AP&T Alimentary Pharmacology and Therapeutics

Use and perceived effectiveness of non-analgesic medical therapies for chronic pancreatitis in the United States

F. Burton*,[1], S. Alkaade*, D. Collins[†], V. Muddana[‡], A. Slivka[‡], R. E. Brand[‡], A. Gelrud[‡], P. A. Banks[§], S. Sherman[¶], M. A. Anderson[**], J. Romagnuolo[††], C. Lawrence[††], J. Baillie[‡‡], T. B. Gardner[§§], M. D. Lewis[¶¶], S. T. Amann[***], J. G. Lieb II[†††], M. O'Connell[‡], E. D. Kennard[‡‡‡], D. Yadav[‡], D. C. Whitcomb[‡] & C. E. Forsmark[†] for the North American Pancreatic Study Group[2]

*St. Louis University, St. Louis, MO, USA.
[†]University of Florida, Gainesville, FL, USA.
[‡]University of Pittsburgh, Pittsburgh, PA, USA.
[§]Brigham and Women's Hospital, Boston, MA, USA.
[¶]Indiana University Medical Center, Indianapolis, IN, USA.
[**]University of Michigan, Ann Arbor, MI, USA.
[††]Digestive Disease Center, Medical University of South Carolina, Charleston, SC, USA.
[‡‡]Duke University Medical Center, Durham, NC, USA.
[§§]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.
[¶¶]Mayo Clinic, Jacksonville, FL, USA.
[***]North Mississippi Medical Center, Tupelo, MS, USA.
[†††]University of Pennsylvania School of Medicine, Philadelphia, PA, USA.
[‡‡‡]Epidemiology Data Center, University of Pittsburgh, Pittsburgh, PA, USA.

Correspondence to:
Dr D. Yadav, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh Medical Center, 200 Lothrop Street, M2, C-Wing, Pittsburgh, PA 15213, USA.
E-mail: yadavd@upmc.edu

[1]Professor Frank Burton passed away during the final review phase of this manuscript.
[2]A full list of contributing investigators is in the Appendix.

Publication data
Submitted 19 August 2010
First decision 6 September 2010
Resubmitted 30 September 2010
Accepted 1 October 2010
EV Pub Online 29 October 2010

SUMMARY

Background
Effectiveness of medical therapies in chronic pancreatitis has been described in small studies of selected patients.

Aim
To describe frequency and perceived effectiveness of non-analgesic medical therapies in chronic pancreatitis patients evaluated at US referral centres.

Methods
Using data on 516 chronic pancreatitis patients enrolled prospectively in the NAPS2 Study, we evaluated how often medical therapies [pancreatic enzyme replacement therapy (PERT), vitamins/antioxidants (AO), octreotide, coeliac plexus block (CPB)] were utilized and considered useful by physicians.

Results
Oral PERT was commonly used (70%), more frequently in the presence of exocrine insufficiency (EI) (88% vs. 61%, $P < 0.001$) and pain (74% vs. 59%, $P < 0.002$). On multivariable analyses, predictors of PERT usage were EI (OR 5.14, 95% CI 2.87–9.18), constant (OR 3.42, 95% CI 1.93–6.04) or intermittent pain (OR 1.98, 95% CI 1.14–3.45). Efficacy of PERT was predicted only by EI (OR 2.16, 95% CI 1.36–3.42). AO were tried less often (14%) and were more effective in idiopathic and obstructive vs. alcoholic chronic pancreatitis (25% vs. 4%, $P = 0.03$). Other therapies were infrequently used (CPB – 5%, octreotide – 7%) with efficacy generally <50%.

Conclusions
Pancreatic enzyme replacement therapy is commonly utilized, but is considered useful in only subsets of chronic pancreatitis patients. Other medical therapies are used infrequently and have limited efficacy.

