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Metoclopramide for the Treatment of Gastroesophageal Reflux Disease in Infants: A Systematic Review

Anna Maria Hibbs, MD, Scott A. Lorch, MD, MSCE

Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVES. Metoclopramide is a commonly used drug to treat gastroesophageal reflux disease in infants. Given its widespread use and growing concern about toxicity in this population, we conducted a systematic review of metoclopramide for the treatment of gastroesophageal reflux disease in infants.

METHODS. We performed a systematic search of PubMed and bibliographies of relevant review articles. We included cohort, case-control, and intervention studies of the efficacy, effectiveness, or toxicity of metoclopramide therapy for gastroesophageal reflux disease in infants. We excluded case reports, case series, review articles, and abstracts.

RESULTS. Twelve articles met our inclusion criteria. Of these, 11 were prospective trials, and 5 were randomized, blinded clinical trials. Study size ranged from 6 to 77 patients. Eight studies showed patient improvement with metoclopramide in at least 1 measured outcome; 1 study showed worsening symptoms with metoclopramide. Of the 5 randomized, blinded trials, 2 showed no effect of metoclopramide on any outcome, and 2 showed a significant placebo effect. Four studies commented on adverse effects of therapy, with irritability being the most frequently reported potential adverse effect of therapy. Other reported adverse effects included dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnea. Among studies, there was marked heterogeneity in the patient populations, dosing, and outcomes studied. Therefore, a meta-analysis was not performed. We both agreed on a US Preventive Service Task Force rating of "poor" for the level of evidence, leading to an "inconclusive" recommendation for the safety and efficacy of metoclopramide in infants.

CONCLUSIONS. The current literature is insufficient to either support or oppose the use of metoclopramide for gastroesophageal reflux disease in infants. In the future, large blinded randomized clinical trials are needed to determine the efficacy and toxicity of metoclopramide in this population.

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Key Words

systematic reviews, metoclopramide, infant, gastroesophageal reflux

Abbreviations

GER—gastroesophageal reflux
GERD—gastroesophageal reflux disease
RCT—randomized, controlled trial
USPSTF—US Preventive Services Task Force

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Address correspondence to Anna Maria Hibbs, MD, Rainbow Babies & Children's Hospital, Division of Neonatology, 11100 Euclid Ave, Cleveland, OH 44106. E-mail: annamariahibbs@hotmail.com

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BOTH BENIGN AND pathologic gastroesophageal reflux disease (GERD) are extremely common in infancy. In a survey of outpatient pediatric practices, two thirds of 4-month-olds regurgitated at least daily.¹ The incidence of GERD is higher in certain medically complicated subpopulations such as premature and neurologically impaired infants and those with congenital malformations. For example, estimates of the incidence of GERD in premature infants range from 40% to 85%.^{2,3} These fragile populations, however, may be at the highest risk from adverse effects of the therapy for GERD. Furthermore, although the North American Society of Pediatric Gastroenterology and Nutrition treatment guidelines emphasize the difference between gastroesophageal reflux (GER) and GERD⁴ (in which there are complications of GER), the complications of GER remain ill-defined in certain high-risk subgroups such as premature infants.⁵⁻⁹

Metoclopramide has been used to treat GERD in infants for several decades.¹⁰⁻¹⁸ However, the recent impetus toward evidence-based prescribing in pediatric populations and reports of adverse drug reactions have spurred public discussion about the efficacy and safety profile of metoclopramide in infants and children.¹⁹⁻²²

In many practices, metoclopramide has become the standard of care without a rigorous approval process. Although the prevalence of metoclopramide use in infants across inpatient and outpatient settings is ill-defined, it is clear that it is commonly prescribed for infants and children. In the United States, >7 million prescriptions for metoclopramide were dispensed in 2004. In the same year, >30% of the annual outpatient visits in which metoclopramide was mentioned were in the pediatric population (aged 0-16 years).²³ The practice patterns in the prescription of metoclopramide for GERD also vary widely. For instance, in a survey of 57 NICUs in England and Wales, 53% reported using dopamine antagonists such as metoclopramide to treat GERD in premature infants, whereas 47% did not.⁶

Therefore, we conducted a systematic review of the literature of metoclopramide for GERD in infants aged 0 to 23 months as a complement to the Cochrane systematic review²⁴ of GERD therapies in children, which found both therapeutic benefit and increased adverse effects with metoclopramide treatment. Although the Cochrane review only included randomized trials and evaluated multiple therapies for GERD, we narrowed the scope of the research, focusing only on metoclopramide therapy for GERD, and broadened our search, accepting a broader variety of study designs in our inclusion criteria.²⁴ This decision was spurred both by the paucity of randomized, controlled trials (RCTs) in infants and a desire to capture any additional reliable and valid evidence presented by cohort and case-control studies.

METHODS

We performed a PubMed search using the search terms "Reglan neonate," "Reglan infant," "metoclopramide neonate," "metoclopramide infant," "gastroesophageal reflux medication," and "gastroesophageal reflux treatment." The search limits included English language, humans, age group "birth to 23 months," and publication dates 1980 to August 2005. Of the review articles identified by this search, the bibliographies of those from 1995-2005 with full-text available on-line were searched for additional articles that were missed by the PubMed search described above. Review articles were used only to screen for articles meeting the inclusion criteria for the study that were not identified by the PubMed search; reviews were not included in the analysis of the data.

We included only published articles in the systematic review. Study designs that met inclusion criteria were cohort studies, case-control studies, and controlled trials. We considered controls to be either a separate group of randomly assigned or nonrandomly assigned patients not receiving metoclopramide or individual patients acting as their own controls. Both blinded and nonblinded studies were included in the review. Abstracts, case reports, case series, and review articles were excluded from this analysis.

Outcomes included in the systematic review were limited to the efficacy, effectiveness, or toxicity of metoclopramide for reflux in infants. We defined efficacy as the therapeutic effect of the drug in a clinical trial and effectiveness as the benefit of the drug outside of a controlled research setting. We defined a toxicity of drug treatment as any unintended adverse consequence of the drug's use, such as dystonic reactions and irritability. Given the difficulty of quantifying GERD in a clinically and physiologically meaningful way, we accepted studies with outcomes that included clinical symptoms, pH-probe results, gastrointestinal motility, growth, or tolerance of feeding. In trials with treatment arms that included pharmacologic interventions other than metoclopramide, such as cisapride or bethanachol, we only considered the analyses comparing metoclopramide to nonintervention or placebo therapy.

We graded the level of evidence according to the scale for strength of overall evidence used by the US Preventive Services Task Force (USPSTF).²⁵ The quality and homogeneity of studies were assessed for suitability in a meta-analysis.

RESULTS

The PubMed search yielded 1284 articles. A search of 9 review article bibliographies^{4,9,24,26-31} yielded 1 additional article.¹⁴ By our consensus, 12 articles met the inclusion criteria.^{10-18,32-34} Of these, 11 were intervention trials,^{10-18,32,34} and 1 was a cohort study.³³

The study sizes ranged from 6 to 77 patients, with the

largest intervention trial consisting of 42 patients.¹⁰ Only 1 study reported a power calculation.³² No studies reported any summary statistics of effect size, such as odds ratio, relative risk, or risk difference. Five of the 12 studies were blinded and randomized, and these trials studied between 10 and 39 infants^{11,12,18,32,34} (see Table 1). Six studies did not report a funding source,^{14–17,33,34} 5 received at least partial funding from a manufacturer of metoclopramide,^{10–13,32} and the remaining trial received only the drug and placebo from a manufacturer.¹⁸

The studies were marked by heterogeneity of patient populations, metoclopramide dosing, and outcomes measured (see Table 1 for details). Preterm infants, infants older than 1 year, postoperative patients, and infants with congenital anomalies were included in many studies. Most of the studies did not specify the treatment history of their populations; those that reported a treatment history^{16,18,32–34} included infants with and without a history of failed medical therapy. Furthermore, not all studies on inpatients and premature infants stated whether the infants were receiving exclusively enteral feeds. Metoclopramide dosing ranged from 0.1 to 1 mg/kg per dose. Three studies tested response to 1 dose of metoclopramide, whereas the remaining studies examined steady-state therapy. Outcomes reported consisted of various pH-probe parameters, gastric emptying, regurgitation, weight gain, feeding tolerance, and apnea.

Results According to Type of Outcome

Four studies assessed symptoms and signs of GERD. One blinded RCT showed no difference in symptom scores,¹⁸ 1 cohort study showed no difference in apnea in premature infants,³³ and 2 nonblinded trials showed efficacy in either the number of regurgitation episodes¹⁴ or feeding tolerance in premature infants.¹⁷

Two randomized studies from the same investigator group examined gastric emptying as measured by gastric fractional emptying rate and gastric fluid output. Metoclopramide was shown to improve gastric emptying in these blinded studies.^{11,12}

Seven studies used pH-probe results as outcomes, including the percent of time that the esophageal pH was <4, the number of reflux episodes lasting >5 minutes, and the duration of the longest episode. Three nonblinded trials showed efficacy in at least 1 measured pH-probe parameter and in at least 1 studied subgroup.^{10,13,16} One nonblinded study showed no improvement in any pH-probe parameter, with an increased number of reflux episodes with metoclopramide.¹⁵ Two blinded RCTs showed no difference between metoclopramide and placebo in any pH-probe measurement,^{32,34} whereas 1 blinded study showed a small improvement in the percent time esophageal pH was <4 with metoclopramide.¹⁸

Results of Blinded RCTs

Only 5 blinded randomized trials were identified by our search.^{11,12,18,32,34} In 1985, Hyman et al¹¹ showed an improvement in the gastric fractional emptying rate in 10 infants during a metoclopramide period compared with a placebo period. In 1988, Hyman et al¹² found a similar improvement in gastric fractional emptying rate in term and postoperative infants but not in premature infants. Tolia et al¹⁸ found no difference in the symptom scores or scintigraphy of 30 infants assessed during metoclopramide and placebo periods. In addition, these infants showed significant improvement during their placebo period compared with their baseline scores. A subgroup analysis of infants >3 months of age suggested improved weight gain during the metoclopramide period when compared with their placebo period. Tolia et al also reported pH-monitoring results; they found a significant improvement in the percent time that esophageal pH was <4 but not in the other pH parameters studied. Two randomized trials used pH-probe monitoring as their primary outcomes.^{32,34} Pons et al³⁴ found no improvement in pH measurements between a metoclopramide and placebo group; because of a significant placebo effect, both the metoclopramide and placebo groups had significant improvements in several pH-probe measurements compared with their baseline studies. Bellissant et al³² also found no difference in any pH-probe parameters in separate groups of infants treated with either placebo or metoclopramide. This was the only study that reported a power calculation.

Toxicity

None of the studies that met our inclusion criteria used toxicity as a primary end point. Furthermore, the methods for surveillance of unintended effects of treatment were not described in any of the studies. Adverse effects were reported in 4 of the 12 studies.^{10,14,15,32} The events reported included dystonic reactions, oculogyric crisis, irritability, drowsiness, emesis, and apnea.

Leung and Lai¹⁴ reported 5 adverse events among the 32 infants in the metoclopramide group in their nonblinded trial. Two infants experienced increased drowsiness, 2 demonstrated increased irritability, and 1 infant had an acute oculogyric crisis after an accidental fourfold overdose. The intended dosing in this study was 0.125 mg/kg per dose every 6 hours.

Hyams et al¹⁰ reported 4 adverse events during treatment with metoclopramide among their population of 42 infants who served as their own controls in a nonblinded trial: 3 infants in this study experienced increased irritability on metoclopramide, and 1 had dystonia. The irritability started 15 minutes after drug injection, lasted for ~2 hours, and occurred in 1 infant in each of the 3 dosing groups (0.1, 0.2, and 0.3 mg/kg per dose). A dystonic reaction occurred in 1 of the 21 infants in the 0.3 mg/kg per dose group.

