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[Intervention Review]

Drug therapies for reducing gastric acidity in people with cystic fibrosis

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ABSTRACT

Background

Malabsorption of fat and protein contributes to poor nutritional status in people with cystic fibrosis. Impaired pancreatic function may also result in increased gastric acidity, leading in turn to heartburn, peptic ulcers and the impairment of oral pancreatic enzyme replacement therapy. The administration of gastric acid-reducing agents has been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and gastro-intestinal symptoms in people with cystic fibrosis. It is important to establish the evidence regarding potential benefits of drugs that reduce gastric acidity in people with cystic fibrosis. This is an update of a previously published review.

Objectives

To assess the effect of drug therapies for reducing gastric acidity for: nutritional status; symptoms associated with increased gastric acidity; fat absorption; lung function; quality of life and survival; and to determine if any adverse effects are associated with their use.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises references identified from comprehensive electronic and non-electronic database searches, handsearches of relevant journals, abstract books and conference proceedings. Both authors double checked the reference lists of the searches

Most recent search of the Group's Trials Register: 26 April 2021.

On the 26 April 2021 further searches were conducted on the clinicaltrials.gov register to identify any ongoing trials that may be of relevance. The WHO ICTRP database was last searched in 2020 and is not currently available for searching due to the Covid-19 pandemic.

Selection criteria

All randomised and quasi-randomised trials involving agents that reduce gastric acidity compared to placebo or a comparator treatment.

Data collection and analysis

Both authors independently selected trials, assessed trial quality and extracted data.

Main results

The searches identified 40 trials; 17 of these, with 273 participants, were suitable for inclusion, but the number of trials assessing each of the different agents was small. Seven trials were limited to children and four trials enrolled only adults. Meta-analysis was not performed, 14 trials were of a cross-over design and we did not have the appropriate information to conduct comprehensive meta-analyses. All the trials were run in single centres and duration ranged from five days to six months. The included trials were generally not reported adequately enough to allow judgements on risk of bias.

However, one trial found that drug therapies that reduce gastric acidity improved gastro-intestinal symptoms such as abdominal pain; seven trials reported significant improvement in measures of fat malabsorption; and two trials reported no significant improvement in nutritional status. Only one trial reported measures of respiratory function and one trial reported an adverse effect with prostaglandin E2 analogue misoprostol. No trials have been identified assessing the effectiveness of these agents in improving quality of life, the complications of increased gastric acidity, or survival.

Authors' conclusions

Trials have shown limited evidence that agents that reduce gastric acidity are associated with improvement in gastro-intestinal symptoms and fat absorption. Currently, there is insufficient evidence to indicate whether there is an improvement in nutritional status, lung function, quality of life, or survival. Furthermore, due to the unclear risks of bias in the included trials, we are unable to make firm conclusions based on the evidence reported therein. We therefore recommend that large, multicentre, randomised controlled clinical trials are undertaken to evaluate these interventions.

PLAIN LANGUAGE SUMMARY

Drugs for reducing stomach acid for people with cystic fibrosis

Review question

We reviewed the evidence for using drugs to reduce stomach acid in people with cystic fibrosis.

Background

Cystic fibrosis causes damage to the lungs and the pancreas. The pancreas produces enzymes which are needed for the body to digest and absorb food. If the pancreas is damaged this can affect how people can absorb food. It can also increase acidity in the stomach, which may lead to heartburn and peptic ulcers. There are drugs that can reduce the amount of acid in the stomach. Trials of these drugs have shown that they can improve problems in the stomach and digestive system and in the absorption of fat. This is an updated version of the review.

Search date

The evidence is current to: 26 April 2021.

Study characteristics

The review included at 17 trials with a total of 273 children and adults. Seven of the trials were limited to children and four trials enrolled only adults, while the remainder enrolled people of any age. All the trials were run in single centres and lasted from five days to six months.

Most trials compared an intervention to placebo (a dummy treatment with no active medication). Six trials compared proton pump inhibitors (drugs which reduce the amount of acid made in the stomach, e.g. omeprazole and esomeprazole) to placebo and seven trials compared a H2 receptor antagonist (a second group of medicines that reduce the amount of acid made in the stomach, e.g. ranitidine and cimetidine) to placebo. One of the trials had three arms and compared a proton pump inhibitor to both a H2 receptor agonist and a placebo. In the remaining five trials, one compared pancrelipase (a combination of three enzymes (lipase, protease, and amylase) normally produced by the pancreas) to a combination of pancrelipase and misoprostol (a drug which protects the lining of the gut from stomach acid); one compared misoprostol to placebo and one trial compared enprostil (similar drug to misoprostol) to ranitidine. Two trials used sodium bicarbonate - one compared to placebo and the second compared to calcium carbonate.

Key results

We were not able to combine the results from these trials due to their design. Individual trials reported some improvements in abdominal pain and fat absorption. However, the trials did not report improvements for other outcomes such as lung function, quality of life, or survival. The different drugs studied caused some adverse events; mainly diarrhoea (two people withdrew from one trial because of this) and bloating due to wind. As we could not combine the results from these trials, we were not able to reach firm conclusions about whether people with cystic fibrosis would benefit from taking these drugs. New long-term trials are needed to examine the benefits and possible adverse effects for people with cystic fibrosis taking drugs to reduce stomach acid.

Quality of the evidence

There were 14 trials which had a cross-over design (where people taking part are given first one treatment and then another treatment) and we did not have the appropriate information to analyse the results properly. Few of the included trials reported clearly on aspects of trial quality or gave enough information to allow us to judge whether any factors might cause a potential risk of bias to the results.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is an autosomal recessive inherited disease that is most common in Caucasian populations having an estimated incidence of 1 in 2500 live births (CF Foundation 1994). It affects the epithelial chloride channels. Defects cause reduced epithelial salt and water secretion, leading to viscous mucus in various organs such as the lungs and pancreas. As a result, exocrine pancreatic insufficiency occurs in the majority of people with CF causing maldigestion of fat and protein. Malabsorption of fat and protein lead to considerable energy losses in the stools and can contribute to poor nutritional status in people with CF (Murphy 1991). Malnutrition affects growth, increases the severity of pulmonary disease, and ultimately plays an important role in the shortening of lifespan in people with CF (Kraemer 1978). Furthermore, nutritional status is also related to lung function and exercise performance in people with CF (Neijens 1985).

Absorption in the small intestine may also be affected by reduced bicarbonate secretion in the small bowel and pancreas, contributing to a lower duodenal pH (Weber 1984). This may impair and irreversibly inactivate pancreatic enzymes, which in turn may lead to increased gastric acidity resulting in heartburn, epigastric pain and gastric or duodenal ulcers.

Description of the intervention

Oral pancreatic enzyme therapy to improve the nutritional status and decrease maldigestion due to pancreatic insufficiency in people with CF has been available for several decades. Despite adequate pancreatic replacement therapy, many people with CF continue to excrete large amounts of fat and protein in their stools, which may contribute to malnutrition and weight loss.