Aliment Pharmacol Ther 2011; **33:** 149–159

doi:10.1111/j.1365-2036.2010.04491.x

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory syndrome with multiple aetiologies, multiple complications and highly variable outcome. Pancreatic injury and inflammation lead to dysfunction and/or loss of acinar cells, duct cells and islet cells. Loss of these cells results in clinical disorders of maldigestion, reduced bicarbonate secretion and diabetes mellitus respectively. The susceptibility of these specialized cells of the pancreas to injury, the inflammatory response and adaptation to recurrent injury are also variable between individuals, with each of these processes modified by genetic, epigenetic, environmental and metabolic factors. The injured pancreas also contains inflammatory cells, pancreatic stellate cells and sensory nerves, which contribute to complications of fibrosis and pain. The deposition of calcified stones and ductal scarring or stricturing may impede the normal flow of pancreatic juice, and the loss of sufficient digestive enzymes leads to maldigestion of ingested nutrients with the clinical sequelae of bloating, cramping, abdominal pain, weight loss and malnutrition.[1, 2] The pancreatic pain syndrome is also very complex, with symptoms arising from multiple sources, including mechanical (obstructive),[3] vascular (ischaemic),[4] inflammatory,[5] neuropathic[6, 7] and possibly hyperstimulatory aetiologies.[8]

The medical treatment of symptomatic CP is difficult to standardize because of the complexity of the disease, the variability between patients and the changing characteristics of disease with progression of fibrosis or development of complications. Thus, a wide variety of empirical treatments are often tried for maldigestion and pain. The spectrum of analgesic requirements by CP patients ranges from acetaminophen and NSAIDs to powerful narcotic agents. Some patients with CP suffer from complications of duct obstruction that can be successfully treated with endoscopic therapy or surgery.[3] In addition, several non-analgesic, mechanism-targeting approaches have been introduced to help alleviate or reduce pain.

Pain from pancreatic hyperstimulation can theoretically be reduced at the duodenum by giving oral pancreatic enzyme replacement therapy (PERT) with meals to short-circuit the stimulation feedback signals by increasing protease activity in the duodenum and decreasing CCK-releasing factor.[9] A second approach is to block pancreatic stimulation with an inhibitory hormone analogue, octreotide, which activates the somatostatin receptor.[10–12] A third approach is to reduce acinar cell oxidative stress and injury by the use of vitamins and/or antioxidants (AO).[13, 14] A fourth approach is to block directly the stimulatory (vagal) and sensory nerves to the pancreas with a coeliac plexus block (CPB). The use and perceived usefulness of these targeted approaches in clinical practice within the US remain unknown.

In the present study, we used the North American Pancreatitis Study 2 (NAPS2) cohort to obtain a cross-sectional assessment of the frequency and physician-perceived effectiveness of PERT, AO, CPB and octreotide in CP patients evaluated at pancreas referral centres in the US. In addition, we evaluated differences in use and perceived effectiveness based on the aetiology of CP and on the presence or absence of exocrine insufficiency (EI) and pain. We assessed the use and efficacy of CPB with other medical therapies as CPB does not qualify as an endoscopic or surgical treatment.

METHODS

North American Pancreatitis Study 2

The study population was identified from within the NAPS2, a 20-centre, prospective, cross-sectional, observational cohort study from the US consisting of 1000 subjects with pancreatitis (recurrent acute pancreatitis = 460; CP = 540), and 695 controls conducted between 2000 and 2006.[15] The methodology of NAPS2 has been detailed previously.[15] The entry criteria for CP included definitive evidence on computed tomography scan and/or endoscopic retrograde cholangiopancreatography with the Cambridge class II or more (83%) or documentation of CP using magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS) or pancreatic histology in other enrollees.[16] Each study subject completed a detailed questionnaire on personal and family history, risk factors, symptoms and quality of life, and an additional questionnaire was completed by a physician-investigator with expertise in pancreatic diseases. The physician questionnaire contained questions relating to clinical phenotype, working diagnosis, risk factors, diagnostic and therapeutic interventions.[15]

Physician questionnaire

The information on use and effectiveness of medical therapies, presence of endocrine or EI and aetiology was obtained from responses provided by the enrolling physician in the physician questionnaire. In the section on therapies, the physician was asked, 'Which therapies were attempted, and which of these were helpful', and given specific categories for medical (including PERT, AO, CPB and octreotide), endoscopic and surgical treatments. If the treatment had been tried, the physician was

asked to select between the following choices: unchanged, worse, helpful or not sure. Information on timing of treatment before study enrolment, dosage, duration and the formulation of PERT (enteric-coated or non-enteric coated) or AO therapy was not asked. A therapy was classified as effective if the physician chose 'helpful' as a response. Patients could be counted for more than one treatment. From 540 patients in the NAPS2 cohort with CP, we excluded 24 (4%) patients in whom the enrolling physicians did not indicate a trial occurred with any of the therapeutic modalities (medical, endoscopic or surgical). The final sample size for analysis for this study was therefore 516/540 (96%) CP patients.

