or proximal extent of the refluxate, thus may not adequately control reflux.4 Thus, it is very difficult to assess primary outcomes in a totally different disease state such as asthma. Nonacid reflux can impact extraesophageal manifestations of GERD.5,6 To properly review effectiveness of GERD therapy in the treatment of extraesophageal manifestations, study subjects should have both disease states, and evidence that reflux impacts the other disease state.	
Peer Reviewer #4	Methods	As noted in the Methods section, they only searched in MedLine for randomized controlled trials to week three of 2009, which is unfortunate because there are significant studies that have been published since then. Also, there are inconsistencies in the Methods section concerning extraesophageal findings, for instance, in the Executive Summary, they state "systematic reviews and updates of randomized clinical trials were included." Whereas in the Methods section they state only "systematic reviews or meta-analyses were utilized," for instance, page 9, lines 12-16, and page 6, lines 6 and 10.	The date of the latest update search for this report has been extended to August 2010. We have an additional statements indicating that if an update of a qualifying systematic review was deemed necessary, we searched for primary studies published after the systematic review using the same inclusion and exclusion criteria.
Peer Reviewer #4	Methods	Cost effectiveness and analysis would have been very valuable for societies and other institutions developing clinical practice guidelines.	We agree with the comment but a cost analysis is not in the scope of this report.
Peer Reviewer #5	Methods	Excellent	Thank you for your comment
Peer Reviewer #6	Methods	Reduce passive tense in methods section, specifically Search strategy (p4)	Thank you. This has been changed to reduce the use of passive voice.
Kathleen Gans-Brangs, PhD; AstraZeneca	Methods	Methods, page 6, “In the interests of efficiency, for the review of extra-esophageal GERD, rather than relying on data from primary studies, we instead capitalized on synthesized data from existing systematic reviews. We included systematic reviews or meta-analyses that aggregated studies focusing exclusively on patients with extra-esophageal GERD symptoms (e.g., chronic cough, laryngitis or hoarseness, asthma).” Elsewhere in the document and in other 2010 AHRQ funded systematic reviews, review papers have been rejected as evidence. Use of review papers as the only source of information may introduce the bias into this report, particularly if the primary studies did not receive high level evidence ratings. Strongly urge use of primary references throughout the document consistent with AHRQ evaluation criteria.	We agree with the comment. We accept the limitations of using data from systematic reviews, and have added these limitations in the Discussion (Page 152)
Peer Reviewer #1	Results	Conclusions are well reasoned. To avoid criticism of bias (see general comment above) the authors	Thank you for your comments. We’ve added a line in the methods to indicate that p<0.05

Commentator & Affiliation	Section	Comment	Response
		should be consistent in 2 deeming a p-value of 0.06 as being significant ('.....serious adverse events was higher....' page 113) and '.....borderline significant.....' for another set of data on page 114. The convention would be to call ALL p-values >0.05 as 'not significant' or 'borderline significant'. There are other places where this handling of a p-value of >0.05 is inconsistently applied.	is considered significant and we changed the language of the results' interpretation in the body of the text accordingly.
Peer Reviewer #2	Results	Detail is adequate, characteristics of studies are clearly described, key messages explicit and applicable, no serious flaws in my opinion	Thank you for your comments.
Peer Reviewer #3	Results	I found no significant omissions. The additional analysis of extra-esophageal manifestations and endoscopic therapies was welcome.	Thank you for your comments.
Peer Reviewer #4	Results	There is no discussion of potential weaknesses of their methodology in the Methods section. Also, definitions need to be more clearly elucidated. More details on the quality of life assessment need to be made. A definition of GERD and more details concerning the quality assessments of individual studies in the categories of B and C would be helpful (page 10). On page 12, the grading of the evidence (lines 36 through 57) is very clearly written and is an outstanding section. Also in the Methods section, chronic GERD should be defined and specifics on diagnostic criteria should be provided for different methods such as GERD symptoms and esophageal pH.	We have acknowledged the limitations of using data from systematic reviews in the discussion section (Page 152). We included the assessment of quality of life (QoL) as defined in the individual publications, when it was based on a validated quality of life-instrument. To be as inclusive as possible, studies that based the diagnosis of GERD on any commonly used criteria were considered. The stringency of the diagnosis was recorded for each study.