How the intervention might work

Orally administered pancreatic enzymes may be inactivated by gastric acid in people with CF with pancreatic insufficiency leading to fat and protein malabsorption (Zentler-Munro 1985). The decrease in pancreatic bicarbonate secretion associated with CF impairs the release of enteric-coated pancreatic enzymes and reduces their effectiveness (Regan 1979). Studies have suggested that drug therapy which reduces gastric acid may improve the effectiveness of pancreatic replacement therapy (DiMagno 2001). Agents to reduce gastric acidity should provide a duodenal environment more conducive to efficient enzyme function. In adults with pancreatic dysfunction secondary to chronic pancreatitis, H2 receptor antagonists or proton pumps that reduce gastric acidity improved fat malabsorption (Bruno 1994). Proton pump inhibitors and H2 receptor antagonists do this directly by inhibiting acid production from parietal cells. Synthetic prostaglandins can also be used to reduce gastric acid secretion and stimulate bicarbonate secretion from the small bowel.

Why it is important to do this review

Improvements in fat absorption and overall nutrition are important in the treatment of people with CF. The major goals in the treatment of people with CF are to improve the quality of life, achieve normal growth, improve respiratory status and increase life expectancy. It is therefore important to establish whether adjunct drug therapy to reduce gastric acidity in people with CF who are being treated with pancreatic enzymes is beneficial.

This version of the review is an update of previous versions (Ng 2003; Ng 2012; Ng 2014).

OBJECTIVES

To test the hypotheses that in people with CF, agents that reduce gastric acidity:

1. improve nutritional status, as assessed by weight, height and other indices of growth;
2. improve symptoms associated with increased gastric acidity such as heartburn and epigastric pain;
3. improve lung function, quality of life and survival;
4. do not have unacceptable adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-randomised controlled trials (published and unpublished).

Types of participants

Children and adults with defined CF, diagnosed clinically and by sweat or gene testing including all ages and all degrees of severity.

Types of interventions

Agents that reduce gastric acidity compared to placebo or a comparator treatment. The major drug groups are:

1. proton pump inhibitors;
2. H2 receptor antagonists.

Other drug therapies such as prostaglandin E2 analogues and sodium bicarbonate which reduce gastric acidity will also be considered. All doses and routes of administration will be considered.

Types of outcome measures

We assessed the following outcome measures.

Primary outcomes

1. Measures of nutritional status as assessed by weight, height and other indices of growth
2. Symptoms related to increased gastric acidity such as epigastric pain, heartburn
3. Complications of increased gastric acidity such as gastric or duodenal ulcers

Secondary outcomes

1. Faecal fat, faecal nitrogen excretion and other measures of fat malabsorption
2. Measures of lung function
3. Measures of quality of life
4. Mortality
5. Any adverse effects reported

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language (we did not exclude studies reported in a language other than English), year or publication status.

Electronic searches

We identified relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the term: antacids.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group website.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 26 April 2021.

We searched the ongoing trails databases clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (Appendix 1).

Searching other resources

The authors also searched the reference lists of the originally included trials to identify if there were any missed trials from non-electronic databases and journal abstracts

Data collection and analysis

Selection of studies

Two authors independently selected the trials to be included in the review. Disagreement did not arise on the suitability of any trials for inclusion in the review or their quality. However, if this should occur during future updates of this review, we will reach consensus by discussion.

Data extraction and management

The authors independently extracted data using standard data acquisition forms. Again, disagreement did not arise between the authors. We will resolve any future disagreements on any extracted data by discussion.

All drugs which reduce gastric acidity were regarded as the intervention to be compared to the placebo and not split into individual drug comparisons.

We planned to group outcome data into those measured at 1, 3, 6 and 12 months and annually thereafter. However, we were unable to group data into the time points we had originally planned and so report results narratively from the end of each trial. The duration of each trial is detailed in the table 'Characteristics of included studies'. For future updates of this review, if outcome data are recorded at other time periods, then consideration will be given to examining these as well.

Assessment of risk of bias in included studies

In order to establish a risk of bias for each included study, each author assessed the methodological quality of each trial using criteria suggested by Jüni (Jüni 2001). In particular, authors examined details of the generation of allocation sequence, the concealment of treatment allocation schedule, whether the trial was blinded, whether intention-to-treat analyses were possible from available data and if the number lost to follow up or subsequently excluded from the trial was recorded. In future updates of the review, we will resolve any disagreements that occur by discussion.

Measures of treatment effect

For future updates of the review, if appropriate data are available, the authors will use the following methods to analyse binary and continuous outcome measures. For binary outcome measures, the authors plan to calculate a pooled estimate of the treatment effect for each outcome across the studies, (the odds of an outcome among treatment allocated participants to corresponding odds among controls). For continuous outcomes, the authors will record either a mean change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD) for each group. They will calculate a pooled estimate of treatment effect by calculating the mean difference where appropriate.

Unit of analysis issues

Ideally, when conducting a meta-analysis combining results from cross-over trials, the authors would have liked to use the methods that are recommended by Elbourne and Curtin (Curtin 2002; Elbourne 2002). However, due to restrictions on the data that were available from the papers the only method that the authors were able to use was to treat the cross-over trials as if they were parallel trials. When trials did not report data in such a way that a correct analysis could be performed, the results were described narratively within the text rather than combine the results using inappropriate techniques. The primary authors of the cross-over trials have been approached for further individual patient data and order of treatment, but no data have yet been made available.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors will seek data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

Due to the lack of trials it was not possible to investigate heterogeneity between trial results using the standard Chi^2 test and I^2 statistic (Higgins 2003). For future updates of the review we will test for heterogeneity using the Chi^2 test and I^2 statistic. We will consider the ranges of I^2 to relate to the degree of heterogeneity as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;

- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We examined the publications for potential reporting biases but were not able to compare the original trial protocols with the final publications. We were therefore unable to identify any potential reporting biases.

Data synthesis

Where between trial variability is not statistically significant we will carry out a fixed effect analysis and if the between trial heterogeneity is statistically significant we will perform a random effects analysis.

Subgroup analysis and investigation of heterogeneity

If there is significant heterogeneity between the trials, the authors plan to perform a subgroup analysis investigating different classes of drugs.

Sensitivity analysis

The authors also plan to perform a sensitivity analysis based on methodological quality of the trials including and excluding quasi-randomised trials, when it is appropriate to do so.

RESULTS

Description of studies

Please refer to the tables for additional information (Characteristics of included studies; Characteristics of excluded studies).

Results of the search

A total of 40 trials were identified from the searches; 17 trials were included and 22 trials were excluded; one trial is still ongoing.

Included studies

There was a large variation between the trials identified in terms of design, intervention, duration of treatment and outcome measures. We included 17 trials in this review. All of the included trials were published, but four of them were published only as abstracts in conference proceedings (Bowler 1993; Chung 2000; Lubin 1979; Weber 1981).

Trial design

Fourteen trials were cross-over in design (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Chung 2000; Durie 1980; Francisco 2002; Heijerman 1990; Heijerman 1991; Heijerman 1993; Proesmans 2003; Robinson 1988; Robinson 1990; Weber 1981). Three trials were of a parallel design (Lubin 1979; Schoni 1984; DiMango 2014).

Trial duration ranged from 12 days (three days in each of the four treatment arms in this cross-over trial) (Francisco 2002) to one year (again in cross-over trials with treatment periods of six months in each arm) (Carroccio 1992; Chalmers 1985); duration was not stated in one trial (Lubin 1979).

Participants

The included trials reported results from a total of 273 participants. Sample size varied from five (Chung 2000) to 38 participants (Schoni 1984), with participants' ages ranging from six months (Robinson 1990) to 42 years (Heijerman 1993). Seven trials were limited to children (Bowler 1993; Chung 2000; Lubin 1979; Robinson 1988; Robinson 1990; Schoni 1984; Weber 1981); and three trials enrolled only adults (Heijerman 1990; Heijerman 1991; Heijerman 1993).