The enrolling physician indicated whether endocrine or EI was present and the method used to establish the diagnosis. We determined the aetiology of CP based on physician's response to the question on working diagnosis. Physicians chose one or more working diagnosis from among the following choices: alcohol, idiopathic, hereditary, cystic fibrosis, pancreas divisum, hyperlipidaemia, hypercalcaemia, trauma and others. Space was provided in the questionnaire to fill in the details. As more than one working diagnosis could be selected, we used a hierarchical algorithm to assign patients sequentially into aetiological groups. In summary, patients in whom 'alcohol' was checked exclusively for its presence or checked with other diagnoses were assigned to the 'alcohol' group; among the remaining patients, those with hereditary or cystic fibrosis diagnosis with or without another diagnoses were assigned to the 'genetic' group; among remaining patients, those with autoimmune pancreatitis diagnosis with or without another diagnoses were assigned to the 'autoimmune' group; among remaining patients, those with an obstructive aetiology with or without another diagnoses were assigned to the 'obstructive' group; among the remaining patients, those identified with a specific aetiology not included in any of the previous group were assigned to 'other aetiologies' group; all the remaining patients were then assigned to 'idiopathic' group.

Patient questionnaire

The information on demographics, and presence and pattern of pain was obtained from responses to the patient questionnaire. Patients were asked if they had abdominal pain, and to choose the pattern and severity of pain from a list consisting of five options.[15, 17, 18] Patients could characterize their pain experience as: (A) episodes of mild-to-moderate pain, usually controlled by medication; (B) constant mild-to-moderate pain usually controlled by medication; (C) usually pain-free with episodes of severe pain; (D) constant mild pain plus episodes of severe pain; and (E) constant severe pain that does not change. We classified patients based on the pattern of pain [intermittent (Group A or C) or chronic (Groups B, D, E)] and the severity of pain [mild-to-moderate (Group A or B) or severe (Groups C, D, E)].

Statistics

Descriptive analyses are presented as proportions for categorical data, and as mean ± standard deviation for continuous data. Univariate analysis for categorical data was performed using the Chi-squared or Fischer's exact test as applicable to evaluate the proportion of patients in whom individual medical therapies were tried, and, if a therapy was tried, the proportion in whom physicians believed that it was effective. Univariate comparisons for continuous variables were made using the Student's *t*-test.

Multivariable logistic regression models were used to determine independent predictors for PERT use and efficacy. Due to small sample sizes for subjects in whom other medical therapies were tried (AO, CPB and octreotide), only univariate analyses were performed for the use and efficacy of these treatments. All variables showing a *P*-value of <0.10 in the univariate analysis were chosen for initial inclusion into the regression models, except for age and gender, which were forced into the models. A backwards selection technique was used to determine significant independent predictors. For class variables, all observations were entered if one value of the class was significant. Data were examined for collinearity, but showed no significant interactions. Two-sided *P*-values <0.05 were considered significant. Data analysis was performed with R Project software (http://www.r-project.org) and SAS system version 9.2 (SAS Software Institute, Cary, NC, USA).

RESULTS

Demographics, aetiology and use of medical therapies

The demographics of the overall NAPS2 cohort have been previously reported.[15, 19] In 516/540 (96%) patients with CP in the NAPS2 cohort, the enrolling physicians indicated the utilization and effectiveness of at least one of the therapeutic modalities (medical, endoscopic or surgical). The sample size for this study therefore consisted of 516 patients. The mean age of these 516 patients was 49.2 ± 15.6 years, 52% were male and 85% were Caucasian. Alcohol was considered a single or

contributing aetiology in 44% patients, idiopathic CP in 29%, obstructive causes in 9%, whereas the remaining patients had other aetiologies. At least one of the four medical therapies was tried in 383/516 (74%) patients. In 283 (55%), only one medical therapy was utilized, while two or more than two medical therapies were used in 89/516 (17%) and 11/516 (2%) patients respectively.

