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Systematic review: efficacy and safety of pancreatic enzyme supplements for exocrine pancreatic insufficiency

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SUMMARY

Background
Pancreatic enzyme supplements are standard therapy for fat malabsorption in patients with exocrine pancreatic insufficiency. The FDA determined that published data are insufficient to support the efficacy and safety of these agents.

Aim
To determine if pancreatic enzyme supplements are: (i) superior to placebo for treating fat malabsorption and (ii) superior to other supplements based on randomized cross-over trials.

Methods
A computer-assisted search of MEDLINE and EMBASE was performed to identify relevant studies. Data extraction on study design, improvement in coefficient of fat absorption, diarrhoea and adverse events using prespecified forms.

Results
A total of 12 manuscripts met inclusion criteria. Most studies (10/12) compared pancreatic enzyme supplements that used different delivery systems, while using similar quantities of enzymes. These studies found no consistent difference in fat malabsorption or gastrointestinal symptoms between different active treatments. Two small placebo-controlled trials (n = 65 patients) demonstrate that pancreatic enzyme supplements are superior to placebo for fat absorption. Data are inadequate to determine if pancreatic enzyme supplements lead to weight gain or improvement in diarrhoea.

Conclusions
Based on data from randomized cross-over trials, pancreatic enzyme supplements appear to improve fat malabsorption. No specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with exocrine pancreatic insufficiency.

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INTRODUCTION

In 2004, the FDA reported that published randomized-controlled trial (RCT) data on pancreatic enzyme supplements were insufficient to support their efficacy and safety. Furthermore, the FDA report on this topic noted that ''currently marketed pancreatic enzyme preparations differ in their composition, enzymatic activities, formulation, stability, and bioavailability. These differences have led to highly variable pancreatic enzyme preparation quality and therapeutic performances … and to unacceptable variability in … quality and therapeutic performance.''[1] With this announcement, the FDA stated that manufacturers of pancreatic enzyme supplements would need to perform new RCTs and to submit these data as part of New Drug Applications (NDA) to continue to market specific pancreatic enzyme supplements.

Pancreatic enzyme supplementation is the 'standard of care' for fat malabsorption among patients with exocrine pancreatic insufficiency, including patients with cystic fibrosis (CF) and alcohol-associated chronic pancreatitis. Our previous systematic review[2] demonstrated that only 4 randomized, parallel-design trials of pancreatic enzyme supplements have been performed and concluded that enzyme supplementation is more likely to improve coefficient of fat absorption (CFA) compared with placebo and that enzyme supplementation improved steatorrhoea. However, enzyme supplementation did not resolve fat malabsorption or steatorrhoea and trials reported very little data on adverse events. Furthermore, important differences in study design, including pancreatic enzyme dosage and measurement of CFA, prevented comparisons of different agents. We also noted that these RCTs did not assess important quality control issues identified by the FDA: (i) the 'shelf-life' or potency of these agents over 12 months; or (ii) the concentration of porcine enzyme in these supplements (i.e., did the supplements consistently contain 100% of labelled claims for potency or was ±65% variation present?).

In our previous systematic review,[2] we excluded randomized cross-over studies from our review. This approach was criticized by reviewers of our previous report, although the use of randomized cross-over studies is problematic because important intra-subject variability has been demonstrated during test-retest studies in the same patient.[3, 4] Furthermore, the FDA's standards for study design in 'Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs'[1] strongly discouraged the use of cross-over studies when stating that ''patients should first be stabilized on existing therapy to establish baseline conditions … if baseline conditions are not re-established between treatment periods [in a cross-over study], or if treatment in one period carries over into the subsequent period, the results likely will not be interpretable.'' Nevertheless, a complete assessment of the efficacy and safety of pancreatic enzyme supplements should include randomized cross-over trial data.

No previous systematic review has qualitatively and quantitatively reviewed the study design and results of published randomized cross-over trials on the efficacy and safety of these agents. This systematic review utilizes an approach that is similar to our previous systematic review of randomized, parallel-design, trials.[2] We focused on trials that report some measurement of fat absorption, including CFA. We extracted data on study design, malabsorption symptoms such as diarrhoea and weight loss and adverse events. Through this additional systematic review of randomized cross-over trials, our aim was to determine if pancreatic enzyme supplements are superior to placebo for improving fat malabsorption and to determine if a specific pancreatic enzyme supplement is superior to other supplements for improving fat malabsorption.

MATERIALS AND METHODS

Literature search

A computer-assisted search was conducted to identify potentially relevant publications in the following databases on 1 September 2008: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, OVID Cochrane Library, and the Centre for Reviews and Dissemination (CRD).

A search of the OVID MEDLINE database from 1980 to 2nd week of August 2008 was performed using the following exploded (exp), medical subject heading (MeSH) and text words: exp Chronic Pancreatitis/dt [Drug Therapy] OR exp Exocrine Pancreatic Insufficiency/dt [Drug Therapy] OR exp Pancreatitis OR exp Cystic Fibrosis OR exp Exocrine Pancreatic Insufficiency OR (pancreatitis or (pancrea$ adj2 insufficien$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] AND exp Enzymes/OR (enzyme$ adj1 (pancrea$ or replace$ or supplement$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] OR

(pancreatin or pancrease or pancrelipase or ultrase or cotazym or creon or kreon or theraclec or encron or protilase or lipase or hydrolase or exolipase or triglyceridase or ALTU-135).mp. [mp=title, original title, abstract, name of substance word, subject heading word]. This was then limited to humans and a search filter designed to retrieve controlled clinical trials, systematic reviews, meta-analyses or RCTs was applied.

The same search strategy was used to search the OVID Cochrane Library. Both the MEDLINE In-Process and Other Non-Indexed Citations and the CRD databases were searched using text word combinations. A search of the EMBASE database from 1980 to week 32 of year 2008 was performed using search terms similar to those used in the MEDLINE search.