In one trial participants were grouped according to acetylation phenotype (slow or fast) and matched according to their age before the trial (Schoni 1984).

Interventions

Most trials compared an intervention to placebo.

Six trials compared proton pump inhibitors with placebo (Chung 2000; DiMango 2014; Francisco 2002; Heijerman 1991; Heijerman 1993; Proesmans 2003). Participants in two trials were randomised to receive either omeprazole or placebo; but in the Francisco trial this was only the case for the adult participants (Chung 2000; Francisco 2002). In a third trial, participants received either esomeprazole 40 mg or placebo twice daily (DiMango 2014). In the later Heijerman trial, participants were given either pancrealipase plus omeprazole or pancrealipase and placebo (Heijerman 1993). In a further trial, one group of participants received omeprazole and the other treatment group received no omeprazole (Proesmans 2003). In a cross-over trial consisting of four comparative treatment periods participants received: firstly a high dose of pancreatic enzyme, pancrelipase (Pancrease®) (four capsules, three times daily) in conjunction with a proton pump inhibitor, omeprazole; secondly, high-dose pancrelipase in conjunction with placebo; thirdly, low-dose pancrelipase (two capsules, three times daily) in conjunction with omeprazole; and fourthly, low-dose pancrelipase in conjunction with placebo (Heijerman 1991).

Seven trials compared a H2 receptor antagonist with placebo (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Durie 1980; Francisco 2002; Schoni 1984). In one trial, participants received one of three treatments in a randomly-assigned sequence: high-dose pancreatic enzyme (Creon®) with the H2 receptor antagonist, ranitidine; high-dose pancreatic enzyme with placebo; or lower-dose pancreatic enzyme with placebo (Bowler 1993). In another trial, participants received pancreatic enzyme alone (Viokase®) or pancreatic enzyme (Viokase®) and the H2 receptor antagonist, cimetidine (Boyle 1980). Carroccio investigated famotidine or placebo given in addition to normal enzyme therapy (Carroccio 1992). In the Chalmers trial, participants received either cimetidine or placebo in addition to normal enzyme therapy (Chalmers 1985). The trial by Durie contained four treatment groups, who received each treatment in a random order; the four interventions that were used were: pancrelipase; sodium bicarbonate; cimetidine; and a combination of sodium bicarbonate and cimetidine (Durie 1980). As part of a trial, already mentioned in the previous paragraph, participants who were pancreatic insufficient were randomised to receive high-dose or low-dose ranitidine compared with placebo in a cross-over trial (Francisco 2002). In the trial by Schoni, the effectiveness of cimetidine compared to placebo was evaluated (Schoni 1984).

One trial compared the normal dose pancrelipase and prostaglandin E2 analogue misoprostol (100 µg every six hours) with the normal dose pancrease alone (Robinson 1988), a further trial compared the prostaglandin E2 analogue misoprostol with

placebo (Robinson 1990). One trial compared sodium bicarbonate with placebo (Weber 1981).

A further trial compared two active treatment arms, the H2 receptor antagonist (ranitidine) with prostaglandin E2 analogue (enprostil) (Heijerman 1990). One trial compared sodium bicarbonate with calcium carbonate (Lubin 1979).

Outcomes

Data for measuring fat malabsorption were presented in different ways such as percentage fat malabsorption (three-day fat excretion/three times mean daily fat intake), faecal fat excretion (percentage daily fat intake), percentage fat absorption, faecal weight (g/24 h), and faecal fat (g/24 h). One trial used a gastro-intestinal symptom score which incorporated a subjective measure for the frequency and severity of symptoms (Heijerman 1990). Gastro-intestinal complaints were each scored: none = 0; little = 1; moderate = 2; severe = 3; and very severe = 4. These scores were then combined to give an overall complaints score which was analysed as a continuous variable. Another trial relied on participants reporting relief from chronic abdominal pain (Robinson 1988).

Excluded studies

In total, 22 trials were excluded for a variety of reasons. Six trials were not RCTs (Cameron 1982; Cox 1981; Dudley 1981; Lloyd-Still 1992; Miller 1985; Miller 1986); seven trials examined agents which are not used to reduce gastric acidity (Ansaldi-Balocco 1988; Geus 1999; Hoffman 1987; Kerr 1982; Mitchell 1981; Stead 1988; Tsang 1994); five trials compared cisapride (a pro-kinetic agent) with a drug for reducing gastric acidity (Cucchiara 1996; Koletzo 1989; Prinsen 1985; Santamaria 1989; Smith 1988); one trial compared the accuracy of fat balance trials at home versus at a clinic (Francisco 1996); one trial contained four treatment periods, three of which were not relevant to the review, so no comparison could be made (Gow 1981); one trial compared the pharmacokinetics of oral versus intravenous famotidine (Maish 1998); and one trial assessed lipase, bile acid and trypsin concentration (Zentler-Munro 1985).

Ongoing studies

One cross-over RCT is ongoing and due to be completed in April 2021 (NCT03551691). Investigators aim to randomise 24 participants aged 12 years or over (either sex) with CF and pancreatic insufficiency (fecal elastase < 200 ug/g stool). Participants will be allocated to receive either 40 mg omeprazole daily for 28 days or an identically-appearing placebo capsule daily for 28 days. The primary outcome is the coefficient of fat absorption; secondary outcomes are the change in duodenal pH as measured by the SmartPill at 28 days and fat absorption via malabsorption blood test (measurement of serum pentadecanoic acid and heptadecanoic acid).

Risk of bias in included studies

In order to assess the risk of bias in the included trials, the authors assessed the methodological quality of the included trials using criteria suggested by Jüni for the following dimensions: concealment of allocation; generation of the randomisation sequence; intention-to-treat; and level of blinding reported (Jüni 2001). The dimensions, concealment of allocation, generation of the randomisation sequence and intention-to-treat were categorised as adequate, unclear or inadequate which related to a low, unclear or high risk of bias respectively; RCTs were categorised according to whether double blinding had been reported or not. There is a decreasing risk of bias to the results when more people are blinded to an intervention.

Allocation

All trials stated that allocation was randomised, but no trials described the method of randomisation used. We therefore judged the risk of bias due to the generation of the randomisation sequence as unclear in all trials.

Concealment of allocation was adequate in only one trial in which the randomisation procedure was carried out at the pharmacy in the hospital (Robinson 1990). The trial organisers were unaware of this sequence until the completion of the trial. We judged this trial to have a low risk of bias. However, concealment of allocation, and also the risk of bias, was unclear in the remaining 16 trials (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Chung 2000; DiMango 2014; Durie 1980; Francisco 2002; Heijerman 1990; Heijerman 1991; Heijerman 1993; Lubin 1979; Proesmans 2003; Robinson 1988; Schoni 1984; Weber 1981).

Blinding

Double-blinding was reported in 13 of the 17 included trials; however, two trials did not report blinding of investigators (Boyle 1980; Lubin 1979). In one trial, Robinson reported that parents of 5 out of 15 children in the treatment group were able to correctly identify the period in which misoprostol was administered by improvements in symptoms such as abdominal pain and offensive bulky bowel motions (Robinson 1990). In two trials the level of blinding was not discussed (DiMango 2014; Durie 1980) and a further trial was not blinded (Proesmans 2003).

We considered the risk of bias from blinding to decrease if more people were blinded to the intervention and the risk of bias to be unclear if this aspect of trial quality was not discussed.