Utilization of PERT

Overall, PERT was tried in 363/516 (70%) patients – by themselves in 263/363 (74%), and in combination with other medical therapies in 100/363 (26%) patients. A significant correlation was seen between PERT usage and the presence of symptoms (pain and/or EI) ($P < 0.001$). Univariate analyses comparing PERT usage in different groups are provided in Table 1. There was no difference in PERT usage based on gender, race, aetiology or presence of endocrine insufficiency. However, compared to almost 75% of patients younger than 65 years of age, PERT had been used in only ~50% of patients who were 65 years or older ($P = 0.003$). PERT usage was also more frequent in patients with EI and/or pain.

On multivariate analysis (Table 2), the strongest predictors for PERT usage were presence of EI and presence of constant pain. Independent of the presence of pain, patients with EI were approximately five times more likely to have used PERT. Similarly, independent of the presence of EI, patients with intermittent pain were twice as likely to have used PERT, and those with constant pain were over three times more likely to have used PERT, than those with no pain. Patients <65 years of age were almost three times more likely to have used PERT compared with patients 65 years or older.

Effectiveness of PERT

In this study, the physicians were not asked to specify whether PERT was effective for symptoms of maldigestion or pancreatic pain. PERT was considered by physicians as effective in 158/363 (44%) patients. The reported effectiveness ranged from 28% to 79%. Results of univariate analyses comparing the efficacy of PERT in different groups are provided in Table 1. Physicians perceived PERT to be most effective in patients with EI without pain (19/24, 79%) followed by EI with pain (49/98, 50%), and least effective in either pain category without EI. In the univariate analysis, PERT was also perceived as more effective in patients with endocrine insufficiency, younger patients and patients without abdominal pain. The effectiveness of PERT appeared to be similar among patients in the three common aetiological groups.

On multivariate analysis, the only significant predictor for effectiveness of PERT was the presence of EI (Table 3). PERT was considered twice as effective in patients with EI vs. those with no EI. The other significant predictors for effectiveness of PERT on univariate analyses were no longer significant in multivariate analyses.

Utilization and efficacy of other medical therapies

In contrast to PERT, other therapies were used infrequently in patients with CP: the second most commonly used modality was AO, in 71/516 (14%), followed by CPB in 34/516 (7%) and octreotide in 28/516 (5%) patients. Similar to PERT, the usage of other therapies correlated with the presence of symptoms ($P < 0.01$). Results of univariate analyses comparing the usage and efficacy of AO, CPB and octreotide in different groups are provided in Table 4. Although no significant differences were seen in the proportion of patients in whom individual therapies were used, largely due to small sample sizes, interesting trends were noted. Not surprisingly, CPB was used more often in patients who reported constant or severe pain, and in patients with alcohol or idiopathic aetiologies, and was used less often in those aged more than 65 years. Octreotide was tried more often in patients who reported pain, had no EI and had obstructive or idiopathic aetiologies.

As indicated in Table 4, the efficacy of AO was generally considered poor, with the best efficacy of ~25% in patients who were young, and in those who had obstructive and idiopathic rather than alcoholic aetiologies ($P = 0.03$). When used, the efficacy of CPB and octreotide was highly variable, ranging from 20% to 100%.

Subgroup analyses

The results of subgroup analyses by gender were generally similar to the overall analyses (data not shown).