Study selection criteria. Study inclusion criteria were: (i) study design-RCT with cross-over design; (ii) study population exocrine pancreatic insufficiency caused by alcohol-associated chronic pancreatitis or CF; (iii) study intervention-pancreatic enzyme supplement [uncoated, enteric coated microspheres (MSP), microspheres (MMSP), microtablets (MT)] vs. placebo or another pancreatic enzyme supplement (Table 1); (iv) study endpoint-change in pancreatic malabsorption of fat; and (v) published as full manuscript in English language. We also extracted data regarding clinical symptoms including diarrhoea and weight loss/gain and adverse events. Studies were excluded if aetiology of malabsorption was nonpancreatic because of bacterial overgrowth, small bowel mucosal disease, short gut, cholestatic liver disease or if patient had secondary pancreatic insufficiency caused by pancreatic cancer/surgery.

Two investigators (P.S., A.W.) independently reviewed the titles and abstracts of all citations identified by the literature search. Potentially relevant studies were retrieved and the selection criteria were applied. Agreement between investigators for selection of studies for the systematic review was >95% and disagreements were resolved by consensus.

Data extraction and assessment of methodological quality of individual studies. Eligible articles were reviewed in a duplicate, independent manner by two investigators (J.T., T.G.). For each study, the investigators recorded the study design, the inclusion and exclusion criteria, aetiology of primary pancreatic insufficiency, number of patients in each arm of study, age of patients, pancreatic enzyme used, dose of pancreatic enzyme, formulation of pancreatic enzyme, timing of enzyme administration, quantification of faecal fat and its method of collection, results of primary endpoint, results of all secondary endpoints and results of adverse event reporting.

There are no specific criteria to assess the quality of study design for clinical trials about pancreatic enzyme supplementation, although there are validated criteria to quantify the study design quality of RCTs.[5] The validated criteria for RCTs include proper randomization techniques, concealed allocation, double-blinding and complete patient follow-up. Although sample size is not included in this list, an appropriately designed RCT needs a sample size calculation, too. Despite the lack of standard criteria for the design of pancreatic enzyme supplementation clinical trials, two study design criteria appear important to produce accurate and unbiased results: (i) confirming the presence of fat malabsorption prior to enrolling patients; and (ii) standardizing measurements of fat malabsorption by monitoring patients in clinical research centres to control dietary fat consumption and to use stool dye markers to demarcate the beginning and end of a 72-h faecal fat collection. In this review, we assessed all of these criteria to quantify the methodological quality of each RCT.

Data analysis. Substantial differences in study design, study population, formulation and dosing of enzyme supplements and definition of study endpoint are present across these RCTs. Therefore, pooling of data into a meta-analysis is not feasible and results of individual RCTs are presented in a tabular form.

RESULTS

Literature Search

The MEDLINE search yielded 312 articles. The EMBASE search yielded 484 articles (Figure 1). Manual searches of reference lists from potentially relevant papers identified 13 additional publications that were not detected using the computer-assisted strategy. All citations were downloaded into Reference Manager™ and then EndNote™, and duplicates were removed. Seven hundred and sixty unique citations were obtained and the titles and abstracts of each citation were reviewed. Six hundred and sixty-four unique citations were excluded after review of the title and

Table 1. Included articles

Author	Journal	Year	Title	*n*
Placebo-controlled trials				
Delchier *et al.*[24]	*Alimentary Pharmacology & Therapeutics* (APT)	1991	Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two pancreatic enzyme preparations	6
Konstan *et al.*[31]	APT	2004	Ultrase MT12 and Ultrase MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: safety and efficacy	59
Nonplacebo-controlled trials				
Bowler *et al.*[23]	*Archives of Disease in Childhood*	1993	A double-blind lipase for lipase comparison of a high lipase and standard pancreatic enzyme preparation in cystic fibrosis	21
Delhaye *et al.*[25]	*European Journal of Gastro and Hepatology*	1996	Comparative evaluation of a high lipase pancreatic enzyme preparation and a standard pancreatic supplement for treating exocrine pancreatic insufficiency in chronic pancreatitis	32
Dutta *et al.*[26]	*Gastroenterology*	1983	Comparative evaluation of the therapeutic efficacy of a pH-sensitive enteric coated pancreatic enzyme preparation with conventional pancreatic enzyme therapy in the treatment of exocrine pancreatic insufficiency	6
Gan *et al.*[27]	APT	1994	Comparison of a high lipase pancreatic enzyme extract with a regular pancreatin preparation in adult cystic fibrosis patients	15
Gouerou *et al.*[28]	*International Journal of Pancreatology*	1989	Alipase versus non-enteric coated enzymes in pancreatic insufficiency	35
Halm *et al.*[29]	APT	1999	A double-blind, randomized, multicentre, cross-over study to prove the equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency	37
Kalnins *et al.*[30]	*Journal of Paediatric Gastroenterology and Nutrition*	2006	Enteric-coated pancreatic enzyme with bicarbonate is equal to standard enteric-coated enzyme in treating malabsorption in cystic fibrosis	22
Lancellotti *et al.*[32]	*Journal of Paediatric Gastroenterology and Nutrition*	1996	High- versus low-lipase acid-resistant enzyme preparations in cystic fibrosis: a cross-over randomized clinical trial	24
Santini *et al.*[33]	*Digestive and Liver Disease*	2000	Comparison of two enteric coated microsphere preparations in the treatment of pancreatic exocrine insufficiency caused by cystic fibrosis	64
Williams *et al.*[34]	*Archives of Disease in Childhood*	1990	Two enteric coated microspheres in cystic fibrosis	39

n = patients enrolled.

abstract because they were not clinical trials about efficacy of pancreatic enzyme supplementation in patients with exocrine pancreatic insufficiency. Of the remaining 96 citations, 67 were excluded after review of the abstracts because they did not meet inclusion and exclusion criteria, including lack of randomization.