Incomplete outcome data

No trials explicitly stated that an intention-to-treat analysis was performed. Neither did any trial state that any participants deviated from the randomised group to which they were assigned. In six trials there were no participant withdrawals reported, but it was not explicitly stated that no participants withdrew (DiMango 2014; Heijerman 1991; Heijerman 1993; Lubin 1979; Schoni 1984; Weber 1981). Therefore we judged the risk of bias to be unclear in these four trials. The remaining 11 included trials experienced participant withdrawals (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Chung 2000; Durie 1980; Francisco 2002; Heijerman 1990; Proesmans 2003; Robinson 1988; Robinson 1990). In 10 trials there were a low number of participant withdrawals and these were described, but in the remaining trial there was a discrepancy between the number of participants entering and completing the trial which was not addressed (Bowler 1993). We judged the risk of bias to be low in the 10 trials which accounted for participant withdrawals, but high in the trial which did not give any reason for the missing data from one participant.

Selective reporting

We were unable to identify any selective reporting in the included trials, but did not have any access to the original trial protocols

to definitely confirm this; we therefore conclude that there is an unclear risk of bias due to selective reporting.

Other potential sources of bias

Durie states that the participants were selected from a restricted geographical area in proximity to the hospital on the basis of an assessment by clinical personnel of their ability to perform a clinical study accurately at home (Durie 1980). This may present a potential risk of bias due to pre-selection of participants by clinic personnel.

Effects of interventions

We were unable to group data into the time points we had originally planned and so report results narratively from the end of each trial. The duration of each trial is detailed in the table Characteristics of included studies.

Drugs for reducing gastric acidity versus placebo

Primary outcomes

1. Measures of nutritional status

Data on growth indices and nutritional status were available from two trials comparing an H2 receptor antagonist with a placebo (Chalmers 1985; Schoni 1984). We were unable to pool data from the trial by Chalmers because there were insufficient data to calculate the SD (Chalmers 1985). Both trials reported that there were no significant improvements in height, weight and skinfold thickness between the treatment and the control group (Chalmers 1985; Schoni 1984). Body mass index and z scores for weight and height were not reported in either trial.

2. Measures of gastro-intestinal symptoms

These measures were recorded in nine trials (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Heijerman 1991; Heijerman 1993; Robinson 1988; Robinson 1990; Weber 1981), but not reported in eight of the trials.

In the 1988 trial, Robinson looked at relief from chronic abdominal pain in the treatment group compared with the control group (Robinson 1988). There were six participants who reported relief in the treatment group and none in the control group. The symptoms returned in five of the six participants after misoprostol was stopped at the end of the trial period.

3. Complications of increased gastric acidity such as gastric or duodenal ulcers

These outcomes were either not reported or the data were not available in any of the trial reports.

Secondary outcomes

1. Measures of fat malabsorption

In the 1993 trial, Heijerman reported the results for faecal fat excretion and found that there was no statistically significant difference between the treatment and control groups (Heijerman 1993). However, previously in his 1991 trial, Heijerman found significantly lower faecal fat excretion (percentage of daily fat intake) ($P < 0.01$) when omeprazole was combined with higher dose pancrelipase enzymes (four capsules, three times daily) (Heijerman 1991). Improvement in faecal fat excretion when omeprazole was added to lower dose pancrelipase (two capsules, three times daily) occurred in seven of the nine adults studied, but was not significant for the whole group. Proesmans reported that the effect of omeprazole on daily faecal fat loss (g/day) was statistically significant ($P < 0.01$) (Proesmans 2003).

The 1988 Robinson trial found a significant reduction of fat malabsorption in the treatment group ($P < 0.02$), only the P value was available from this trial (Robinson 1988). The later Robinson trial reported that there was a significant reduction in fat malabsorption while taking misoprostol ($P < 0.01$) with no change in daily fat intake (Robinson 1990).

Boyle showed that cimetidine significantly reduced the mean stool weight ($P < 0.005$) (Boyle 1980). Carroccio also showed that famotidine significantly reduced faecal weight ($P < 0.0001$) (Carroccio 1992). Weber showed no significant difference between sodium bicarbonate and placebo (Weber 1981).

No significant improvement was found for faecal fat (g/day) between treatment and placebo groups in the Weber trial (Weber 1981). Chalmers reported a significant reduction in faecal fat in the treatment group ($P < 0.05$), but no statistical difference was found for mean faecal wet weight (g/day) (Chalmers 1985). A trial by Bowler showed no significant difference in faecal fat or faecal weight when comparing both high lipase enzyme and with the addition of ranitidine to control (Bowler 1993). A trial by Boyle comparing cimetidine with placebo reported a significant difference in faecal fat (g/day) ($P < 0.05$) (Boyle 1980). A trial by Francisco reported no significant difference in fat absorption between high-dose or low-dose ranitidine compared with placebo groups in children or between omeprazole and placebo groups in the adult participants (Francisco 2002). Chung also reported no significant difference in malabsorption between high-dose omeprazole or placebo groups (Chung 2000).

Boyle reported a significant improvement in fat absorption in the treatment group compared with the placebo group ($P < 0.05$) (Boyle 1980).

Durie calculated faecal fat and nitrogen as g/24 h and percentage of intake (Durie 1980). Cimetidine and sodium bicarbonate, both individually and in combination with each other, significantly improved fat and nitrogen excretion. However, the results from the combination of cimetidine and sodium bicarbonate were no better than those from cimetidine and sodium bicarbonate individually. Durie suggested that this meant that response to the single drug regimens were maximal (Durie 1980).

2. Measures of lung function

Data for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow rate ($FEF_{25-75\%}$) were not available in any of the trials.

Both the Chalmers and the DiMango trials reported objective measures of lung function narratively (Chalmers 1985; DiMango 2014). Chalmers found no significant difference in mean change in peak flow or Crispin-Norman score after six months of treatment (Chalmers 1985) and the DiMango abstract reported that neither the esomeprazole group or the placebo group demonstrated a significant change in FEV_1 after 24 weeks (DiMango 2014). One trial measured lung function (Schoni 1984) and another trial measured Crispin-Norman scores (Carroccio 1992), but no data were reported.

3. Measures of quality of life

Only the Di Mango abstract, mentioned quality of life and reported that neither the esomeprazole group or the placebo group demonstrated a significant change in CFQ-R (DiMango 2014).

4. Mortality

These outcomes were either not reported or the data were not available in any of the trial reports.

5. Adverse effects

The trial by Robinson reported diarrhoea as an adverse effect experienced by participants on the prostaglandin E2 analogue, misoprostol (Robinson 1990). Two participants had to be withdrawn from the trial because of diarrhoea that did not subside after five days.

Durie reported that two participants complained of gaseous abdominal distension while taking sodium bicarbonate and one participant was forced to withdraw from the trial because of possible neurological complications due to cimetidine (Durie 1980).

DiMango reported that participants receiving esomeprazole experienced a shorter time to first exacerbation compared with placebo, but the difference was not statistically significant. Further, five of eight participants receiving esomeprazole compared with two of six participants receiving placebo developed a pulmonary exacerbation during the six-month follow up (P = 0.11) (DiMango 2014).

H2 receptor antagonist ranitidine versus prostaglandin E2 analogue enprostil

Primary outcomes

1. Measures of nutritional status

These outcomes were either not reported or the data were not available in the trial report (Heijerman 1990).