TABLE 1 Summary of Studies Meeting Inclusion Criteria

Study	N	MCP Dose	Population	Design	Outcomes: Significant Effect	Outcomes: No Effect Seen	Adverse Events
Sankaran et al ¹⁷ (1982)	6	0.1 mg/kg per d ÷ TID	Preterm infants; GA 26–35 wk; postnatal age 25–70 d; history: feeding intolerance	Clinical trial; not randomized; not blinded; infant as own control; before and after MCP; feeding tolerance and intestinal transit studied	Gastric aspirate (mL/d); weight gain (g/d); intestinal transit time (h); feed volume (mL/kg per d)	None reported	None reported
Leung and Lai ¹⁴ (1984)	41	0.5 mg/kg per d ÷ QID	Age 21–1215 d (mean: 160); weight 2.73–17.2 kg (mean: 6.35); history: regurgitation, FTT, and/or apnea; several infants with prematurity; cardiac, gastrointestinal, and neurologic anomalies included	Clinical trial; randomized (9 in control group, 32 in treatment group); not blinded; symptoms recorded	Frequency of regurgitation	None reported	2 drowsiness; 2 irritability; 1 oculogyric crisis
Hyman et al ¹¹ (1985)	10	1 mg/kg, single dose	Age 3–16 mo (mean: 6); weight 2.2–9.4 kg (mean: 5.6); history: recurrent vomiting, postoperative ileus, gastroparesis of prematurity, or intestinal pseudo-obstruction; 2 patients on parenteral nutrition; GA not reported	Clinical trial; randomized; blinded; each patient was randomly assigned to receive placebo, MCP, or bethanachol on 3 consecutive study days; gastric emptying measured	Gastric fractional emptying rate (%/min); gastric fluid output (mL/min)	Gastric acid secretion	None reported
Hyams et al ¹⁰ (1986)	42	0.1 mg/kg per dose (n = 10), 0.2 mg/kg per dose (n = 11), or 0.3 mg/kg per dose (n = 21) every 4 h × 3 doses	Age 0.5–13 mo (mean: 3.2); history: vomiting, FTT, apnea, wheezing; GA not reported	Clinical trial; not randomized; not blinded; infant as own control; before MCP; pH-probe study	0–2 h post–dextrose meal in 0.3 mg/kg per dose group; % time esophageal pH <4 and mean acid clearance time (min/episode)	All pH-probe results at 0.1 and 0.2 mg/kg per dose; at 0.3 mg/kg; all pH-probe parameters postformula and 2–4 h post–glucose meal	3 irritability; 1 dystonic reaction
Rode et al ¹⁶ (1987)	18	0.2 mg/kg per dose every 6 h	Mean age 6.5 mo (SD: ±4.02); mean weight 5.9 kg (SD: ±2.2); history: did not respond to medical therapy or admitted for complications of GER; GA not reported	Clinical trial; not randomized; not blinded; infant as own control; before MCP; pH-probe study	No. of reflux events; % time pH <4; No. of refluxes >5 min	Longest reflux (min); esophageal clearance time (min); ambient pH of lower esophagus	None Reported
Machida et al ¹⁵ (1988)	28	0.125 mg/kg per dose QID	Mean 9 mo old (SD: ±11 mo); history: regurgitation, apnea, FTT; GA not reported	Clinical trial; not randomized; not blinded; infant as own control; before MCP; pH-probe study	No. reflux events in 24 h (more frequent with Reglan)	% time pH <4; No. of episodes >5 min; longest episode	3 irritability
Hyman et al ¹² (1988)	22	1 mg/kg, single dose	Age ≤12 mo; weight 1.5–8.0 kg; history: postoperative (n = 6), regurgitation (n = 9), prematurity (n = 7; GA 28–36)	Clinical trial; randomized; blinded; infant as own control; gastric-emptying study	Term infant groups: gastric fractional emptying rate (%/min)	Premature infant group: gastric fractional emptying rate (%/min) (slower reported)	None reported
Kearns et al ¹³ (1988)	6	0.15 mg/kg per dose every 6 h	Age 1–5.5 mo; history: referred for GERD	Clinical trial; not randomized; not blinded; infant as own control; pH probe pre-MCP, after first dose, and after tenth dose	Tenth dose vs baseline: No. of reflux events >5 min; longest episode pH <4 (min)	First dose vs baseline: all parameters; emptying with Reglan but no P value reported	None reported
Toila et al ¹⁸ (1989)	30	0.1 mg/kg per dose QID	Age 1–9 mo (median: 2); term; no underlying medical conditions; GER diagnosed by pH probe	Clinical trial; randomized; blinded; infant as own control; baseline, placebo, and MCP periods; pH probe; scintigraphy, symptom score	% time pH <4 (placebo effect: symptom scores on placebo were significantly improved from baseline)	Symptom score; daily weight change; gastric emptying; No. of episodes pH <4; No. of episodes >5 min	None reported
Pons et al ¹⁴ (1993)	24	0.1, 0.2, or 0.4 mg/kg per dose, underlying medical conditions excluded	Age 1–18 mo; history: GER diagnosed by pH study; underlying medical conditions excluded	Clinical trial; randomized; blinded; infant randomly assigned to receive placebo or MCP after baseline measurement; pH-probe study	None (placebo effect: several pH-probe parameters improved from baseline in the placebo group)	All pH-probe parameters	None reported
Bellissant et al ¹² (1997)	39	0.2 mg/kg per dose TID	Mean age 105 d (SD: ±74); mean weight 5.6 kg (SD: ±1.9); history: GER diagnosed by pH study; underlying medical conditions excluded	Clinical trial; randomized; blinded; infant randomly assigned to receive placebo or MCP after baseline measurement; pH-probe study	None	All pH-probe parameters; weight	1 apnea; 1 emesis; 1 irritability
Kimball and Carlton ¹³ (2001)	77 ^a	Mean dose: 0.4 mg/kg per d	Premature GA 23–36 wk (mean: 30); birth weight 630–3000g (mean: 1390); treated in NICUs	Retrospective cohort; chart review; infant own control; apnea frequency before and after treatment with cisapride or MCP	None (Control analysis of methylxanthine treatment showed significantly decreased apnea)	Apnea frequency	Not reported