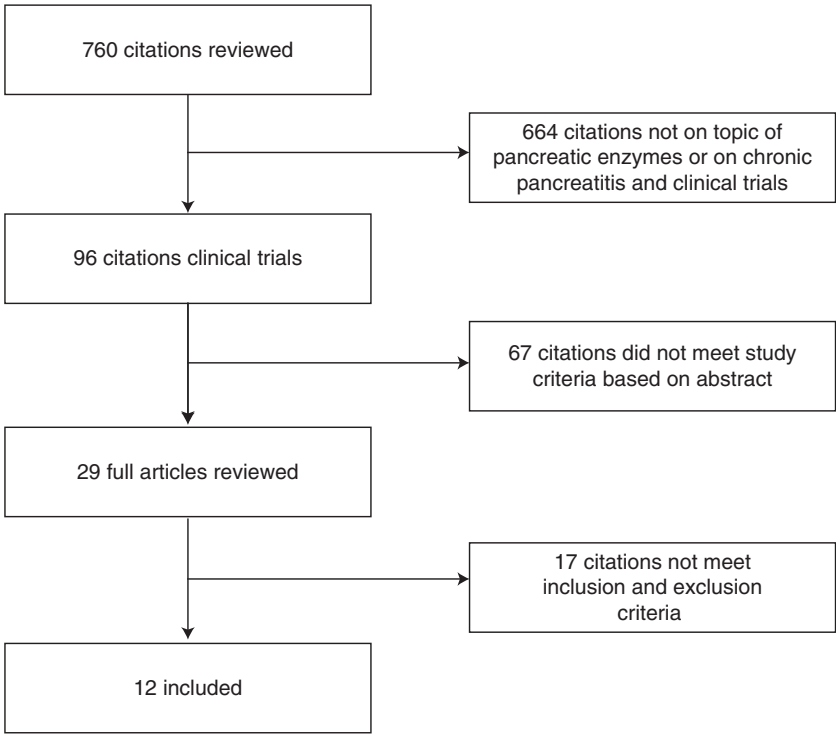

Figure 1. Study Flow Diagram.

Twenty-nine relevant studies were identified, retrieved and completely reviewed. Seventeen studies[6–22] did not meet study selection criteria because of a variety of exclusion criteria, including inappropriate or incomplete reporting about changes in fat absorption, non-use of cross-over design, or use of inappropriate patient populations. Twelve studies[23–34] met all inclusion criteria and were available in full manuscript form for inclusion in this systematic review (Table 1).

Summary of demographic data and methodological quality of trials

Seven studies focused on CF patients[23, 27, 30–34] while five studies[24–26, 28, 29] primarily enrolled patients with alcohol-related chronic pancreatitis. In the trials examining patients with alcohol-related chronic pancreatitis, fewer than 20% of study patients had idiopathic, familial or unspecified aetiology for chronic pancreatitis (Table 2). In these studies, results were not stratified between patients with alcohol-associated chronic pancreatitis or chronic pancreatitis from another cause. Also, it is unclear if the patients with alcohol-associated chronic pancreatitis had ongoing alcohol use.

The sample size of all studies was quite small with no study enrolling more than 64 patients and over 80% (10/12) of studies enrolled fewer than 40 patients. In studies with alcohol-associated chronic pancreatitis patients, the mean age of patients clustered around 50 years, whereas the mean age of patients in the CF trials clustered around 10–20 years. The gender distribution was quite disparate in the studies of patients with alcohol-associated chronic pancreatitis with 98 men: 11 women, while the CF trials generally had equal numbers of men and women enrolled in their trials. Only two trials[24, 31] used a placebo control. All remaining studies compared two different pancreatic enzyme supplements or compared two different dosages of the same enzyme supplement. Studies quantified fat malabsorption with CFA or calculated faecal fat excretion (FFE). Most studies (11/12) reported on changes in some gastrointestinal symptoms associated with fat malabsorption, including stool frequency, stool consistency, abdominal discomfort and/or global symptom improvement, although the reporting was frequently inadequate.

The methodological quality of individual trials is summarized in Table 3. Consistent with the inclusion criteria for this systematic review, all twelve trials used a randomized cross-over technique, although only one study[31] reported using concealed allocation with randomization. Seventy-five percent (nine of 12) of studies were double-blinded, and almost all studies (11/12) had follow-up data for more than 90% of study