2. Measures of gastro-intestinal symptoms

The included trial reported a gastro-intestinal complaints score measured at 14 days comparing H2 receptor antagonist ranitidine with prostaglandin E2 analogue enprostil (Heijerman 1990). In the original paper, participants receiving the H2 receptor antagonist ranitidine were reported to have significantly less gastro-intestinal complaints compared with participants receiving prostaglandin E2 analogue enprostil (P < 0.05).

3. Complications of increased gastric acidity such as gastric or duodenal ulcers

These outcomes were either not reported or the data were not available in the trial report (Heijerman 1990).

Secondary outcomes

1. Measures of fat malabsorption

The included trial found no significant difference in mean percentage faecal fat excretion (Heijerman 1990).

2. Measures of lung function

These outcomes were either not reported or the data were not available in the trial report (Heijerman 1990).

3. Measures of quality of life

These outcomes were either not reported or the data were not available in the trial report (Heijerman 1990).

4. Mortality

These outcomes were either not reported or the data were not available in the trial report (Heijerman 1990).

5. Adverse effects

The included trial reported diarrhoea and abdominal discomfort as adverse effects in participants on the prostaglandin E2 analogue, enprostil treatment (Heijerman 1990). One person in the enprostil group withdrew during the treatment period because of these effects.

Sodium bicarbonate versus calcium carbonate

Only one trial compared sodium bicarbonate to calcium carbonate (Lubin 1979). This trial only reported on one outcome of interest to this review.

Secondary outcomes

1. Measures of fat malabsorption

Data were not reported in a way that allowed us to enter them into the meta-analysis. The abstract reported no significant difference in the percentage of fat absorbed and presented means and SDs for percentage of fat absorption with and without antacids (mean (SD) 65 (22)% and 66 (22)% respectively) (Lubin 1979).

DISCUSSION

Agents that reduce gastric acidity have been increasingly used as an adjunct to pancreatic enzymes in an attempt to improve nutritional status and gastro-intestinal symptoms in people with CF. The effectiveness of long-term treatment is therefore of major clinical relevance.

Summary of main results

This review found 17 RCTs which examined the effects of drug therapies to reduce gastric acidity in people with CF. All the trials were single-centre trials and the duration of treatment was variable, ranging from five days to six months.

Drugs for reducing gastric acidity versus placebo

A total of 15 trials (253 participants) are included in this comparison. Six trials compared proton pump inhibitors with placebo (Chung 2000; DiMango 2014; Francisco 2002; Heijerman 1991; Heijerman 1993; Proesmans 2003), seven trials compared a H2 receptor antagonist with placebo (Bowler 1993; Boyle 1980; Carroccio 1992; Chalmers 1985; Durie 1980; Francisco 2002; Schoni 1984), one trial compared sodium bicarbonate with placebo (Weber 1981), one trial compared the normal dose pancrelipase and prostaglandin E2 analogue misoprostol with the normal dose pancrease alone (Robinson 1988) and a further trial compared misoprostol with placebo (Robinson 1990).

Only two trials comparing a H2 receptor agonist with placebo reported on our primary outcome of nutritional status and found no significant differences in changes in height, weight and skinfold thickness between groups (Chalmers 1985; Schoni 1984). Nine trials recorded measures of gastro-intestinal symptoms, but only

one trial comparing pancrelipase plus misoprostol to pancrelipase alone reported results; this trial found six participants from the combination group reported relief in the treatment group compared to none in the control group, the symptoms returned in five of the six participants after misoprostol was stopped (Robinson 1988). In terms of fat malabsorption, six trials found no difference in fecal fat excretion between groups (Bowler 1993; Chalmers 1985; Chung 2000; Francisco 2002; Heijerman 1993; Weber 1981), but three trials found treatment improved fecal fat excretion (Boyle 1980; Durie 1980; Heijerman 1991; Proesmans 2003).

With regards to our secondary outcomes, one trial found that pancrelipase plus misoprostol reduced fat malabsorption compared to pancrelipase alone (Robinson 1988); and the later trial by the same investigator found misoprostol alone reduced fat malabsorption compared to placebo (Robinson 1990). While there was no difference in fecal fat excretion, Boyle reported that cimetidine reduced mean stool weight more than placebo (Boyle 1980); a further trial also reported that famotidine reduced faecal weight ($P < 0.0001$) (Carroccio 1992). Limited data were available for lung function measures, four trials measured lung function but only two reported narrative results and found no difference between treatment and control groups (Chalmers 1985; DiMango 2014). Only one trial measured quality of life and found no difference between groups (DiMango 2014). Three trials reported on adverse effects (DiMango 2014; Durie 1980; Robinson 1990). In one trial (n = 21), investigators reported that while there was no difference in the treatment group in the time to first exacerbation compared with placebo, five of eight participants receiving esomeprazole compared with two of six participants receiving placebo developed a pulmonary exacerbation during the six-month follow-up (DiMango 2014). A second trial (n = 21) reported that two participants complained of gaseous abdominal distension while taking sodium bicarbonate and one participant was forced to withdraw from the trial because of possible neurological complications due to cimetidine (Durie 1980). The third trial (n = 17) reported that two participants taking misoprostol withdrew due to diarrhoea that did not subside after five days (Robinson 1990).

No trial reported on complications of increased gastric acidity or mortality.

H2 receptor antagonist ranitidine versus prostaglandin E2 analogue enprostil

One trial (eight adult participants) compared the H2 receptor antagonist (ranitidine) with prostaglandin E2 analogue (enprostil) (Heijerman 1990). This trial reported participants receiving ranitidine had fewer gastro-intestinal complaints compared with those receiving enprostil at 14 days. Investigators reported diarrhoea and abdominal discomfort as adverse effects in participants on enprostil treatment and one participant withdrew because of these effects (Heijerman 1990).

The trial did not report on measures of nutritional status, complications of increased gastric acidity, measures of fat malabsorption, lung function or mortality.

Sodium bicarbonate versus calcium carbonate

One trial compared sodium bicarbonate with calcium carbonate in 12 children with CF and found no difference in the percentage of fat absorbed (Lubin 1979). None of the review's other outcomes were assessed in this trial.

Overall completeness and applicability of evidence

There were limitations to the review. The number of trials assessing different agents for reducing gastric acidity was small. The trials included both children and adults with a total of 273 children and adults. Seven of the trials were limited to children and four trials enrolled only adults. A total of 14 trials were of a cross-over design and we did not have the appropriate information to conduct comprehensive meta-analyses, but trial authors have been contacted for further information in order that a more complete analysis can be carried out. Available data were limited, therefore, we were unable to make firm conclusions based on the evidence that was reported in these trials.

Quality of the evidence

All trials stated that allocation was randomised, but no trials described the method of randomisation used. We therefore judged the risk of bias due to the generation of the randomisation sequence as unclear in all trials. Concealment of allocation was adequate in only one trial and we judged this trial to have a low risk of bias. Concealment of allocation, and also the risk of bias, was unclear in the remaining 16 trials. The domains which would allow us to assess the quality of the trials included within this review were generally not reported adequately. The evidence remains limited as few of the included trials reported clearly on aspects of trial quality or gave enough information to allow us to judge whether any factors might cause a potential risk of bias to the results.

Potential biases in the review process

We have undertaken comprehensive searching and it is unlikely that we have not identified any relevant trials for this review. Neither author has any potential conflict of interest to declare.

Agreements and disagreements with other studies or reviews

Since the last review published on this topic, comparisons to previous published systematic reviews remain unavailable. There is no NICE guidance available for this topic specifically for people with CF, there are only NICE guidelines outlining principles of management of gastro-oesophageal reflux in general children and young people (NICE 2019).