DISCUSSION

The present study reports on the use and perceived effectiveness of medical therapies that are used for treating pain in CP by targeting possible pain-generating mechanisms. A number of observations from this study confirm and strengthen previous observations, and add perspective to a complex condition. The primary finding was that PERT were widely used, whereas the use of AO, CPB and octreotide in clinical practice in the US is relatively infrequent. In this group, more than half of the patients treated did not have EI. As expected, PERT were very helpful in treating patients with EI, although physicians still considered it helpful in one-third of subjects

Table 1 | Univariate associations for the use and efficacy of PERT in chronic pancreatitis patients in the North American Pancreatitis Study 2

Attribute	% in sample (N = 516)	% enzymes tried	P-value*	% enzymes effective	P-value†
Gender					
Male	52	68	0.29	42	0.44
Female	49	73		46	
Age					
<35	18	77	**0.003**	39	0.36
35–44	21	79		38	
45–64	44	70		47	
65+	16	52		50	
Race					
White	85	69	0.27	44	0.63
Other	15	76		41	
Aetiology					
Alcohol	44	70	0.68	47	**0.04**
Obstructive	9	78		49	
Idiopathic	29	69		47	
Other	19	71		28	
Pain presence					
Yes	77	74	**0.002**	40	**0.015**
No	23	59		56	
Pain pattern					
No pain	23	59	**<0.0001**	56	0.05
Constant	43	81		40	
Intermittent	34	65		41	
Pain severity					
No pain	23	59	**0.005**	56	**0.04**
Mild-moderate	17	69		36	
Severe	60	75		42	
Exocrine insufficiency (n = 480)					
Yes	29	88	**<0.0001**	56	**0.0005**
No	71	61		36	
Patient group (n = 480)					
Pain (+), EI (−)	57	66	**<0.001**	36	**<0.001**
Pain (+), EI (+)	23	90		50	
Pain (−), EI (+)	6	80		79	
Pain (−), EI (−)	14	39		35	
Endocrine insufficiency (n = 480)					
Yes	26	69	0.80	55	**0.008**
No	74	70		39	

Values in bold denote statistically significant P-values.

EI, exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; '% in sample', proportion of overall study sample (i.e. patients in whom any medical, endoscopic or surgical treatment modality was utilized, n = 516); '% enzymes tried', proportion of individual subgroup in whom PERT was tried; '% enzymes effective', among patients receiving PERT, proportion in whom they were considered to be effective.

* P-value – differences in proportion for utilization of enzymes.

† P-value – differences in proportion for effectiveness of enzymes.

Table 2 | Independent predictors of PERT use in chronic pancreatitis patients in the North American Pancreatitis Study 2 based on multivariate analyses

Variable	Odds ratio	95% confidence interval
Gender: male vs. female	0.86	0.56–1.32
Age		
<35 vs. 35–44	1.03	0.50–2.09
45–64 vs. 35–44	0.62	0.34 –1.10
65+ vs. 35–44	0.35	0.18–0.71
Pain		
Constant vs. no pain	3.42	1.93– 6.04
Intermittent vs. no pain	1.98	1.14–3.45
Exocrine insufficiency	5.14	2.87–9.18

Gender and age were forced into the model. Other variables entered into the model were severity of pain, endocrine insufficiency, aetiology and race. Interaction between pain and exocrine insufficiency was not significant.

PERT, pancreatic enzyme replacement therapy.

Table 3 | Independent predictors of PERT efficacy in chronic pancreatitis patients in the North American Pancreatitis Study 2 based on multivariate analyses

Variable	Odds ratio	95% confidence interval
Gender: male vs. female	0.83	0.53–1.29
Age		
<35 vs. 35–44	1.16	0.59–2.31
45–64 vs. 35–44	1.51	0.85–2.69
65+ vs. 35–44	1.67	0.76–3.66
Exocrine insufficiency	2.16	1.36–3.42

Gender and age were forced into the model. Other variables entered into the model were frequency of pain, severity of pain, endocrine insufficiency and race.

PERT, pancreatic enzyme replacement therapy

with pain, but without EI. AO appeared to be most useful in patients with non-alcohol-related CP, although it was ranked as the least helpful of the three medications under all conditions. Octreotide appeared to be most helpful treatment in patients with alcohol-related CP.