MCP indicates metoclopramide; TID, 3 times per day; QID, 4 times per day; GA, gestational age; FTT, failure to thrive. In studies of metoclopramide and another drug, only results comparing metoclopramide to a nondrug control are reported. ^aThe number of infants receiving metoclopramide was not specified.

In 28 infants serving as their own nonblinded controls, Machida et al¹⁵ found an increase in the number of reflux episodes when the patients were treated with metoclopramide, from a mean of 41 (SD: 29.7) during the placebo period versus a mean of 54 (SD: 44.9) episodes per 24 hours during the metoclopramide period. Three infants were so irritable after their metoclopramide infusions that manometry could not be repeated. The authors then attempted to perform a small double-blinded placebo-controlled trial in which parents kept weekly records documenting the frequency and amount of emesis. Fifteen families refused to participate in this study because of worsening of symptoms or irritability during the drug phase of the original trial. Of the 8 patients who participated, 5 received placebo and 3 received metoclopramide. All 3 of the infants who participated in the metoclopramide arm dropped out of the study because of increased irritability and vomiting. No families who participated in the placebo arm stopped therapy. Dosing in both the pH-probe and outpatient phases of this study was 0.125 mg/kg per dose every 6 hours.

Summary Statistics

Because of the heterogeneity of the studied patient populations, the variable dosing, and the different outcome measures used in the 12 studies, both reviewers deemed a meta-analysis inappropriate. Thus, no pooled estimates of effect or risk of therapy are reported. Similarly, combined estimates of dose response were not considered appropriate in light of the wide variability in patient populations and outcome measures in the literature. This heterogeneity, the mixture of study designs, and the nature of the outcomes made a funnel plot to assess for publication bias infeasible.

Level of Evidence

We graded the level of evidence according to the scale for strength of overall evidence used by the USPSTF.²⁵ We both classified the quality of the literature as “poor” on the basis of the limited number of studies, small sample sizes, quality of study designs, and lack of consistency of the literature. This corresponds to a recommendation grade of “I,” meaning that the level of evidence for both benefit and harm was insufficient to recommend for or against routine use of metoclopramide (see Appendices 1 and 2).

DISCUSSION

Despite the long history of use of metoclopramide in infants, only 12 articles met our inclusion criteria for this systematic review. The literature is marked by small study sizes, a paucity of randomized and blinded studies, and heterogeneity of patient characteristics, dosing, and outcome measures. Therefore, the available evidence substantiates neither clinically significant benefit nor

harm from metoclopramide in the treatment of GERD in infants. However, these studies highlight both the clinical questions and the potential methodologic issues that remain to be addressed by future studies.

In this systematic review we reached a different conclusion than that of the Cochrane review of therapies for GERD in infants, which stated that, “Overall, there is evidence that suggests that metoclopramide will reduce the clinical symptoms and reflux index when compared with placebo in infants with GERD.”²⁴ Our methodology differed from the Cochrane study in several key ways. Our study focused only on the evidence for this pharmacologic therapy for GERD. We accepted a wider range of study designs than the Cochrane review, including case-control, cohort, and RCTs. Unlike the Cochrane review, we limited our criteria to full-length published articles and did not include abstracts in our search. We both felt that quality and heterogeneity of the studies made combining studies in a meta-analysis for an overall estimate of effect inappropriate. These concerns about the body of literature, as well as the small sample sizes of the published studies, led to our rating the quality of evidence “poor”; therefore, our recommendation is “inconclusive” (see Appendices 1 and 2).

The heterogeneity of the patient populations in the 12 identified studies raises important biological questions about the effect and toxicity of metoclopramide. It is likely that different populations, such as preterm, neurologically impaired, or postoperative patients, may have different efficacy and toxicity profiles than otherwise healthy term infants. In addition, given that the natural history of GERD in the majority of infants is improvement and resolution over time, particular attention must be given to the age of patients and the duration of the studies. However, there are no data to determine the effect of metoclopramide on these different patient populations.

The heterogeneity of the types of end points reported in the literature highlights the difficulty in choosing meaningful and reliable outcome measures for GERD therapy in infants. Inconsistent measurement strategies and case definitions of pathologic reflux and adverse events have been applied in these 12 studies. For instance, small reported changes in pH-probe parameters may or may not correlate with clinically meaningful changes in patient status. This issue is particularly relevant, because no studies in our systematic review reported a normalization of pH-probe results with the use of metoclopramide. Similar concerns exist with changes in the rate of gastric emptying. Although clinical symptoms would seem to be the ideal outcome of interest, the measurement and quantification of reflux symptoms are fraught with difficulties. For example, simple quantification of emesis frequency or amount seems appealing at first glance. However, many pediatricians consider emesis resulting from reflux in an otherwise healthy

child to be benign GER and not GERD.⁴ Irritability may be meaningful to parents and doctors, but because this qualitative outcome is also a reported adverse effect of metoclopramide itself, blinding and the development of validated measurement scales would be of utmost importance. In premature infants, a subpopulation frequently treated with metoclopramide, the task of separating benign from pathologic reflux and identifying which symptoms are caused by reflux is particularly difficult. For instance, although GERD is often implicated by clinicians and researchers in the pathogenesis of apnea, this connection has been challenged in the literature.⁵⁻⁹ Similarly, feeding intolerance in premature infants is likely multifactorial, making the relative contribution of GERD difficult to ascertain. Failure to thrive because of reflux may be one of the most concrete potential study outcomes, but it is rare and also likely to coincide with, and be confounded by, other disease states. Finally, there is a paucity of data on the impact of metoclopramide on the respiratory manifestations of GERD, such as wheezing and aspiration risk. This lack of a well-defined clinical end point for studies of GERD makes the evaluation of therapy difficult.

The Cochrane review concluded that there were increased adverse effects with metoclopramide therapy.²⁴ However, given the small study sizes, the frequency of nonblinded designs, the lack of systematic criteria to define or identify adverse outcomes, and the heterogeneity of both the patient populations and metoclopramide dosing in all 12 studies, we could make no firm conclusions about the incidence of adverse events, the patient populations most at risk, or the doses at which adverse effects are most likely to occur. No studies that met the inclusion criteria for our systematic review addressed potential adverse effects on long-term developmental outcome.

No studies reported measures of effect sizes, such as relative risk or risk difference, and only 1 study reported a power calculation.³² The absence of estimates of effect size, either from the individual articles or a meta-analysis, makes it difficult to assess the clinical significance of any statistically significant results.

Furthermore, because all the studies published were relatively small, it is possible that the negative studies in the literature were underpowered to detect an effect.

The results of our systematic review are limited by the availability of studies in the public domain and, specifically, on PubMed. Because of the heterogeneity of studies and the types of outcomes reported, we were unable to formally assess for publication bias, although it does seem likely that many small negative studies remain unpublished.

There remains a lack of definitive evidence regarding either the efficacy or the toxicity of metoclopramide for the treatment of GERD in infants. Under such conditions, clinicians cannot adequately assess the risk-benefit

profile of the drug when treating infants with GERD. Additional work is needed to clarify the subpopulations most likely to be harmed or benefited by metoclopramide therapy, the optimal dosing for these subgroups, and the most valid and clinically significant outcome measures in these populations. Ultimately, a large randomized placebo-controlled clinical trial of metoclopramide will be necessary. Until such a study is completed, clinicians can only continue to judiciously treat and monitor the infants with GERD under their care.

APPENDIX 1 USPSTF Standard Recommendation Language²⁵

Recommendation	USPSTF Language
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.)
C	The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.)
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)

APPENDIX 2 US Preventive Service Task Force Recommendations Grid Based on Levels of Evidence²⁵

Quality of Evidence	Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

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Anna Maria Hibbs and Scott A. Lorch

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