AUTHORS' CONCLUSIONS

Implications for practice

There is very limited evidence to suggest that agents that reduce gastric acidity in people with cystic fibrosis (CF) may be associated with improvement in gastro-intestinal symptoms and fat absorption; but due to the unclear risks of bias of the included trials, we are not able to draw firm conclusions from the evidence available. At present, there is insufficient evidence from randomised controlled trials to indicate whether there is an improvement in nutritional status, lung function, quality of life, or survival in people with CF treated with agents that reduce gastric acidity.

Implications for research

This systematic review has identified the need for well-designed, adequately-powered, multicentred randomised controlled trials to assess the effects and possible adverse events associated with the use of agents that reduce gastric acidity in people with CF. Trials should be carried out over a longer duration to provide further information on long-term effects of lung function, quality of life measures to assess acceptability of treatment to people with CF and survival. If clear benefit is demonstrated, there will be a need for trials comparing different gastric reducing agents and assessing long-term outcomes. We would urge trialists to recognise that the results of individual randomised controlled trials are likely to be included in systematic reviews such as this. They should therefore consider standardising the presentation of outcomes to enable the data to be aggregated.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bowler 1993

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled cross-over trial. 3-arm trial for successive 2-week treatment periods.
Participants	14 children with CF, mean age 11.9 years, age range 5.5 - 16.3 years. Inclusion criteria: all receiving > 30 pancreatic enzyme capsules a day and faecal fat output > 15 g/day or fat absorption < 85%.
Interventions	3 groups: 1. high-dose pancreatic enzyme (Creon®) and H2 receptor antagonist ranitidine; 2. high-dose pancreatic enzyme (Creon®) and placebo; 3. low-dose pancreatic enzyme and placebo.
Outcomes	Faecal fat output, stool weight.
Notes	We were unable to include the results from the Bowler trial in the meta-analysis due to insufficient data.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Bowler 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind in text but no further details given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Discrepancy between the number of participants entering and completing the trial which was not addressed.

Boyle 1980

Study characteristics	
Methods	Randomised cross-over trial, 2 groups for successive 5-day treatment periods (2-day equilibration and 3-day stool collection).
Participants	8 people with CF, mean age 16 years, age range 12 - 25 years.
Interventions	2 groups: 1. pancreatic enzyme (Viokase®) alone; 2. pancreatic enzyme (Viokase®) plus the H2 receptor antagonist cimetidine .
Outcomes	Faecal bile acids, weight and fat, and postprandial serum bile acids.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Did not report blinding of investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stool collection from 1 participant was not complete, so stool data based on 7 participants only.

Carroccio 1992

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled cross-over trial for 2 successive 6-month treatment periods.
Participants	10 children with CF (7 males, 5 females), mean age 12.5 years, age range 7 - 18 years, with persistent steatorrhoea on enzymatic supplements (12 children were originally enrolled, but 2 were excluded).
Interventions	2 groups: 1. usual enzyme therapy plus famotidine 1 mg/kg/day; 2. usual enzyme therapy plus placebo.
Outcomes	Faecal weight, fat absorption, weight and height changes, serum calcium, triglycerides, cholesterol, phosphate, iron, Hb, albumin, Crispin Norman score, Shwachman score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind in text but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 children were originally enrolled, but 2 were excluded with severe pulmonary infections.

Chalmers 1985

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled cross-over trial for 2 successive 6-month periods.
Participants	17 people with CF (7 males, 10 females) age range 5 - 19 years. Results reported from the 13 who gave adequate faecal samples.
Interventions	2 groups: 1. usual enzyme therapy plus cimetidine 25 mg/kg/day; 2. usual enzyme therapy plus placebo.
Outcomes	Faecal fat, weight, nitrogen, bile acids, anthropometric measurements, bone age, peak flow, Crispin Norman score, Shwachman score, haemoglobin, albumin, calcium, creatinine and plasma vitamin A levels.

Chalmers 1985 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind in text but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 10 months 1 participant withdrew from group originally assigned to cimetidine (withdrew whilst taking placebo) due to deterioration in respiratory function. This left 8 participants in each group.

Chung 2000

Study characteristics

Methods	Randomised double-blind placebo-controlled cross-over trial for 2 successive 6-week treatment periods with 1-week washout period.
Participants	6 children with CF randomised, 1 excluded because of positive *H. pylori*. Data from 5 children aged 5 - 12 years.
Interventions	2 groups: 1. placebo; 2. omeprazole 10 mg/day or 20 mg/day depending on weight.
Outcomes	Faecal fat, CBC, SMAC, prealbumin, height, weight, malabsorption symptom checklist, genotype analysis, H. pylori status.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind in text but no further details given.

Chung 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 child excluded because of positive H. pylori, data available from 5 remaining participants.

DiMango 2014

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial over 24 weeks; participants were evaluated every 8 weeks.
Participants	21 people screened, 2 withdrew consent prior to randomisation, 2 were ineligible. 17 people (9 to active treatment, 8 to placebo) with CF, age >18, of which 15 completed the trial.
Interventions	2 groups: 1. esomeprazole 40 mg 2x daily; 2. placebo.
Outcomes	Primary outcome measure: time to first exacerbation (defined as initiation of treatment with IV or oral antibiotics for at least 7 days based on respiratory symptoms). Secondary outcome measures included: assessment of CF related quality of life (CFQ-R); GSAS; exacerbation rate; and lung function.
Notes	2 week run-in period prior to randomisation, during which all participants underwent 24-hour amublatory pH probe monitoring. Participants and investigators blinded to the results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given. Used a 1:1 ratio of treatment to placebo regardless of pH probe results, stratified by study centre and FEV_1 decile.
Allocation concealment (selection bias)	Unclear risk	Colombia University Research Pharmacy prepared study medications.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 loss to follow-up in esomeprazole arm (moved), 1 discontinued in placebo arm because of lung transplantation. For participants withdrawn after randomisation, longitudinal analyses compared each value at the start of the treatment period to the last observed value carried forward for each variable.

Durie 1980

Study characteristics

Durie 1980 *(Continued)*

Methods	Randomised cross-over trial of 4 periods of 7 days treatment.
Participants	21 people with CF, age range 10 - 17 years. 6 withdrawals: 2 voluntarily after 3 days; 3 on evidence of poor drug and diet compliance and inadequate stool collection; and 1 with a possible complication with cimetidine.
Interventions	4 groups: 1. pancreatic supplement (Pancrelipase, 27 capsules per day); 2. pancreatic supplement plus cimetidine (20 mg/kg body weight/24h); 3. pancreatic supplement plus sodium bicarbonate (15g/m2/24h); 4. pancreatic supplement plus cimetidine (20 mg/kg body weight/24h) and sodium bicarbonate (15g/m2/24h).
Outcomes	Faecal fat (gm/24 h and %)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Level of blinding not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 withdrawals: 2 voluntarily after 3 days; 3 on evidence of poor drug and diet compliance and inadequate stool collection; and 1 with a possible complication with cimetidine.

Francisco 2002

Study characteristics

Methods	Randomised double-blind placebo-controlled cross-over trial of 4 different 3-day treatment periods.
Participants	22 participants: 10 adults with CF, aged 18 - 36 years; 12 children with CF aged 6 - 17 years. One adult dropped out of the study after completing 2 of the 4 treatment arms.
Interventions	4 treatment arms compared to placebo 2x daily: 1. children < 40 kg - ranitidine 5 mg/kg; 2. children < 40 kg - ranitidine 10 mg/kg;2. 3. children > 40 kg and adults - ranitidine 150 mg 4. children > 40 kg and adults - ranitidine 300 mg twice daily.