The present study has major strengths and limitations. The strengths include its multi-centre approach, the use of pancreatic experts for phenotyping and the use of best available tools for this study. The primary limitation is that this was a single visit analysis of a large, cross-sectional cohort of CP patients evaluated at expert centres in the US, and therefore reflects the therapies tried until the time of enrolment and may not fully reflect the practice of the expert consultant. Secondly, the indication(s) for prescribing medical therapies were unknown. Third, the specific dosage or formulation of PERT (enteric- or non-enteric coated) or AO was not evaluated. Fourth, as in all observational studies, it was not possible to standardize treatment dose or duration, the measures of effect, and/or end point(s) and there were no placebo controls limiting our ability to address potential physician bias. There may also be a referral bias of patients from the community to referral centres who failed standard therapies. The study was also limited by small number of patients in whom AO, octreotide and CPB were attempted. Furthermore, comparison of subjects by presence and type of pain was based on the time of enrolment, and not necessarily at the time of attempted treatment. These factors limit the analysis of the data set to observations of the use of medical therapies in the community, and their perceived usefulness under typical practice conditions. However, it provides very important information about current use of these therapies in the US, and may be very useful in determining feasibility and power in future prospective studies.

Pancreatic enzyme supplements

Pancreatic enzyme replacement therapy is used both for treating maldigestion and for treating pain. There is no controversy as to whether PERT is both useful and medically necessary in the treatment of patients with EI (e.g. cystic fibrosis, advanced CP and pancreatic resection). Defining the physiological threshold for pancreatic insufficiency is complicated by poorly defined or inconsistent endpoints (e.g. biochemical measures of protein nutrition,[20] faecal elastase concentrations[21, 22] and steatorrhea[23]), by the varying nutritional needs and meal sizes of individual patients. Furthermore, the threshold for prescribing PERT by the managing physician is also variable, often depending on the signs and symptoms of maldigestion (e.g. unexplained weight loss, bloating, abdominal cramping, diarrhoea, steatorrhoea) and patient complaints rather than relying on measures of pancreatic exocrine function and nutritional needs. The findings of the present study strongly support the role of PERT in the treatment of patients with EI with and without pain.

Isaksson and Ihse[24] reported a double-blinded, placebo-controlled, randomized trial of non-enteric-coated PERT in patients with CP for the treatment of pain.

Table 4 | Univariate associations for the use and efficacy of vitamins and antioxidants, coeliac plexus block and octreotide in chronic pancreatitis patients in the North American Pancreatitis Study 2

Attribute	% in sample (N = 516)	Vitamins/antioxidants		Coeliac plexus block		Octreotide	
		% Tried	% Effective	% Tried	% Effective	% Tried	% Effective
Gender							
Male	52	16	16	6	40	5	64
Female	48	11	11	8	37	6	43
Age							*
<35	18	17	25	6	67	5	20
35–44	21	12	8	9	40	6	57
45–64	44	14	16	7	25	6	77
65+	16	13	0	2	50	4	0
Race							
White	85	14	15	6	39	5	57
Other	15	13	10	8	33	6	40
Aetiology							
Alcohol	44	12	4	7	40	4	75
Obstructive	9	16	29	2	100	4	50
Idiopathic	29	17	24	9	36	7	55
Other	19	12	9	4	25	7	29
Pain presence							
Yes	77	13	11	8	40	6	56
No	23	15	22	3	25	3	33
Pain pattern							
No pain	23	15	22	3	25	3	50
Constant	43	14	13	13	36	7	60
Intermittent	34	13	9	1	100	6	33
Pain severity				*			
No pain	23	15	22	3	25	3	33
Mild–moderate	17	11	10	5	75	7	33
Severe	60	14	12	8	35	6	63
Exocrine insufficiency (n = 480)						*	
Yes	29	16	18	9	25	1	54
No	71	12	7	6	47	7	100
Endocrine insufficiency (n = 480)							
Yes	26	13	12	8	30	4	60
No	74	13	10	6	46	6	55

'% in sample', proportion of overall study sample (i.e. patients in whom any medical, endoscopic or surgical treatment modality was utilized, n = 516); '% tried', proportion of individual subgroup in whom treatment was tried; '% effective', among patients who received treatment, proportion in whom it was considered to be effective.

* $P < 0.05$.

Fifteen of 19 (79%) patients treated with a pancreatic enzyme supplement during the 1-week treatment period had an average pain reduction of 30%.[24] Four additional studies were subsequently published, including one positive study using non-enteric-coated enzymes[25] and three negative studies using enteric-coated enzymes,[26–28] but the individual, and combined results[9] failed to demonstrate significant benefit over placebo. However, an argument has been made that this approach is effective in minimal change, or 'small duct' CP, and requires the use

of high potency, uncoated pancreatic enzymes,[12] preferably with acid suppression.[29] After reviewing this literature, Brown *et al.*[9] concluded that what is needed is an adequately powered study, with emphasis on minimizing patient and drug heterogeneity and use of enzyme preparations that provide adequate concentrations of proteases in the duodenum. The present study does suggest that many physicians treating CP patients with pain, but without EI, have used PERT. There appears to be perceived usefulness in treating patients without EI, and this effect appeared to be similar in patients with (36%) and without pain (35%). Due to the cross-sectional design, it is unclear if PERT were used in the latter group to treat symptoms of maldigestion or pain without clinically obvious EI or whether this apparent improvement in symptoms reflects of placebo effect. However, in patients with pain, PERT was judged to be more useful in patients with EI (50%) than in those with pain alone (36%). Thus, PERT appear to have an important role in the treatment of CP patients, but the effect on pain is smaller than on EI alone (79%). The possibility that PERT are effective in a special subset of patients with 'small duct' disease,[12] or hereditary pancreatitis[30] has not been excluded. Whether PERT is helpful in patients with pain alone needs to be addressed in prospective trials with appropriate study design and follow-up.

Vitamins/antioxidants

A nonsignificant result for perceived effectiveness between aetiologies overall could be due to small sample sizes (resulting in a type II error), which limits our ability to draw definite conclusions. However, when comparing effectiveness of AO in subgroup analyses, physicians did report a significantly higher effectiveness for AO in patients with idiopathic and obstructive aetiologies ($P = 0.03$) when compared with alcohol-related CP (Table 4).

While early trials on the use of a single AO were disappointing,[13] two recent studies suggest that combination AO may be useful for the treatment of pain in a subset of patients with CP.[14, 31] In the study by Kirk *et al.*,[31] 36 patients with CP were recruited, but only 23 patients completed the study. Data from pain diaries were disregarded and the results represented the data from the SF-36 questionnaires completed by patients who completed the study. This study showed that a combination AO improved abdominal pain and several aspects of quality of life in patients with CP. It is hard to compare the results of this study to ours because the aetiology of CP was not specified.[31] On the other hand, a more recent study from India evaluated AO in 127 patients, most of whom had idiopathic CP.[14] It showed that combination AO (much higher doses compared with those in the previous study) was effective in reducing the number of painful days per month, requirement of analgesics, need for hospitalization and the percentage of patients who became pain-free. However, significant postrandomization dropouts and other methodological issues limit the strength of the conclusion of this trial.[32] Our study suggests that providers considered AO to be more helpful in obstructive and idiopathic CP than alcoholic CP, but the 25% effectiveness rate is similar to placebo in many randomized trials of abdominal pain.

Coeliac plexus block

The utility of CPB for pancreatic pain was first recognized in patients with pancreatic cancer.[33] Wiersema and Wiersema[34] first demonstrated that CPB could be done using EUS, and Gress *et al.*[35] went on to demonstrate that it could provide significant improvement in pain scores with reduction in pain medication usage in half of treated patients. In the current study, CPB was used in 6% of men and 8% of women. Although the numbers are small, it appears that this therapy was used more often in patients with constant pain, but was more effective in those with mild-moderate pain.

Octreotide

Octreotide has been evaluated for pain in CP mainly when other medical therapies have failed. Octreotide is a potent inhibitor of pancreatic exocrine secretion[36] and may work through several mechanisms,[37] including a direct effect[38] and inhibiting neural stimulation.[39] It may have anti-inflammatory properties[40] and reduce sphincter of Oddi pressure.[41]

A few small studies published in abstract form[42–44]or as full manuscripts[11, 45, 46] have reported on the efficacy of octerotide in painful CP. In 1993, in a placebo-controlled, double-blind, dose-finding study, octreotide 200 μg given three times a day was reported to be more effective than placebo in reducing pain.[43] The benefit was more prominent in the subgroup of patients with constant daily pain.[43] An open label extension published in 1994[44]suggested that by 6 weeks, 50% of patients still had continued pain relief for 6 weeks.[44] In contrast, a small German study showed no difference in pain control or analgesic use during a short-term (3 days) double-blind cross-over study.[11] In 2009, a study from the US compared long-acting octreotide with short-acting octreotide in the treatment of painful CP in a small open-label, unblinded pilot study.[46] Lieb *et al.*[46] reported that in seven patients with

severe CP and constant daily pain, once-monthly depo-octreotide (Octreotide LAR; Novartis, East Hanover, NJ, USA), 60 mg intramuscular injection, may be a useful substitute for short-acting octreotide that must be injected three times a day. We found that octreotide was seldom used in the clinical practice of gastroenterologists at the NAPS2 sites, but was judged by the provider to be of some benefit in a few patients.

CONCLUSION

The current report provides a cross-sectional perspective on the current use of non-analgesic medical therapies in CP in the US. The major finding is that PERT is the most commonly used treatment in this class, and provides a significant perceived benefit not only for EI but also for pain in a subset of patients, especially those with EI. The second finding is that AO do appear to be useful in patients with non-alcohol-related CP, but not in alcoholic CP. Thirdly, CPB and octreotide treatment may be useful in a small subset of patients, but the limited use of these therapies limits any further interpretations.

ACKNOWLEDGEMENTS

Professor Frank Burton, MD, passed away on 2 August 2010 during the final review phase of this manuscript which he had developed from the NAPS2 data set and was the lead investigator.

Dr Burton was Professor of Internal Medicine at Saint Louis University School of Medicine and staff physician at the St. Louis Department of Veterans Affairs Medical Center. Dr Burton had a distinguished career as a leading physician-scientist with numerous publications and national presentations. Since 2001 he has been recognized among "Best Doctors in America". Dr Burton was one of the first and most productive members of the Midwest Multicenter Pancreatic Study Group and the North American Pancreas Study 2 (NAPS2) who, over a decade, generated the cohort on which the data in the above paper was derived. Members of the NAPS2 research group fondly remember Frank for his great "can do" attitude, his insights into improving pancreatic imaging, his contagious laugh, his enthusiasm for teaching and his dedication to mentoring. He was also the model family man, with a large, loving and successful family. Indeed, he will also be remembered for bringing his wife and/or children to meetings to meet his colleagues and to spend irreplaceable time with them. The outpouring of gratitude and respect by patients, friends, colleagues and his extended family attests to the true greatness of this man. He will be greatly missed.

Declaration of personal interests: All authors had access to the data, had a role in writing the manuscript, and met the authorship criteria. The authors thank the following individuals from the Department of Medicine, University of Pittsburgh, Pittsburgh, PA – Kathy Bauer, RN, Beth Elinoff, RN, MPH for help in patient recruitment, Emil Bauer and Pat Schuetz for data entry and data management. *Declaration of funding interests*: Support for the NAPS2 project was from NIDDK DK61451 (DCW). Dr Muddana and O'Connell were supported, in part, through an investigator-initiated study funded by Abbott Pharmaceuticals (DCW).

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APPENDIX

The following physicians and centres also contributed patients to the NAPS2 study: Mary E. Money, Washington County Hospital, Hagerstown, MD; Robert H. Hawes, MD; Peter B. Cotton, MD, Digestive Disease Center, Medical University of South Carolina, Charleston, SC; James DiSario, MD, Department of Medicine, University of Utah Health Science Center, Salt Lake City, UT; Simon K. Lo, MD, Department of Medicine, Cedars-Sinai Medical Center, University of California, Los Angeles; Mark T. DeMeo, MD, Department of Medicine, Rush University Medical Center, Chicago, IL; William M. Steinberg MD, Washington Hospital Center, Washington, DC; Michael L. Kochman, MD, Department of Medicine, University of Pennsylvania, Philadelphia, PA; Babak Etemad, MD, Department of Gastroenterology and Hepatology, Ochsner Medical Center, New Orleans, LA.