Table 2. Demographics of study population

Article	Aetiology of pancreatic insufficiency	No. patients enrolled/no. patients completed study	Gender (M/F)	Mean (*M*) ± standard deviation (s.d.) or median (*m*) Age in years	Age range (years)
Placebo-controlled trials					
Delchier *et al.*[24]	Chronic pancreatitis 5 patients alcoholic 1 patient familial	6/6	5/1	*M* = 50	29–61
Konstan *et al.*[31]	Cystic fibrosis	59/47 Group 1: 26/22 Group 2: 32/25	Group 1: 15/7 Group 2: 18/7	Group 1: 16.1 Group 2: 16.8	Group 1: 8–36 Group 2: 7–36
Nonplacebo-controlled trials					
Bowler *et al.*[23]	Cystic fibrosis	21/18	Unknown	*m* = 11.5	4.9–14.1
Delhaye *et al.*[25]	Chronic pancreatitis 23 alcoholic 2 idiopathic	32/25	24/1	*M* = 52.4 ±−1.7	40–69
Dutta *et al.*[26]	Chronic pancreatitis 6 alcoholic	6/6	6/0	*M* = 50	48–53
Gan *et al.*[27]	Cystic fibrosis	15/13	6/7	*M* = 27.7	19–46
Gouerou *et al.*[28]	Chronic pancreatitis 33 alcoholic 2 did not specify aetiology	35/27 Group 1: 20 Group 2: 15	33/2 Group 1: 19/1 Group 2: 14/1	Group 1: *M* = 50.5 ± 9.8 Group 2: *M* = 57.9 ± 11.4	18–75
Halm *et al.*[29]	Chronic pancreatitis did not specify aetiology	37/23	30/7	*M* = 52 ± 10	Unknown
Kalnins *et al.*[30]	Cystic fibrosis	22/21	7/14	*M* = 20.6 ± 11.5	8.8–41.9
Lancellotti *et al.*[32]	Cystic fibrosis	24/20	14/10	*M* = 17.67 ± 4.82	10.9–29.5
Santini *et al.*[33]	Cystic fibrosis	64/60 Group 1: 26 Group 2: 34	35/25 Group 1: 16/10 Group 2: 19/15	*M* = 12.5 ± 5.7 Group 1: *M* = 11.9 ± 6 Group 2: *M* = 12.9 ± 5.5	6–34 Group 1: 6–34 Group 2: 6–30
Williams *et al.*[34]	Cystic fibrosis	39/27 Group 1: 13 Group 2: 14	15/12	*m* = 9.7	5–17

patients. Most CF trials (six of seven) included a sample size calculation, whereas none of the alcohol-associated chronic pancreatitis trials included a sample size calculation. Only three studies[23, 24, 31] demonstrated appropriate timing of faecal fat collection with stool markers and only three studies[24, 26, 31] monitored fat intake during faecal fat collection. Overall, only a single study[31] published in 2004 met the criteria for performing a rigorously designed trial of pancreatic enzyme supplements.

Summary of results from trials of CF patients

The seven studies of CF patients[23, 27, 30–34] provide very little data on the efficacy and safety of pancreatic enzyme supplements and only one of these studies[31] is placebo-controlled. Most studies simply compared pancreatic enzyme supplements that used different delivery systems[23, 27, 30, 32, 33] while using similar quantities of lipase, amylase, and protease. With the exception of one study by Bowler *et al.*,[23] comparisons between the effects of various active treatments detected no difference in CFA or FFE and no consistent difference in weight gain, stool frequency/consistency or other GI symptoms between different active treatments. Therefore, these studies cannot determine if different dosages of pancreatic enzyme supplements are more or less effective for fat malabsorption and these studies suggest that no specific branded product or specific delivery system is superior for treatment of

Table 3. Assessment of methodological quality of individual studies

Article	Randomized	Concealed allocation	Double blind vs. single blind vs. open	Sample size calculation	CFA before study*	Controlled timing of faecal fat collection†	Monitoring fat intake during faecal fat collection‡	Assessment of symptom improvement§
Placebo-controlled trials								
Delchier *et al.*[24]	Yes	Unknown	DB	No	No	Yes	Yes	No
Konstan *et al.*[31]	Yes	Yes	DB	Yes	Yes	Yes, used carmine red dye	Yes	Yes
Nonplacebo-controlled trials								
Bowler *et al.*[23]	Yes	Unknown	DB	Yes	No	Yes, but only 48-h fat collection. They used radio-opaque markers (did not specify which ones)	No	Yes; tx group comparison, but no comparison to pre-tx symptoms
Delhaye *et al.*[25]	Yes	Unknown	Open	No	No	No	No	Yes
Dutta *et al.*[26]	Yes	Unknown	DB	No	No	No	Yes	Yes
Gan *et al.*[27]	Yes	Unknown	DB	No	No	No	No	Yes
Gouerou *et al.*[28]	Yes	Unknown	DB	No	No	No	No	Yes
Halm *et al.*[29]	Yes	Unknown	DB	Yes	No	No	No	Yes
Kalnins *et al.*[30]	Yes	Unknown	DB	Yes	Yes	No	No	Yes
Lancellotti *et al.*[32]	Yes	Unknown	Open	Yes	No	No	No	Yes
Santini *et al.*[33]	Yes	Unknown	DB	No	No	No	No	Yes
Williams *et al.*[34]	Yes	Unknown	Single-blind (physicians blinded)	Yes	No	No	No	Yes

* Confirmed fat malabsorption before study enrolment with CFA.
† Demonstrated appropriate timing of faecal fat collection through the use of stool markers to ensure that the patient monitored diet at the beginning and end of faecal fat collection.
‡ Monitored in an inpatient setting.
§ Assessment of symptom assessment includes stool frequency, stool consistency, abdominal discomfort and/or global symptom improvement.

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fat malabsorption in CF patients. However, these studies did not enroll adequate patients to demonstrate non-inferiority and most of these studies[23, 30, 33, 34] did not use an appropriate wash-out period per FDA standards.[1] With the exception of the single placebo-controlled trial,[31] these studies did not report on adverse events[23, 30, 34] or provided inadequate data on adverse events.[27, 32, 33]

Among the trials without a placebo arm, statistically significant results came from the study by Bowler *et al.*[23] that compared a standard acid-resistant microsphere (Nutrizym GR) to an identical capsule *half-filled* with minitablets of an acid resistant high lipase preparation (Nutrizym 22) and demonstrated a significant improvement in fat absorption and faecal fat output with the preparation half-filled with high dose lipase (Tables 4 and 5). Although the study abstract states that 'there were fewer gastrointestinal symptoms [with]… high lipase preparation', review of results does not demonstrate any statistically significant difference. The authors conclude that the high lipase minitablets are more effective than standard acid resistant microspheres. Also, the study by Santini *et al.*[33] demonstrated a small, but statistically significant, difference in stool fat excretion which favoured Pancrease vs. Creon, although no significant difference in CFA, stool frequency/consistency or adverse events was reported.

The single placebo-controlled trial[31] met all criteria for an appropriately designed study (Table 3), used an appropriate wash-out period per FDA standards[1] and is the only trial of CF patients that provides detailed data on adverse events. This multi-centre study compared Ultrase MT12 to placebo and Ultrase MT20 to placebo in two separate trials. In both trials, patients treated with Ultrase absorbed more protein and fat compared with patients treated with placebo (Table 5). Detailed adverse event reporting did not identify statistically significant differences in adverse event rates between Ultrase and placebo, although placebo-treated patients had numerically higher rates of flatulence (56% vs. 35%) and abdominal discomfort (57% vs. 23%) compared with Ultrase-treated patients.

Summary of results from trials of alcohol-associated chronic pancreatitis patients

The five studies of alcohol-associated chronic pancreatitis patients[24–26, 28, 29] provide very little data on the efficacy and safety of pancreatic enzyme supplements and only one of these studies[24] is placebo-controlled. Most studies simply compared pancreatic enzyme supplements that used different delivery systems or different types of pH-sensitive enteric coating[25, 26, 28, 29] while using similar quantities of lipase, amylase, and protease. These studies[25, 26, 28, 29] found no difference in CFA or FFE between different active treatments. Except for a significant improvement in abdominal distention with Pancrease (with enteric coating) vs. Eurobiol (without enteric coating),[28] and a significant increase in mean bowel movement frequency with unencapsulated Pancreatin vs encapsulated Cotazyme and Pancrease,[26] no significant differences were identified for weight gain, stool frequency/consistency, or other GI symptoms between different active treatments. Again, these studies cannot determine if different dosages of pancreatic enzyme supplements are more or less effective for fat malabsorption and these studies suggest that no specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with alcohol-associated chronic pancreatitis. With the exception of one study,[29] these studies were not designed to demonstrate non-inferiority, and the remaining studies[24–26, 28] enrolled inadequate sample sizes of only 6, 32, 6 and 35 patients respectively. Most of these studies[25, 26, 29] did use an appropriate wash-out period between administrations of active treatments per FDA standards.[1] Two studies[28, 29] reported adequate data on adverse events, two studies[24, 26] did not report adverse event data and one study[25] provided inadequate adverse event data.

The sole placebo-controlled trial[24] in alcohol-associated chronic pancreatitis patients only enrolled 6 patients and demonstrated that Eurobiol reduced daily FFE by 24% more than placebo ($P > 0.05$) and Eurobiol 25000 reduced daily FFE by 43% ($P < 0.05$) more than placebo. Notably, patients in this trial consumed the same number of capsules and hence these data suggest that formulations with higher quantities of pancreatic enzyme produce larger reductions in daily FFE. Delhaye *et al.*[25] also compared two different delivery systems, Pancrease HL (3 capsules/day) and Creon (9 capsules/day), with or without omeprazole. In this 4-arm cross-over trial of 35 patients, faecal fat and protein excretion was similar for each pancreatic supplement. Notably, addition of omeprazole to the enzyme supplement 'was associated with a marked decrease in the fat-protein content ratio, suggesting an improvement in the fat digestive process but a decrease in the efficiency of protein digestion.' Although the authors concluded that the addition of

Table 4. Study design

Author	Study design (no. study groups)	Washout: Pre-tx: PTW between: BTW	Treatment time	Formulation per capsule (L = lipase, A = amylase, P = protease) EC = = enteric coated; MT = microtablets; MS = microspheres; MMS = mini microspheres	Dose (Rx) Timing (T) Diet (D)
Placebo-controlled trials					
Delchier *et al.*[24]	Drug/drug/ placebo (3)	PTW: 8 days BTW: 15 days	**21 days total:** 7 days on each enzyme and 7 days on placebo	**Eurobiol (freeze-dried pig pancreas):** 1 dose = 5 g; Lipase/dose: 96 776 IU **Eurobiol 25 000 (EC: MT)** 1 dose = 2 capsules; lipase/dose: 76 521 IU **Placebo:** (enteric-coated pork filet tablets) L: none	**Rx:** One dose/meal **T:** During meals **D:** 100 g fat/day
Konstan *et al.*[31]	Drug/drug and drug/placebo (4)	PTW: 4 days BTW: 4 days	**12 days total:** 6 days in each group (3 placebo/3 enzyme)	**Ultrase MT 12 (EC: MS)** L: 12 000 IU **Ultrase MT 20 (EC: MS)** L: 20 000 IU No difference in mean lipase dose/day b/w groups	**Rx: MT 12:** Enzyme (E) and placebo (P) then P–E **MT 20:** E–P then P–E. **T:** Unknown **D:** >100 g fat/day
Nonplacebo controlled trials					
Bowler *et al.*[23]	Drug/drug (2)	PTW: none BTW: none	**28 days total:** 14 days on each enzyme	**Nutrizym GR (EC: MSP)** L: 11 100 BPU; A: 12 000 BPU; P: 740 BPU **Nutrizym-22 (EC: MT)** L: 11 800 BPU; A: 13 300 BPU; P: 815 BPU	**Rx:** Instructed to take same dose of enzymes as they did prior to study **T:** During meals **D:** Nonstandard
Delhaye *et al.*[25]	Drug/drug drug ± ppi (4)	PTW: none BTW: none	**56 days total:** 2 weeks in each of 4 groups (Each enzyme with and without ppi)	**Pancrease HL (EC: MS)** L: 25 000 EPU; A: 22 500 EPU; P: 1250 EPU **Creon (EC: MS)** L: 8000 EPU; A: 9000 EPU; P: 450 EPU **Omeprazole (ppi):** 20 mg	**Rx:** *Groups*: (a+b with ppi; c+d no ppi) *a*: Pancrease HL(pHL) 1 cap; *b*: Creon 3 caps; *c*: pHL 1 cap; *d*: Creon 3 caps **T:** During meals **D:** 100 g fat/day last 5 days of each 2 week tx

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Table 4. (Continued)

Author	Study design (no. study groups)	Washout: Pre-tx: PTW between: BTW	Treatment time	Formulation per capsule (L = lipase, A = amylase, P = protease) EC = = enteric coated; MT = microtablets; MS = microspheres; MMS = mini microspheres	Dose (Rx) Timing (T) Diet (D)
Dutta *et al.*[26]	Drug/drug and drug/dose (4)	PTW: none BTW: none	**24 days total:** 6 days on each enzyme	**Pancreatin (uncoated tab):** Mean L/tab: 684 U **Cotazyme (uncoated tab):** Mean L/tab: 8804 U **Pancrease (EC: MS):** Mean L/tab: 4933 U	Rx: *Groups*: (no. tabs/meal TID) *a*: Pancreatin: 10 *b*: Cotazyme: 4 *c*: Pancrease: 4 *d*: Pancrease: 8 **T:** During meals **D:** 100 g fat/day
Gan *et al.*[27]	Drug/drug (2)	PTW: none BTW: none	**28 days total:** 14 days on each enzyme	**Pancrease (EC: MS)** L: 5000 BPU; A: 2900 BPU; P: 320 BPU **Pancrease HL (EC: MS)** L: 25 000 BPU; A: 22 500 BPU; P: 1250 BPU	Rx: *Groups*: (Both groups had 20 mg ppi daily) *a*: 4 tabs pancrease + 1 tab placebo/meal *b*: 4 tabs placebo + 1 tab pancrease hl/meal **T:** Before meals **D:** Mean fat/day: 117.7 g
Gouerou *et al.*[28]	Drug/drug (2)	PTW: 10 days BTW: none	**42 days total:** 21 days on each enzyme	**Pancrease (EC: MS)** Unknown dose Pancrease (P): 9 caps/day **Eurobiol (uncoated tab)** Unknown dose Eurobiol (E): 3 vials/day	Rx: *Groups*: *a*: Pancrease (P) then Eurobiol (E) *b*: E then P **T:** Unknown **D:** Not specified
Halm *et al.*[29]	Drug/drug (2)	PTW: 2 weeks BTW: 1 week	**28 days total:** 14 days on each enzyme	**Creon 10 000 EC (MMS)** L: 10 000 FIP **Creon 10 000 EC (MS)** L: 10 000 BPU	Rx: 4 caps w/meals; 2 caps w/snacks **T:** During meals **D:** Last 4 days pre-stool collection: 70–80 g fat/day

Table 4. (Continued)

Author	Study design (no. study groups)	Washout: Pre-tx: PTW between: BTW	Treatment time	Formulation per capsule (L = lipase, A = amylase, P = protease) EC = = enteric coated; MT = microtablets; MS = microspheres; MMS = mini microspheres	Dose (Rx) Timing (T) Diet (D)
Kalnins *et al.*[30]	Drug/drug (2)	PTW: none BTW: none	**28 days total:** 14 days on each enzyme	**Pancrecarb (EC: Buffered)** L: 8000 U FIP; A: 40 000 FIP; P: 45 000 FIP; 1.5 meq bicarb; *In vitro* L: 11 500 IU **Cotazym ECS (EC: Non-buffered)** L: 8000 BPU; A: 30 000 BPU; P: 30 000 BPU; *In vitro* L: 11 960 IU	**Rx:** ~24 caps/day was 'Usual enzyme dose' **T:** Before or before and during meals **D:** *Mean g fat/day: Pancrecarb: 90.2 Cotazym: 83.6
Lancellotti *et al.*[32]	Drug/drug (2)	PTW: none BTW: none	**10 days total:** 5 days on each enzyme	**Pancrease (EC: MS)**; (P) L: 5000 BPU; A: 2900 BPU; P: 329 BPU **Pancrease HL (EC: MS)**; (pHL) L: 25 000 BPU; A: 22 500 BPU; P: 1250 BPU	**Rx:** Average caps/day (P) = 30, pHL = 6 *Group a*: (P) then pHL; *Group b*: pHL then (P) **T:** (P): before, during & after meals pHL: during meals **D:** 1.98 g fat/kg/day
Santini *et al.*[33]	Drug/drug (2)	PTW: none BTW: none	**14 days total:** 7 days on each enzyme	**Creon (EC: MS)** L: 8000 FIP; A: 9000 FIP; P: 450 FIP **Pancrease (EC: MS)** L: 5350 FIP; A: 6957 FIP; P: 462 FIP	**Rx:** *Group a*: Creon then Pancreas *Group b*: Pancrease then Creon Creon: 10.6 caps/day; 2298 u/kg lipase/day Pancrease: 16.5 caps/day; 2265 u/kg lipase/day **T:** Unknown **D:** 2 g fat/kg/day

Table 4. (Continued)

Author	Study design (no. study groups)	Washout: Pre-tx: PTW between: BTW	Treatment time	Formulation per capsule (L = lipase, A = amylase, P = protease) EC = = enteric coated; MT = microtablets; MS = microspheres; MMS = mini microspheres	Dose (Rx) Timing (T) Diet (D)
Williams *et al.*[34]	Drug/drug (2)	PTW: 2 weeks BTW: none	**56 days total:** 28 days on each enzyme	**Pancrease (EC: MS)** L: 5000 BPU; A: 2900 BPU; P: 330 BPU **Creon (EC: MS)** L: 8000 BPU; A: 9000 BPU; P: 210 BPU	**Rx:** *Groups*: *a*: Pancrease then Creon *b*: Creon then Pancrease **T:** Unknown **D:** 66.2–78.1 g fat/day

* Difference was not statistically significant.

omeprazole did not produce a clinically important impact on fat-protein absorption, the use of omeprazole (or H2 antagonists) is a simple over-the-counter potential treatment options to adjunctively treat fat malabsorption.[35]

DISCUSSION

In 2004, the FDA reported that published RCT data on pancreatic enzyme supplements was insufficient to support their efficacy and safety.[1] Therefore, we performed a systematic review of published parallel-design RCT data[2] and this systematic review of cross-over RCT data to assess this conclusion. Through these reviews, we sought to determine if pancreatic enzyme supplements were superior to placebo for treating fat malabsorption and if a specific pancreatic enzyme supplement appeared to be superior for improving fat malabsorption. Our review found no difference in CFA, FFE, GI symptoms associated with fat malabsorption, or adverse events between different pancreatic enzyme supplements. Most studies reported that CFA was >80% with supplements, and this should be reassuring to physicians and patients using pancreatic enzyme supplements. Based on very limited placebo-controlled trial data (n = 2 trials which studied 65 patients), pancreatic enzyme supplements appear superior to placebo for improving fat malabsorption. However, data are inadequate to determine if these supplements improve symptoms associated with fat malabsorption like steatorrhoea and weight loss. Therefore, published cross-over RCT data do not appear to meet the standard for pivotal Phase III trials that are usually required by the FDA for new products, and the FDA appears justified in concluding that published RCT data are insufficient to support clearly the efficacy and safety of pancreatic enzyme supplements.

Our previous systematic review[2] found four well-designed, parallel-group, placebo-controlled RCTs, which consistently demonstrated that enzyme supplementation improves coefficient of fat malabsorption (CFA) compared to placebo, but fat malabsorption and steatorrhea remained despite enzyme supplementation. These studies also demonstrated that stool frequency and consistency improved with enzyme supplementation, but trials were too brief to demonstrate any changes in weight. However, this systematic review was limited because we excluded cross-over RCTs. None of the randomized, placebo-controlled, parallel-design studies in our previous review[2] performed a

Table 5. Results

Author	*n*	Results*	Statistical significance
Placebo-controlled trials			
Delchier *et al.*[24]		**Mean FFE (g/day)**	**Mean FFE**
	6, 6	Eurobiol: 32 ± 7.8; Placebo: 42 ± 4.5	Eurobiol vs. placebo: ND (no *P*-value given)
	6, 6	Eurobiol 25 000: 24 ± 1.5; Placebo: 42 ± 4.5	Eurobiol 25 000 vs. placebo: **SS ($P < 0.05$)**
			Eurobiol 25 000 vs. Eurobiol: **SS ($P < 0.05$)**
Konstan *et al.*[31]		**Mean CFA (%)**	**Mean CFA**
	23, 22	MT 12 Enzyme: 79.4 ± 12.5; Placebo: 46.7 ± 35.8	MT 12 Enzyme vs. placebo: **SS ($P = 0.0002$)**
	25, 25	MT 20 Enzyme: 87.3 ± 10.2; Placebo: 58.7 ± 16.5	MT 20 Enzyme vs. placebo: **SS ($P = 0.0001$)**
Nonplacebo controlled trials			
Bowler *et al.*[23]	18	**Mean CFA (%)**	**Mean CFA**
		Before Tx: Not recorded; After Tx: Nutrizym-22: 91; After Tx: Nutrizym-GR: 76	Nutrizym-22 vs. Nutrizym-GR: **SS ($P = 0.002$)**
		Mean FFE (g/day)	**Mean FFE**
		Nutrizym-22: Before Tx: 8.035; After Tx: 8.7	Nutrizym-22: ND ($P = 0.45$)
		Nutrizym-GR: Before Tx: 11.8; After Tx: 26.1	Nutrizym-GR: **SS ($P < 0.0001$)**
			Nutrizym-22 vs. Nutrizym-GR: **SS ($P = 0.003$)**
Delhaye *et al.*[25]	25	**Mean CFA (%)**	**Mean CFA**
		Pancrease HL + ppi: 83.8 ± 2.4; Creon + ppi: 83.1 ± 3.3; Pancrease HL: 82 ± 2; Creon: 82.1 ± 2.3	ND ($P > 0.05$) between groups
			Mean FFE
		Mean FFE (g/day)	ND ($P > 0.05$) between groups
		Pancrease HL + ppi: 20.3 ± 2.7; Creon + ppi: 20.7 ± 3.4; Pancrease HL: 21.4 ± 2.3; Creon: 21.4 ± 2.3	
Dutta *et al.*[26]	6	**Mean FFE (g/day)**	**Mean FFE**
		Before Tx: 31 ± 5	Before-tx vs. After-tx (each group): **SS ($P < 0.005$)**
		After Tx: Pancreatin: 19 ± 4; Cotazyme: 15 ± 5; Pancrease 12: 13 ± 5; Pancrease 24: 11 ± 4	Pancreatin vs. Pancrease 24: **SS ($P < 0.01$)**
			ND between other Groups (no *P*-value given)
Gan *et al.*[27]	13	**Mean CFA (%)**	**Mean CFA**
		Before Tx: Pancrease + Pancrease HL both <90; After Tx: Pancrease: 84.6, Pancrease HL: 84.5	After Tx: ND between groups ($P > 0.05$)
Gouerou *et al.*[28]		**Mean FFE (g/day)**	**Mean FFE**
	20	Before Tx: Group a: Pancrease then Eurobiol: 25.8 ± 31.8	Before Tx: Group a vs. b: ND (no *P*-value given)
	15	Before Tx: Group b: Eurobiol then Pancrease: 20.3 ± 15.1	After Tx: Pancrease vs. Eurobiol: ND (no *P*-value given)
		After Tx for both Groups a + b: Pancrease: 13.9 ± 12.96; Eurobiol: 12.32 ± 9.48	
Halm *et al.*[29]		**Mean CFA (%)**	**Mean CFA**
	23	Intention-to-treat: Creon MMS: 80.1 ± 13.6; Creon MS: 80.6 ± 17.5	Intention-to-treat: ND ($P = 0.07$)
	18	Per-Protocol-Analysis: Creon MMS: 81.9 ± 10.6; Creon MS: 83.3 ± 12.1	Per-Protocol Analysis: **SS ($P = 0.02$)**

Table 5. (Continued)

Author	*n*	Results*	Statistical significance
Kalnins *et al.*[30]	21	**Mean FFE (%)** Before Tx: 28 ± 16; After Tx: Pancrecarb: 20.7% ± 10.9; After Tx: Cotazym: 20.2% ± 12.4	**Mean FFE** Before Tx vs. After Tx: ND (no *P*-value given) Pancrecarb vs. Cotazym: ND ($P > 0.05$)
Lancellotti *et al.*[32]		**Fat excretion Coefficient (%)** [Pancrease = (P); Pancrease HL = (pHL)]	**Fat excretion Coefficient:**
	9	Group a: (P): 10.13 ± 7.23; (pHL) : 16.39 ± 11.25	Group a: (P) vs. (pHL): ND ($P = 0.112$)
	11	Group b: (pHL): 16.96 ± 16.92; (P): 14.77 ± 24.57	Group b: (pHL) vs. (P): ND ($P = 0.112$)
Santini *et al.*[33]	60	**Mean CFA (%)** After Tx: Creon: 87.2 ± 7.7; After Tx: Pancrease: 89.2 ± 6.5 **Mean FFE (g/day)** After Tx: Creon: 11.3 ± 7.3; After Tx: Pancrease: 9.9 ± 6.5	**Mean CFA:** ND **Mean FFE: SS ($P < 0.05$)**
Williams *et al.*[34]		**Median CFA (%)**	**Median CFA**
	13	Group a: Pancrease: 91.32; Creon: 92.36	Group a: ND ($P = 0.36$)
	14	Group b: Creon: 85.07; Pancrease: 87.88	Group b: ND ($P = 0.36$)

CFA, coefficient of fat absorption; FFE, faecal fat excretion; SS, statistical significance; ND, no difference; *P* = *P*-value; *n* = no. of patients.
* If CFA is not listed in results, then the value is unknown.

head-to-head comparison of different pancreatic enzyme supplements. We overcome this limitation in our current review and these cross-over RCTs do not demonstrate consistent differences in fat malabsorption or gastrointestinal symptoms between different active treatments.

Most studies in this systematic review suffer from substantial methodological limitations that include lack of sample size to demonstrate non-inferiority, lack of a placebo controlled study arm, lack of an appropriate wash-out period between active treatments, lack of detailed reporting on adverse events and poor reporting of 'before treatment' vs. 'after treatment' fat absorption. Randomized cross-over trials can be particularly problematic because important intra-subject variability has been demonstrated during test-retest studies in the same patient.[3, 4] Proper establishment of baseline conditions would probably require standardized quantification of steatorrhoea with dye markers during 72-h stool collection and carefully monitored dietary fat intake. With the exception of one trial,[31] none of the randomized cross-over studies in the current systematic review meets FDA-recommended criteria. Furthermore, studies in this systematic review do not stratify results based on whether patients had alcohol-associated chronic pancreatitis or assess the impact of on-going alcohol use on the effectiveness of pancreatic enzyme therapy. Also, these studies cannot determine if higher dosages of pancreatic enzyme supplements are more effective for fat malabsorption.

The methodological limitations of the studies in this systematic review should be addressed in future studies. First, the presence of fat malabsorption should be established with a 72-h faecal fat collection while fat intake is being carefully monitored. This is important because many potentially eligible study patients may not actually have fat malabsorption. In fact, one of the largest ($n = 64$ patients) parallel-design RCTs[36] demonstrated that over 50% of study patients who used supplements for steatorrhoea actually did not have fat malabsorption after careful testing off supplements. Second, to ensure proper measurement of 72 faecal fat collections, dye markers should be considered to identify the beginning and end of the 72-h stool collection and dietary fat intake could be

monitored through the use of inpatient general clinical research centres. Third, almost all studies that compare supplements 'head-to-head' have insufficient sample sizes to demonstrate non-inferiority. Fourth, most RCTs are too short (<7 days) to determine if any pancreatic enzyme supplementation can significantly alter weight gain. Fifth, currently available data do not report adequate information about adverse events. Sixth, future studies should stratify results based on whether the aetiology of chronic pancreatitis appears to be alcohol-induced, secondary to CF or because of another aetiology. In addition, new data suggest that only about 40% of patients have alcoholic chronic pancreatitis and there might have been a misclassification bias in earlier studies.[37] Finally, currently available data do not confirm if escalating dosages of pancreatic enzyme supplements are routinely effective in reducing fat malabsorption, although the single, well-designed, placebo-controlled cross-over RCT[31] in this review suggests that higher dosages of enzyme supplements are better in reducing fat malabsorption.

In conclusion, our systematic review identified 12 cross-over RCTs on the efficacy and safety of pancreatic enzyme supplementation in patients with exocrine pancreatic insufficiency. None of these trials provides data on stability of enzyme preparations over 12 months, bioavailability, or batch-to-batch consistency in quantity of enzyme supplement per capsule, which is currently recommended by the FDA. The two placebo-controlled RCTs do demonstrate that enzyme supplements are superior to placebo for improvement in fat absorption, and most RCTs demonstrated that CFA was >80% with pancreatic enzyme supplements. The published trials do not demonstrate any consistent differences between different supplements with respect to improvement in fat malabsorption or adverse events. Data are inadequate to determine if escalating dosages of enzyme supplements produce incremental improvements in fat malabsorption.

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