Francisco 2002 *(Continued)*

	Adults also received omeprazole 20 mg daily as adjuvant therapy to pancreatic enzymes compared with placebo.
Outcomes	Faecal fat absorption.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One adult dropped out of the study after completing 2 of the 4 treatment arms. For 12 of the 96 admissions (12.5%) recognisable errors were made in the protocol. Analyses were performed including and excluding these admissions.

Heijerman 1990

Study characteristics

Methods	Randomised, double-blind, placebo-controlled cross-over trial for 2 successive 14-day treatment periods.
Participants	8 adults with CF (5 males, 3 females) mean age 28 years, range 21 - 43 years. 1 withdrawal during treatment period with enprostil because of severe diarrhoea and abdominal discomfort.
Interventions	2 groups: 1. oral ranitidine 2x 150 mg; 2. enprostil 2x 35 mcg as adjunct to Pancrease.
Outcomes	Faecal fat, weight, gastrointestinal symptoms.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed

Heijerman 1990 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind in text but no details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal during treatment period with enprostil because of severe diarrhoea and abdominal discomfort.

Heijerman 1991

Study characteristics	
Methods	Randomised, double-blind. placebo-controlled cross-over trial with 4 successive 14-day treatment periods.
Participants	9 adults with CF, mean age 29 years, age range 23 - 42 years. There were no withdrawals.
Interventions	4 consecutive 14-day treatment periods: 1. a high dose pancreatic enzyme, pancrelipase (Pancrease®) (4 capsules, 3 times daily) in conjunction with an oral proton pump inhibitor omeprazole 20 mg daily; 2. a high dose pancreatic enzyme, pancrelipase (Pancrease®) (4 capsules, 3 times daily) in conjunction with placebo; 3. a low dose pancreatic enzyme, pancrelipase (Pancrease®) (2 capsules, 3 times daily) in conjunction with an oral proton pump inhibitor omeprazole 20 mg daily; 4. a low dose pancreatic enzyme, pancrelipase (Pancrease®) (2 capsules, 3 times daily) in conjunction with placebo.
Outcomes	Faecal fat.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded in text but no details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 participants randomised, data for all 9 presented, therefore there were no withdrawals.

Heijerman 1993

Study characteristics

Heijerman 1993 *(Continued)*

Methods	Randomised, double-blind, placebo-controlled cross-over trial for successive 14-day treatment periods.
Participants	11adults with CF (5 males, 6 females), age range 20 - 42 years. There were no withdrawals.
Interventions	2 groups: 1. pancrealipase plus placebo; 2. pancrealipase plus oral omeprazole 20 mg.
Outcomes	Faecal fat, serum trypsin, pancreatic polypeptide, insulin and gastrin, PABA in urine.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded in text but no further details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 participants randomised, data for 11 participants presented, therefore there were no withdrawals.

Lubin 1979

Study characteristics

Methods	Parallel trial, single centre.
Participants	12 children with CF.
Interventions	Group 1: $NaHCo_3$ 10% solution, dose 15cc 1 hour after meals. Group 2: $CaCo_3$ suspension, 1g/5cc, dose 5cc 1 hour after meals.
Outcomes	Mean fat absorption (%), serum calcium.
Notes	Only published as abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States participants randomly allocated, but no details given.

Lubin 1979 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals described.

Proesmans 2003

Study characteristics	
Methods	Randomised controlled cross-over trial. Not blinded.
Participants	24 participants were eligible for the study, of these 9 were excluded from the analysis. Results from 15 participants (12 boys and 3 girls), median age was 8.7 years (range 3.5 - 15.9 years).
Interventions	2 groups: 1. participants with less than 20 kg body weight were treated with 10 mg omeprazole daily; participants weighing more than 20 kg received 20 mg omeprazole daily; 2. no omeprazole.
Outcomes	Daily fat loss (g/day).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded (treatment versus nothing).
Incomplete outcome data (attrition bias) All outcomes	Low risk	24 participants were eligible for the study, of these 9 were excluded from the analysis (1 had viral illness during stool collection while taking omeprazole; in 8 participants residual fat loss could not be confirmed in stool collection when not taking omeprazole). Results from 15 participants.

Robinson 1988

Study characteristics

Robinson 1988 *(Continued)*

Methods	Randomised, double-blind, cross-over trial for 2 successive 14-day treatment periods.
Participants	22 children with CF (18 males, 4 females) mean age 4.4 years, range 1.5 - 10.5 years. 2 children withdrew.
Interventions	2 groups: 1. pancrease 4x daily; 2. pancrease plus 100 mcg misoprostol 4x daily.
Outcomes	Faecal fat.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded in text but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants withdrawn due to protracted diarrhoea, 20 completed study.

Robinson 1990

Study characteristics

Methods	Randomised, double-blind, placebo-controlled cross-over trial for 2 successive 3-week treatment periods.
Participants	17 children with CF (11 males, 6 females), mean age 6.2 years, range 0.5 - 13.8 years.
Interventions	2 groups: 1. usual enzyme therapy plus placebo 4x daily; 2. usual enzyme therapy plus misoprostol 100 mcg 4x daily.
Outcomes	Faecal fat.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Robinson 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Low risk	Randomisation carried out at the pharmacy in the hospital.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded, participants each given 2 bottles of identical looking medication at start of trial (1 bottle of active misoprostol and 1 bottle of inert placebo). Parents of 5 out of 15 children were reported to be able to identify the misoprostol treatment period by improvements in symptoms such as abdominal pain and bulky bowel movements.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals, 1 aged 6 months due to marked diarrhoea while taking misoprostol and 1 because of poor compliance.

Schoni 1984

Study characteristics	
Methods	Randomised, double-blind placebo-controlled trial over 4 months.
Participants	38 children with CF (22 males, 16 females) mean age 12 years and 13.5 years respectively. Participants grouped according to acetylation phenotype (slow or fast) and matched according to their age before the trial. No withdrawals mentioned.
Interventions	2 groups: 1. cimetidine 600 mg/m^2 BSA; 2. placebo.
Outcomes	Clinical state, weight, height, skinfold thickness, lung function tests, PABA peptide test, plasma lipid and lipoprotein.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded in text but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals mentioned.

Weber 1981

Study characteristics	
Methods	Randomised, double-blind placebo-controlled cross-over trial for 2 successive 8-day treatment periods.
Participants	18 children with CF, age range 3 - 13 years. No mention of withdrawals.
Interventions	2 groups: 1. sodium bicarbonate 1 mEq/kg/meal; 2. placebo.
Outcomes	Faecal fat, chymotrypsin, bile acid, faecal weight.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blinded in text but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of withdrawals.

BSA: body surface area
CBC: complete blood count
CF: cystic fibrosis
CFQ-R: cystic fibrosis questionnaire - revised
GSAS: gastroesophageal assessment score
Hb: haemoglobin
H. pylori: Helicobacter pylori
mEq: milliequivalent
PABA: para-aminobenzonic acid

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ansaldi-Balocco 1988	Trial does not assess a gastric reducing supplement.
Cameron 1982	This is a non-randomised clinical controlled trial.
Cox 1981	This is a non-randomised clinical cross-over trial.