Peer Reviewer #4	Results	Also, statistical methods were not described in the Methods section. The extraesophageal manifestations Methods section, results included 8 randomized trials and not just systematic reviews. The Methods section needs to address this. The Results section, especially in Question 1 up through extraesophageal section, the amount of detail presented is appropriate, the characteristics of the studies are concisely written and clearly describe the evidence tables, are appropriate and discuss key issues. The figures and tables are adequate. I do not have adequate expertise to know if any studies were overlooked in that area. The conclusions in Questions 1A through 1F are adequate.	Since there is no quantitative synthesis, no statistical methods were used. Our methods indicate that we searched for primary studies published after the systematic review using the same inclusion and exclusion criteria.
Peer Reviewer #4	Results	Specific Comments on Extraesophageal 1. Asthma: Asthma is a very heterogeneous disease where multiple asthma triggers elicit bronchoconstriction and alter airway inflammation. Reflux is one of many triggers that can precipitate airway responses, and control of one trigger may not significantly impact the disease state as a whole. Furthermore, both asthma and reflux are common in our population and may be present in the same individual. However, the two disease states may not interact within that individual. It is probable that reflux therapy improves asthma outcomes only in selected	Thank you for your comments. We agree that a major clinical dilemma is identifying asthmatic patients with reflux triggered asthma. Treatment of asthmatic patients with PPIs will include a treatment population of responders (participants with reflux triggered asthma) and non-responders (participants whose asthma is not reflux triggered). This will dilute the overall treatment effect. Without

Commentator & Affiliation	Section	Comment	Response
		asthmatics. Randomized, controlled trials in asthmatics with a particular asthma severity without attention to specific asthma triggers would unlikely show significant improvement with GERD treatment. In many randomized controlled trials, reflux definition includes reflux symptoms and not whether reflux is a trigger of that person's asthma. What is currently needed in this field is to identify predictors of asthma response with GERD therapy. Preliminary predictors have been identified; however, they have not been validated in confirmatory studies. There are no tests or biomarkers that correctly identify asthmatics with reflux-triggered asthma. This review of asthma includes all randomized controlled trials up to the cutoff date. Furthermore, utilizing primarily systematic reviews may not be the best way to analyze outcomes because of heterogeneous patient entrance criteria. Furthermore, as often occurs, major randomized clinical trials were omitted from this review most likely because their publication occurred after the cutoff date for researching articles. Because of the paucity of patients and randomized controlled trials evaluating asthma outcomes with PPI therapy, it may be worthwhile to reexamine the data after including two recent trials. The first trial was Kiljander, TO et al., published in the American Journal of Respiratory and Critical Care Medicine, 2010; 181:1042-8. This study included 828 moderate to severe asthmatics with reflux symptoms and utilized 24 weeks of 20 mg or 40 mg of esomeprazole or placebo, and examined a primary outcome of morning peak expiratory flow (PEF) rates. There was improvement in morning PEF rates and asthma quality of life; however, PFT improvement was minimal.7 The reason for including this study is that it added a significant number of subjects evaluated in this way. Another study verifies an important concept that the addition of PPIs may not be helpful in patients with inadequately controlled asthma who do not have reflux symptoms. This question was addressed by the American Lung Association Asthma Clinical Research Centers and published by Mastronarde et al. in the New England Journal of Medicine, 2009; 636:1487-99.8 This study examined 412 inadequately controlled asthmatics who did not have significant reflux symptoms to determine whether treatment with high dose PPI improved asthma symptoms, quality of life, and pulmonary function studies. Proton pump inhibitor therapy did not improve any of these outcomes. This study further validates a subgroup analysis of Kiljander's study published in the American Journal of Respiratory and Critical Care Medicine, 2006, pg 1091-7, showing that PPIs	any tests and biomarkers to identify reflux triggered asthma, we are underestimating the benefit from PPIs. We have added a note to this effect in the discussion (Page 152) as well as in the future research needs section (Page ES-13, Page 153). Of the two citations included in the comment, one of them (Kiljander, TO et al., published in the American Journal of Respiratory and Critical Care Medicine, 2010; 181:1042-8) was included in the update. While the second one (Mastronarde et al. in the New England Journal of Medicine, 2009; 636:1487-99.8) addressed the issue of whether PPIs are useful in patients with asthma and no reflux symptoms, it was rejected because not all of the participants had GERD and Asthma, as per out inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
		(esomeprazole) did not improve asthma outcomes in asthmatics who do not have reflux symptoms.9 This subset of 201 patients (101 on esomeprazole and 100 on placebo) further substantiates the fact that asthmatics who do not have reflux symptoms should not be treated with PPIs.	
Peer Reviewer #4	Results	Many of the studies have significant design flaws as pointed out by this manuscript. The evidence-based tables are appropriate and grade the evidence appropriately. For what is available, but keep in mind the studies examine the entire group of subjects with a disease, i.e., asthma, and not asthma patients with GERD-triggered asthma, cough, and hoarseness.	Thank you for your comment.
Peer Reviewer #4	Results	A major concern with extraesophageal manifestations of GERD is that all of these extraesophageal manifestations have multiple underlying etiologies or triggers that exacerbate the primary disease so that reflux may not be an important factor in patients with that specific extraesophageal manifestation. Thus, reflux therapy may only improve outcomes in selected patients who have reflux as a potential trigger or cause of the underlying disease state such as asthma or cough or otolaryngology findings. Reflux therapy-responsive asthma, for instance, may represent a distinct asthma phenotype, and currently we cannot identify these patients. Furthermore, in patients with chronic persistent cough (CPC), there are multiple etiologies, and all of these etiologies have to be evaluated and treated if they are present. Dr. Richard Irwin did describe a potential clinical phenotype that predicts which individuals with CPC have reflux as an etiology.10 Future randomized controlled trials could potentially examine this specific group of cough patients. This field is extremely complex and the current state of randomized controlled trials might not be the way to actually examine this group of disease states. Current medical therapy does not adequately treat nonacidic reflux that can still occur and cause both cough and airway responses. Future studies for cough should identify subjects with cough caused by GERD by ensuring that other common cough causes are excluded or treated prior to randomization examining the impact of GERD treatment on GERD-related cough. Also, careful attention as to whether GERD was adequately treated in these subjects by combined esophageal pH impedance monitoring since nonacid GERD elicits cough and PPIs do not control nonacid GER events. Many subjects do not have esophageal GERD symptoms. Poe et al.'s study goes through such a protocol, but does not include a placebo group and follows a cough cohort over time.12 In reviewing	Thank you for your comment. Your input on potential research areas has been included in the future research needs section (Page ES-14, Page 153)

Commentator & Affiliation	Section	Comment	Response
		other sections, including key Questions 2 and 3, I find that the analyses are adequate and have no specific comments. Concerning Question 3, Adverse Events, studies are ongoing and some studies have been published since the cutoff date. However, in my opinion, these studies do not change the assessment.	
Peer Reviewer #5	Results	More than sufficient detail.	Thank you for your comment
Kathleen Gans-Brangs, PhD; AstraZeneca	Results	Results, page 27 "In addition to the PPIs mentioned in the previous report, the 2010 GERD update also includes studies that examined dexrabeprazole and dexlansoprazole." Dexrabeprazole is not an approved product in the United States and as an investigational product, it should either be removed from this review or noted that the product is not approved for sale in the US. Results, page 28. The report failed to incorporate the Schmitt paper, comparing esomeprazole 40 mg and omeprazole 20 mg, a pivotal trial submitted in the NEXIUM New Drug Application. The citation is provided below. Schmitt C, Lightdale CJ, Hwang C, et al. A multicenter, randomized, double-blind, eight week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006;51:844-850. In the appendix, it was noted that the study was rejected because it lacked a >5 year follow-up. We request that it be included for the following reasons: 1- This was an 8 week healing study, not a maintenance study. As such, it was not designed as a long-term study. A > 5-year follow-up is not needed in healing studies. 2- Studies published in 2006 cannot, by definition, have >5 year follow-up in 2010. 3- Other healing studies of 8 week duration without a >5 year follow-up were included in this report. 4-This was one of the pivotal trials submitted during the approval process for NEXIUM Results, page 28.	Thank you for your comments. Drugs that are not approved by the FDA have been removed. It has been explicitly stated in the methods that only FDA approved drugs are included (Page 6). The Schmitt 2006 paper has now been included.
Kathleen Gans-Brangs, PhD; AstraZeneca	Results	"In two studies of 4 weeks and 6 months duration, dexlansoprazole 30 mg showed better heartburn control than dexlansoprazole 60 mg doses, although this effect was not statistically significant." Suggest restructuring this sentence for greater clarity. Recommend "In two studies of 4 weeks and 6 months duration, heartburn control with dexlansoprazole 30 and 60 mg doses were not statistically different." Results, page 94. "Specifically, one RCT found that the healing rate was only significantly different between PPI treatment groups in patients with grade I (less severe) esophagitis, while the other RCT found that healing rate was only significantly different between PPI treatment groups in patients with grade C (more severe) esophagitis." Different studies use different grading systems for erosive	Thank you for your comments. This has been clarified. (Page 105)

Commentator & Affiliation	Section	Comment	Response
		esophagitis making any comparison difficult in the absence of a comparative trial. Please consider providing additional context as to definition of grade I versus grade C (scales).	
Glenn A. Weiglein; Takeda Pharmaceuticals North America, Inc	Results	1. Intragastric pH - A multiple-dose crossover study examined the effect on 24-hour intragastric pH of administering 60-mg dexlansoprazole (n=20) and 30-mg lansoprazole (n=23) once daily for 5 days.1 On day 5 of administration, intragastric pH was >4 for a longer amount of time with dexlansoprazole than it was with lansoprazole - 71% for dexlansoprazole compared with 60% for lansoprazole. In addition, mean 24-hour intragastric pH was higher on day 5 with dexlansoprazole than it was with lansoprazole. 2. Healing of EE - Two multicenter, double-blind, randomized, active-controlled, 8-week trials evaluated dexlansoprazole for healing all grades of EE as classified by the Los Angeles Classification Grading System (Grades A-D).2 The 2 trials, conducted at 188 US centers and 118 non-US centers, enrolled 4092 patients with endoscopically confirmed EE, 29% of which had moderate-to-severe EE (Grade C or D). Both studies demonstrated that dexlansoprazole 60 mg provided consistently high EE healing rates at week 8 (87% and 85% respectively). In one study, the proportion of patients with healed EE at week 8 was significantly higher in the dexlansoprazole 60 mg arm than the lansoprazole 30 mg arm by a margin of 6 percentage points (p=0.004). In the other study, this outcome was higher in the dexlansoprazole 60 mg arm than the lansoprazole arm by a margin of 2 percentage points, which was not statistically significant.1,2 3. EE maintenance - A 6-month, multicenter, double-blind, randomized, placebo-controlled trial evaluated dexlansoprazole for maintenance of healed EE and symptom resolution in patients who successfully completed an EE healing study, with endoscopically confirmed healed EE.3 A total of 445 patients who met these criteria were enrolled. The analysis revealed that dexlansoprazole provided effective maintenance of healed EE. Two-thirds, or 66%, of patients treated with dexlansoprazole 30 mg remained healed over the 6-month period, as confirmed by endoscopy. This result was statistically significant versus the 14% EE remission rate attained with placebo ($P \leq .00001$). 4. Treating heartburn in symptomatic nonerosive GERD - A multicenter, double-blind, placebo controlled, randomized, 4-week study investigated dexlansoprazole for 24-hour heartburn relief in patients with symptomatic nonerosive GERD.4 The study enrolled 947 patients and randomized them to once-daily dexlansoprazole 30 or 60 mg or placebo for 4 weeks. For patients	Thank you for your comments. The studies listed are included in the report, conditional on meeting the inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
		who received dexlansoprazole 30 mg, there was a statistically significant greater percentage of heartburn-free 24-hour periods than for those who were administered placebo (55% versus 19%, *P*<.00001). When data were analyzed to determine the percentage of patients who were heartburn-free on each day of the study, a greater proportion of patients in the dexlansoprazole 30-mg group were found to have heartburn-free 24-hour periods compared with placebo. In fact, patients receiving dexlansoprazole 30 mg began to experience heartburn relief as early as the first 3 days of treatment, which persisted throughout the treatment period. 5. Antireflux surgery – The American Gastroenterological Association (AGA) medical position statement on the management of GERD outlines the appropriate indications for antireflux surgery. According to the AGA statement, patients with esophagitis who are intolerant of PPIs, patients with esophageal GERD syndrome poorly controlled by PPIs (ie, persistent troublesome regurgitation), and patients with extraesophageal GERD syndromes in whom reflux has been identified as the cause of the condition, will likely benefit from antireflux surgery.5 However, recommendations for antireflux surgery must include a thorough discussion of the potential adverse effects associated with the procedure: dysphagia, a significant increase in flatulence, an inability to belch, and increased bowel symptoms. Due to the superior safety profile of the PPI class, it is strongly recommended that PPIs are used as initial therapy.5 Furthermore; up to 30% of patients who have undergone antireflux surgery require continued therapy with a PPI approximately 5 years after the procedure. The position statement notes that there are no studies comparing the efficacy of PPIs versus antireflux surgery for stricture prevention. Also, controlled studies have not demonstrated a change in the prevalence of Barrett's esophagus or in the incidence of adenocarcinoma when comparing surgery to medical treatment. At the present time, there are no studies comparing the safety and efficacy of dexlansoprazole with antireflux surgery. 6. Nocturnal heartburn – In a 4-week, prospective, randomized, double-blind, placebo-controlled, parallel-group study, the efficacy of dexlansoprazole modified release (MR) 30 mg was evaluated for the relief of nocturnal heartburn symptoms in patients with a history of moderate-to-very severe nocturnal heartburn and GERD-related sleep disturbances.6 The study included 305 patients; dexlansoprazole MR 30 mg (n=152) and placebo (n=153). The primary efficacy endpoint, percentage of nights without heartburn	

Commentator & Affiliation	Section	Comment	Response
		over 4 weeks, assessed by daily diary, was significantly greater in patients receiving dexlansoprazole MR 30 mg daily as compared with placebo (median of 73.1% vs 35.7%, p<0.001). Patients with more severe nocturnal heartburn symptoms at baseline experienced greater therapeutic gain (mild-to-moderate symptoms [30.2%], moderate-to-severe [32.1%], and severe-to-very severe heartburn [65.6%]). For secondary efficacy endpoints, percentage of patients with relief of nocturnal heartburn and GERD-related sleep disturbances during the last 7 days of treatment, a significantly greater percentage of patients receiving dexlansoprazole MR 30 mg reported relief of heartburn symptoms and sleep disturbances as compared with placebo (47.5% vs 19.6% and 69.7% vs 47.9%, respectively; p<0.001 for both variables). Heartburn severity was significantly less in patients receiving dexlansoprazole MR 30 mg (median mean severity score of 0.48 vs 1.15, respectively; p<0.001). The percentage of nights with sleep disturbances due to GERD was significantly lower with dexlansoprazole MR compared with placebo (median of 11.1% vs 36.8%; p<0.001) and the percentage of 24-hour heartburn free days was significantly greater in patients receiving dexlansoprazole MR (median of 53.3% vs 14.3%; p<0.001). At baseline and Week 4 (Final Visit), 3 patient-reported outcome questionnaires were completed to assess sleep quality, nocturnal GERD symptom severity and its impact, and work productivity: the Pittsburgh Sleep Quality Index (PSQI), the Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ), and the Work Productivity and Activity Impairment: Special Health Problem (WPAI) questionnaire to assess sleep quality, respectively. Improvements in sleep quality at Week 4 were significantly greater with dexlansoprazole MR 30 mg compared with placebo (mean of -2.70 vs -1.35; p=0.001) as assessed by PSQI. Total scores were greater in the dexlansoprazole MR 30 mg group on the N-GSSIQ (p<0.001). Lastly, a significantly greater decrease in overall work productivity impairments was observed in the dexlansoprazole MR group.	
Glenn A. Weiglein; Takeda Pharmaceuticals North America, Inc	Results	1. Clopidogrel and Proton Pump Inhibitors a. Takeda notes that the Food and Drug Administration (FDA) has issued multiple alerts regarding the potential drug-drug interaction with clopidogrel and certain PPIs. The FDA alerts have resulted in recommendations for healthcare professionals.11 Based on the FDA alerts; AHRQ may want to consider additional investigation into these potential drug interactions. b. On October 27, 2010, the FDA issued a statement to	We did not assess drug interaction independently, unless reported in the primary studies. However, we are aware of the importance of the FDA alerts, and have included a discussion of this issue in the Executive Summary (Page ES-14) and Discussion (page 154). Among other

Commentator & Affiliation	Section	Comment	Response
		remind healthcare professionals to avoid the concomitant use of clopidogrel with certain PPIs.12 The reminder emphasized that not all PPIs have the same inhibitory effect on the cytochrome P450 2C19 enzyme which is responsible for the conversion of clopidogrel to its active form. c. Dexlansoprazole is metabolized, in part, by cytochrome P450 enzymes CYP2C19 and CYP3A4.1 In vitro studies have shown that dexlansoprazole is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, clinical drug-drug interaction studies in mainly CYP2C19 extensive and intermediate metabolizers have shown that dexlansoprazole does not affect the pharmacokinetics of diazepam, phenytoin, or theophylline. d. Takeda has completed a phase 1, randomized, open-label, 2 period, crossover study to evaluate the effect of dexlansoprazole and other PPIs on the pharmacokinetics and pharmacodynamics of clopidogrel in healthy subjects.13 The findings of the study are expected to be presented in 2011. a. On November 8, 2010, the ACCF/ACG/AHA published their updated consensus document on the concomitant use of proton pump inhibitors and thienopyridines.14 In summary, the expert consensus group made the following recommendations regarding the use of acid suppressive therapies and thienopyridines: i. Use of PPI or histamine-2 receptor antagonist (H2RA) reduces the risk of upper gastrointestinal (GI) bleedings compared with no therapy. PPIs reduce upper GI bleeding to a greater degree than do H2RAs. ii. PPIs are recommended to reduce GI bleedings among patients with a history of upper GI bleeding. PPIs are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy. iii. Routine use of either a PPI or an H2RA is not recommended for patients at lower risk of upper GI bleeding, who have much less potential to benefit from prophylactic therapy. iv. Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. The strongest evidence for an interaction is between omeprazole and clopidogrel. It is not established that changes in these surrogate endpoints translate into clinically meaningful difference in clinical outcomes. No prospective trials directly compare the clinical events of different PPIs in patients treated with clopidogrel. 2. Bone Fractures and Proton Pump Inhibitors a. May 2010, the FDA issued a consumer update regarding a possible increased risk of bone	outcomes, we only looked at endpoints that were considered to be important by the Technical Expert Panel.

Commentator & Affiliation	Section	Comment	Response
		fractures of the hip, wrist, and spine with prescription and over-the-counter (OTC) PPIs.15 According to the consumer update; the FDA has evaluated 7 published studies reporting an increased risk of bone fractures with the use of PPIs. The FDA stated that based on available data, it is not clear whether the use of PPIs is the cause of the increased risk of fractures. However, the agency is working with pharmaceutical manufacturers to further evaluate the possible risk. As a precaution, the FDA has asked manufacturers to revise the labels for all prescription and OTC PPIs. b. The following statement has been added to the product labels for dexlansoprazole and lansoprazole:1,7 Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. 3. Changes in Gastric Histology – The long-term histological safety of dose-titrated lansoprazole was evaluated in an 82-month open-label study involving 195 patients with EE.16 Gastric biopsies were obtained from the gastric body and antrum at baseline and annually to the end of the study. The biopsy specimens were collected to evaluate changes in active and chronic inflammation, intestinal metaplasia, atrophy, endocrine cell density, and to assess Helicobacter pylori (*H. pylori*) status. At final visit, 60% and 73% of patients receiving lansoprazole experienced a reduction in active inflammation of the gastric body (n=40) and antrum (n=44), respectively from baseline. Similarly, among patients with chronic inflammation of the gastric body (n=153) and antrum (n=152), 54% and 55% respectively experienced a reduction in grade from baseline. A reduction in active and chronic inflammation was observed regardless of H. *pylori* status. From baseline to final visit, overall no histologically significant changes in intestinal metaplasia, atrophy, or endocrine cell changes were observed. 4. Safety profile of dexlansoprazole modified release (MR) - The objective of the study was to assess the safety of dexlansoprazole MR from the phase 3 clinical trial program (6 randomized, double-blind, controlled studies and one randomized, open-label, 12-month, long-term study).	
Bruce Wolfe,	Results	There is no mention of the GERD treatment in morbid obese patients.	Thank you for your comments. For evaluation

Commentator & Affiliation	Section	Comment	Response
MD; Robin Blackstone, MD;Jamie Ponce, MD;John Morton, MD; American Society for Metabolic & Bariatric Surgery		Bariatric surgery should be considered in morbid obese patients as the first line treatment option for GERD and no other treatment will address the main problem of obesity which contributes to the exacerbation or persistence of the reflux. We believe that morbidly obese patients with GERD who are referred for Nissen fundoplication would benefit more from primary bariatric surgery intervention. It is well known that the primary therapies for GERD including proton pump inhibitors and Nissen fundoplication do not perform well in the obese. Furthermore; the gastric bypass procedure is known to be the best anti-reflux procedure given the small gastric pouch's inability to produce acid. Studies comparing Laparoscopic fundoplication with laparoscopic gastric bypass in the University Health Consortium database (n=27,264) show hospital complications were significantly lower in the laparoscopic gastric bypass group. The mean length of stay, observed mortality, risk-adjusted mortality and hospital costs were comparable between the two treatment groups. Other case series also demonstrate that morbid obese patients referred for surgical therapy of Gastroesophageal Reflux Disease would be more cost effectively treated with gastric bypass rather than Nissen Fundoplication. Gastric Bypass resolved GERD syndromes in most patients 6 months after the procedure. A prospective comparison of 12 morbid obese patients with GERD: 6 Nissen and 6 Gastric Bypass showed mean postoperative DeMeester scores were normal after surgery and there was no significant difference between the two groups in regard to GERD. 7 Surgically induced weight loss would be preferable to Nissen fundoplication for GERD, as it is more effective and treat many of the other comorbid consequences of severe obesity, including a markedly impaired quality of life.	of surgical treatment, we only included studies examining total (Nissen and Nissen-Rossetti) or partial (Toupet) fundoplication, either as an open or as a laparoscopic procedure, as per the input from our technical expert panel, as these techniques represent the most commonly used surgical approaches for the treatment of GERD.
Peer Reviewer #1	Discussion	Well handed.	Thank you for your comments.
Peer Reviewer #2	Discussion	Implications of the findings are clear enough, limitations adequately described. No major literature missing. Future research should refer to my comments above (in introduction) and I can imagine that follow-up on side effects can best be researched in routine healthcare databases.	Thank you for your comments. We recognize that importance of the variability in diagnosis of GERD but to incorporate a discussion of this issue is outside the scope of this report. A note on this has been incorporated into Remaining Issues and Future Research Needs section. (Page ES-13 and Page 153).
Peer Reviewer #3	Discussion	The data on drug therapy are rather clear cut pertaining to esophagitis and heartburn. Less so with respect to refractory esophageal and extraesophageal symptoms thought to be GERD related. These would be a more important focus for future work. What	Thank you for your input. These have been added to the Remaining Issues and Future Research Needs section. (Page ES-13 and Page 153)..

Commentator & Affiliation	Section	Comment	Response
		about twice daily PPI therapy (about 30% of prescriptions)?	
Peer Reviewer #4	Discussion	The major findings are correctly expressed in this section with brief reviews of the major questions asked, and concisely updated major clinical findings since the topic was previously reviewed in 2005. Concerning weaknesses and limitations, it adequately discusses those that they found in analyzing the randomized controlled trials. A meta-analysis, however, medical therapy of GERD remains less than optimal since all medication available control acid and not the individual acid events themselves. Currently the only prokinetic agent available has significant systemic side effects, limiting its use. There is a great need to develop medications that actually inhibit transient LES relaxations in an effective way that have a safe side effect profile. It is difficult to ascertain the role of behavioral therapy for reflux. Maybe that should be a future question to analyze the role of behavioral therapy on reflux. Future research needs may also include careful evaluation of potential predictors of response in the extraesophageal manifestations of GERD that would allow future development of randomized controlled trials to analyze outcomes with reflux therapy. Otherwise, the future research section is clear and could be potentially translated into new research areas. The usability of this report is structured and outlined as listed in the Table of Contents; main points are clearly presented. The evidence tables are outstanding and clear	Thank you for your comment. Your input on potential research areas has been included in the future research needs section (Page ES-14, Page 153)
Peer Reviewer #5	Discussion	Yes, very well done.	Thank you for your comment
Glenn A. Weiglein; Takeda Pharmaceuticals North America, Inc	Discussion	1. Geriatric patients (>65 years) were included in Takeda's clinical study program of dexlansoprazole, comprising 11% of patients in the trials.1 No overall differences were seen in the safety or effectiveness of dexlansoprazole in young or geriatric patients. Other clinical trial experience has not identified significant differences in responses between geriatric and younger patients. 2. Pediatric patients - Lansoprazole is FDA approved for use in pediatric patients age 1-11 years for the short-term treatment of symptomatic GERD and short-term treatment of erosive esophagitis.7 Dosing is based on weight. Children weighing ≤30 kg are recommended to receive lansoprazole 15 mg once a day and for children >30 kg lansoprazole 30 mg once a day for up to 12 weeks. Lansoprazole is also approved for use in adolescents age 12-17 years for the short-term treatment of symptomatic GERD. For this age group, dosing recommendations are as follows: non-erosive GERD 15 mg once a day and for erosive esophagitis 30 mg once a day for up to 8 weeks. The safety of	Thank you for your comments. The studies listed are included in the report, conditional on meeting the inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
		lansoprazole capsules was evaluated in 66 pediatric patients aged 1 to 11 years. Of the 66 patients with GERD, 85% (56/66) received lansoprazole for 8 weeks and 15% (10/66) for 12 weeks. The most frequently reported (2 or more patients) treatment-related adverse reactions (N=66) were constipation (5%) and headache (3%). The safety of lansoprazole capsules was also assessed in 87 adolescents 12-17 years of age. Of the 87 patients with GERD, 6% (5/87) took lansoprazole for less than 6 weeks, 93% (81/87) for 6 to 10 weeks, and 1% (1/87) for greater than 10 weeks. The most frequently reported (at least 3%) treatment-related adverse reactions in adolescent patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). 3. Pediatric patients - Dexlansoprazole is not FDA approved for use in patients less than 18 years of age.1A phase 1, randomized, open-label, multicenter study to evaluate the pharmacokinetics and safety of dexlansoprazole in adolescents 12-17 years of age with symptomatic GERD has been completed.8 A second phase 1 study to evaluate the pharmacokinetics and safety of dexlansoprazole in pediatric patients 1-11 years old with symptomatic GERD is currently recruiting.	
Peer Reviewer #2	Conclusion	The conclusions are OK, but with reference to what is mentioned above and in the perspective of primary care a discussion of improving diagnostics to get the proper indication for treatment should be added.	Thank you for your comments. We recognize that importance of the variability in diagnosis of GERD but to incorporate a discussion of this issue is outside the scope of this report. A note on this has been incorporated into Remaining Issues and Future Research Needs section. (Page ES-13 and Page 153)
Peer Reviewer #4	Conclusion	Conclusions made can inform policy and practice decisions, but this does not apply to the Extraesophageal section.	Thank you for your comment.
Peer Reviewer #4	References	The references are clearly outlined.	Thank you for your comment.
Peer Reviewer #1	General	As with the 2005 report I again felt that the authors have been more critical of the value of surgical reports than of medical reports.	We do our utmost to look at the data from a perspective of evidentiary strength. We used standard criteria to judge quality of studies and the strength of evidence. It is not our intent to be critical of a particular field of management. That said, the report has been revisited to make sure our analysis is objective.
Peer Reviewer #1	General	Entire report is too lengthy for general use. However the synopsis and conclusions would be useful to disseminate if fleshed out with appropriate specific references.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	This is a clinically very meaningful report on treatment aspects of GERD. Adding comparisons with OTC dosages, adding comparisons with other dosage regimes, adding comparisons between surgical and endoscopic interventions and adding comparisons on side effects of treatment are very valuable. The report passes by another major problem in GERD, which is to define the most adequate methods and timing in an episode of typical symptoms to accept the diagnosis GERD in individual patients. This is not resolved with the 2006 criteria. The report might improve by discussing this a bit more elaborate.	Thank you for your comments. We recognize that importance of the variability in diagnosis of GERD but to incorporate a discussion of this issue is outside the scope of this report. A note on this has been incorporated into the Remaining Issues and Future Research Needs section. (Page ES-13 and Page 153).
Peer Reviewer #3	General	This is a thorough review of clinical evidence pertaining to GERD therapies. The key questions are explicit and good.	Thank you for your comments.
Peer Reviewer #3	General	The structure is good and major points clear. I don't see any major implications in terms of policy or practice.	Thank you for your comments.
Peer Reviewer #4	General	This review is very helpful and clinically important. The target population is stated. Key answers are appropriate. What is missing is a cost analysis which would be very helpful for different medical, surgical and endoscopic therapies for gastroesophageal reflux disease (GERD). This is especially important with comparison between proton pump inhibitors (PPIs), their dosing, whether PPIs are available in generic or over the counter (OTC) formulations , whether the increased cost of PPI medications that are not available OTC or in generic form are worth their extra cost in model analysis. The review was very helpful in that it examines comparative effects of different PPIs, medical versus surgical versus endoscopic therapies for GERD. Of note, it only addresses adult GERD, so the title should be changed to "Comparative Effectiveness of Management Strategies for Adults with Gastroesophageal Reflux Disease," since this review does not evaluate GERD therapy in children.	Thank you for your comments. While we recognize that a cost analysis is needed to inform decision making, it is not in the scope of this report. However, the data included in this report provides the parameters for a subsequent cost effectiveness analysis. We agree that the title should include "…Adults with GERD…". However, due to restrictions on the number of words that are allowed in the title, we were unable to include it. We do, however, make that it explicit that only adult populations were considered in the abstract, executive summary and the main body of the report.
Peer Reviewer #5	General	Excellent	Thank you for your comment
Kathleen Gans-Brangs, PhD; AstraZeneca	General	General Comments: The attached information is supplied in response to an open public comment period. These materials may include information that is not found in the currently approved prescribing information for NEXIUM® (esomeprazole magnesium) delayed-release capsules. The enclosed information is intended to provide pertinent data as part of the public comment opportunity and should in no way be construed as a recommendation for the use of these products in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for NEXIUM. Prescribing information for NEXIUM may be obtained	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
		from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.	
Glenn A. Weiglein; Takeda Pharmaceuticals North America, Inc	General	We respectfully request that AHRQ correct the dosing of Dexilant (dexlansoprazole) in the report. The FDA approved dosing for dexlansoprazole is 30 mg or 60 mg once daily. Several places in the draft report, 10 mg is mistakenly referenced as the dose for dexlansoprazole. We would also ask AHRQ to consider excluding products from the report that are not approved by the FDA (ie, dexrabeprazole sodium).	Thank you for your comments. The 10 mg referred to dexrabeprazole, and the typographical error has been corrected. Drugs that are not approved by the FDA have been removed. It has been explicitly stated in the methods that only FDA approved drugs are included (Page 6).