Study	Reason for exclusion
Cucchiara 1996	This is a randomised trial comparing cisapride (a pro-kinetic agent) and ranitidine (an agent that reduces gastric acidity). This does not fulfil the inclusion of trials criteria.
Dudley 1981	This is a non-randomised clinical cross-over trial.
Francisco 1996	This trial compares the accuracy of fat balance trials performed at home versus at a Clinical Research Centre.
Geus 1999	This is a trial of gastric and duodenal pH. This does not fulfil the objective of the review. It is not a trial involving a gastric reducing agent.
Gow 1981	This trial contained 4 treatment periods, 3 of which used interventions that were not relevant to the review, therefore no comparisons could be made.
Hoffman 1987	This is a trial of fecal excretion of carbohydrate compared to fat excretion in school-age cystic fibrosis children. This does not fulfil the objective of the review. It is not a trial involving a gastric reducing agent .
Kerr 1982	This trial measures gastric inhibitory polypeptide and insulin response in CF. This does not fulfil the objective of the review. It is not a trial involving a gastric reducing agent.
Koletzo 1989	This trial assessed the effects of cisapride, which is a pro-kinetic agent and not an agent that reduces gastric acidity.
Lloyd-Still 1992	This is a non-randomised controlled clinical trial.
Maish 1998	This is a randomised trial comparing the pharmacokinetics between different modes of delivery of famotidine, that is oral versus intravenous route. This does not fulfil the objective of the review.
Miller 1985	This is a non-randomised controlled clinical trial.
Miller 1986	This is a non-randomised clinical controlled trial looking at duodenal pH and lipase concentration. This does not fulfil the objective of the review.
Mitchell 1981	This trial on N-acetylcysteine is not included because this is not an agent currently used to reduce gastric acidity. This does not fulfil the objective of the review.
Prinsen 1985	This trial is on effects of cisapride which is a pro-kinetic agent and not an agent that reduces gastric acidity.
Santamaria 1989	This trial is on effects of cisapride which is a pro-kinetic agent and not an agent that reduces gastric acidity. This does not fulfil the objective of the review.
Smith 1988	This trial is on effects of cisapride which is a pro-kinetic agent and not an agent that reduces gastric acidity. This does not fulfil the objective of the review.
Stead 1988	This trial investigated the effects of enteric-coated microspheres of pancreatin compared with non-enteric-coated pancreatin combined with cimetidine. Enteric coated and non enteric coated pancreatin are not gastric reducing substances.
Tsang 1994	Trial looking at the immunosuppressant cyclosporin.
Zentler-Munro 1985	This trial assessed lipase, bile acid and trypsin concentration. This does not fulfil the objective of the review.

Characteristics of ongoing studies *[ordered by study ID]*

NCT03551691

Study name	Proton pump Inhibitors and fat absorption in subjects with cystic fibrosis and pancreatic insufficiency
Methods	RCT. Cross-over design. Quadruple blinded (participant, care provider, investigator, outcomes assessor).
Participants	Aim to randomise 24 participants aged 12 years or over (either sex) with CF and pancreatic insufficiency (fecal elastase < 200 ug/g stool).
Interventions	Treatment: omeprazole 40 mg daily for 28 days. Control: identically-appearing placebo capsule to omeprazole daily for 28 days.
Outcomes	**Primary outcome**: coefficient of fat absorption. **Secondary outcomes**: change in duodenal pH as measured by the SmartPill at 28 days, fat absorption via malabsorption blood test (measurement of serum pentadecanoic acid and heptadecanoic acid). All measures to be evaluated at 28 days.
Starting date	07 August 2018.
Contact information	Principal Investigator: Virginia A Stallings, MD, Children's Hospital of Philadelphia, USA. Contacts: Jefferson N Brownell (brownellj@chop.edu) and Joan I Schall (schall@chop.edu).
Notes	Due to be completed April 2021.

CF: cystic fibrosis
RCT: randomised controlled trial

APPENDICES

Appendix 1. Search strategies for ongoing trials databases

Database	Search strategy	Date last searched
US National Institutes of Health database (clinicaltrials.gov/)	Simple search using the terms 'Cystic fibrosis' in the condition, and 'antacids' in the other terms box.	26 April 2021
WHO ICTRP (www.who.int/ictrp/en/)	Simple search using the terms 'Cyctic Fibrosis and antacids'	28 July 2020 (not available in 2021)

WHAT'S NEW

Date	Event	Description
26 April 2021	New citation required but conclusions have not changed	As no new references have been added at this update, our conclusions remain the same.
26 April 2021	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review. Searches of online trials registries (Clinicaltrials.gov and the WHO ICTRP) identified a single ongoing trial (NCT03551691).

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 2, 2003

Date	Event	Description
18 August 2016	New citation required but conclusions have not changed	The review's previous co-author (Angelo Franchini) has stepped down and been replaced by Dr Helen Moore. No new data were added at this update, so our conclusions remain the same.
18 August 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified a single new reference to an already included trial (DiMango 2014).
10 July 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Trials Register identified a single new reference which has been included in the review (DiMango 2014).
10 July 2014	New citation required but conclusions have not changed	Although a single new abstract was identified which was eligible for inclusion in the review, the limited narrative information provided has not led to any change in the conclusions of this review.
16 February 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any references potentially eligible for inclusion in this review.
16 February 2012	New citation required but conclusions have not changed	No new references have been added to the review at this update.
15 April 2010	New search has been performed	A search of the Cystic Fibrosis Trials Register identified two studies potentially eligible for inclusion in the review. One of these has been included (Lubin 1979) and the other has been excluded (Tsang 1994).
13 May 2009	Amended	No changes - republished to fix technical problem.
16 June 2008	Amended	Converted to new review format.
13 June 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any references potentially eligible for inclusion in this review.

Date	Event	Description
22 August 2007	Amended	The plain language summary has been re-drafted in light of the current guidance from The Cochrane Collaboration.
22 August 2007	New search has been performed	A search of the Group's Cystic Fibrosis Trial's Register did not identify any new references which were eligible for inclusion in this review.
16 August 2006	New search has been performed	A search of the Group's Cystic Fibrosis Trial's Register did not identify any new references which were eligible for inclusion in this review.
17 August 2005	New search has been performed	Two trials have been included within the review (Durie 1980; Proesmans 2003). Three trials have been added to the 'Excluded studies' section of the review (Ansaldi-Balocco 1988; Gow 1981; Stead 1988).
17 August 2005	Amended	It was decided by the review authors to remove the data analysis that was previously included within the review. It was felt that this analysis was inappropriate and it would be of more benefit to the reader to report the individual trial results narratively under the relevant outcomes.
24 February 2004	New search has been performed	A search found two new trials for inclusion in the review (Chung 2000; Francisco 2002). However, we were not able to include any new data.

CONTRIBUTIONS OF AUTHORS

Both authors independently selected trials, assessed methodological quality and extracted data.

The lead author completed the write-up of the review and updates with contributions from the co-author and acts as guarantor of the review.

DECLARATIONS OF INTEREST

Sze May Ng declares no potential conflict of interest.

Helen Moore declares no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [drug therapy]; Cystic Fibrosis [*complications] [drug therapy]; Dietary Fats [pharmacokinetics]; Gastric Acid [*metabolism]; Gastrointestinal Agents [therapeutic use]; Histamine H2 Antagonists [*therapeutic use]; Intestinal Absorption [drug effects]; Pancreas [enzymology]; Proton Pump Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans