Is Timing of Medical Therapy Related to Outcome in Painful Chronic Pancreatitis?

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Objectives: The authors investigated if timing of medical treatment is associated with the analgesic effect of pregabalin or placebo in patients with chronic pancreatitis (CP).

Methods: Sixty-four patients received pregabalin (150–300 mg twice a day) or matching placebo for 3 consecutive weeks. Responders to treatment were defined as patients with a reduction in clinical pain scores of 30% or greater. Factors associated with timing of pain treatment (ie, duration of CP and opioid usage) were collected at baseline. In addition, other factors that potentially could influence outcome (eg, clinical pain scores prior to study medication, diabetes, and exocrine pancreatic insufficiency) were also included. Conventional groupwise logistic regression and analysis on the individual patient level with a machine learning technique were used to predict treatment response.

Results: In the conventional statistical analysis duration of CP (odds ratio, 0.9; 95% confidence interval, 0.8–1.1; $P = 0.3$) and opioid treatment (odds ratio, 1.0; 95% confidence interval, 0.9–1.1; $P = 0.6$) were not associated with pain relief. In addition, none of the supplementary factors were associated with treatment response (all $P > 0.1$). Likewise, in the individual patient-level analysis, none of the included variables reached classification accuracies greater than chance level (all $P > 0.1$).

Conclusions: Pregabalin can be added as adjuvant analgesic at any time point during the disease course of CP.

Key Words: chronic pancreatitis, pain, prediction, timing of therapy, treatment

(*Pancreas* 2016;45: 381–387)

Chronic pancreatitis (CP) is a fibroinflammatory disease of the pancreas that causes permanent damage to the pancreatic tissue accompanied by fibrosis.[1] Most patients report abdominal pain during their disease course and eventually develop exocrine and endocrine pancreatic insufficiency along with more advanced disease stages.[2] The chronic pain syndrome is often worsened by acute pain exacerbations, which frequently lead to hospitalizations, lost ability to work, and significantly reduced quality of life. No universal accepted theory of the origin of CP pain exists, and in most patients, the pain etiology is complex and multifactorial.[3] Consequently, pain management in CP is difficult and frequently comprises a long and painful trial-and-error process before an appropriate therapy is found for the individual patient.

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Received for publication December 1, 2014; accepted June 11, 2015.

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The Danish Council for Strategic Research, The Danish Agency for Science, Technology and Innovation funded this study.

The authors declare no conflict of interest.

The complex pain etiology of CP and wide variability in treatment outcome make it important to identify factors linked to outcomes of pain treatment in individual patients. In a previous study from our group, quantitative sensory testing was used to investigate pain processing in CP patients and its association to outcome of analgesic therapy (ie, pregabalin treatment; a gabapentinoid mostly used for treatment of neurogenic pain).[4] Interestingly, a link between sensitization of the central nervous system and analgesic efficacy of pregabalin was evident. Hence, the presence of central sensitization discriminated responders to pregabalin treatment from nonresponders with an accuracy of 84%.[4] Sensory testing, however, is not widely available in the clinical setting, and this may limit the dissemination of the findings into clinical practice. Consequently, simple and clinically available predictors of treatment responses are highly needed in the setting of pain treatment and CP.

In a recent retrospective study of CP patients undergoing surgery for intractable pain, Ali and colleagues[5] investigated the association between timing of surgery and surgical outcome. They identified longer disease duration, preoperative opioid consumption, and frequent endoscopic procedures to be associated with a negative clinical outcome. The authors suggested that longstanding CP resulted in chronification of pain and thus made patients at more advanced disease stages less responsive to surgery.[5] This is compatible with findings from another study where sensitization of central pain pathways was associated with the disease stage of CP.[6] However, in contrast to surgery, the relationship between timing and outcome of medical therapy has never been investigated in CP.

In the present study, we investigate the link between timing and outcome of medical pain therapy in patients with CP. A previously published randomized, placebo-controlled clinical trial of pregabalin in patients with painful CP provided the opportunity to test such a putative association.[7] However, in contrast to the original report, which was based on conventional group-level analysis of the primary efficacy parameter (pain relief), the current study aimed to identify parameters associated with pain relief in the individual patient. We hypothesized pregabalin to be less efficacious in CP patients characterized by long disease duration and high opioid consumption prior to pregabalin treatment. The aim of this study was to test this hypothesis by testing the ability of disease duration and opioid consumption to predict pregabalin efficacy in patients with painful CP. In addition, other factors that potentially influence the outcome of pain treatment were also included as supplementary factors. These were sex, age, etiology of CP, continued alcohol consumption and smoking, clinical pain score and its variability, previous surgery for CP, exocrine pancreatic insufficiency, and diabetes.

METHODS

Study Population

Patients were recruited from a placebo-controlled, randomized controlled trial of pregabalin for painful CP conducted in

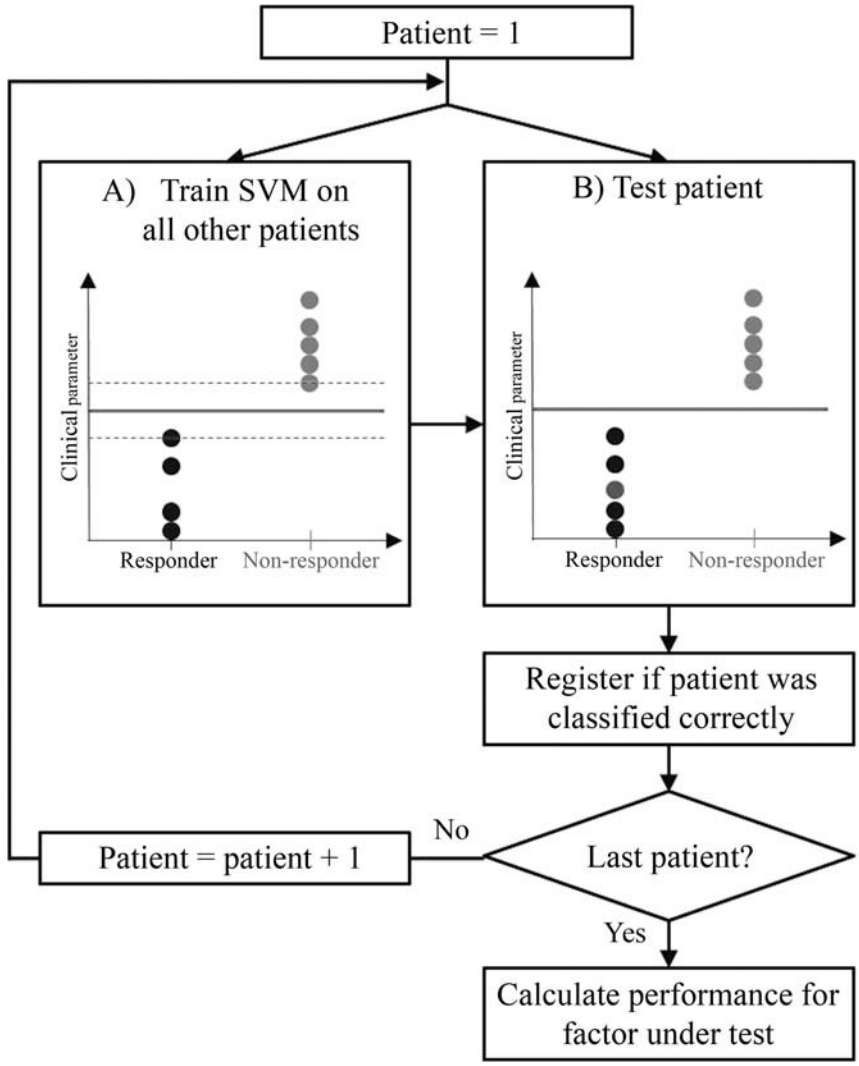

FIGURE 1. A schematic illustration of the SVM analysis. For simplicity, only 5 patients in each group are shown in a perfectly separable scenario. The algorithm was tested independently for each of the clinical parameters and with patients tested in a leave-one-out (LOU) scenario. The basic principle of the SVM is to calculate a decision boundary to discriminate responders and nonresponders (A). The decision boundary (solid black line) is calculated by maximizing the margin from the boundary to each of the 2 conditions (the 2 dotted black lines). In the LOU strategy, each patient is one-by-one discarded from the calculation of the boundary and used only for test (dark grey circle) to validate if the correct response could be predicted (B). After testing each patient, the performance is calculated as the ratio of correctly classified patients divided by the total number of patients to obtain a single score of the predictive power for each clinical parameter.

Denmark (Department of Gastroenterology and Hepatology, Aalborg University Hospital) and The Netherlands (Department of Surgery, Radboud University Medical Center, Nijmegen).[7] The present study investigates the link between baseline demographic and clinical parameters and analgesic efficacy of pregabalin or placebo.

Key inclusion criteria were a diagnosis of CP based on The Mayo Clinic Diagnostic Criteria and the presence of chronic abdominal pain (ie, pain ≥3 days per week in at least 3 months).[2] Patients taking concomitant analgesic medication were allowed to enter the study if they were expected to stay on a stable regimen during the trial. The prior analgesic regimen was continued throughout the trial. Patients with an obstructive component of pain were treated by endotherapy or surgery according to local clinical practice prior to enrolment, and patients with painful conditions other than CP were excluded from the study. All patients provided written informed consent prior to investigation. The responsible ethical committees in both countries approved the study.

Study Design and Treatment

The study was an investigator-initiated, double-blind, placebo-controlled, parallel-group study of pregabalin titrated to analgesic effect and tolerability. It consisted of a baseline assessment of clinical pain scores for 1 week followed by a 3-week period of pregabalin or placebo treatment. A detailed description of the study design and study procedures is reported in Olesen et al.[7] In brief, patients received escalating doses of pregabalin (300–600 mg/d) or matching placebo capsules. Daily dosages were split into 2 equivalent doses, one administered in the morning and one in the evening. If the patient experienced unacceptable adverse effects, a single downward dose titration was allowed, after which

TABLE 1. Pregabalin-Treated Patients

Factor		Responders (n = 16)	Nonresponders (n = 15)	OR (95% CI)	*P*
Timing of pregabalin treatment	Duration of CP, y	9.2 ± 7.0	11.7 ± 5.7	0.9 (0.8–1.1)	0.3
	Opioid equivalents (10 mg)	9.0 ± 9.6	10.8 ± 10.6	1.0 (0.9–1.1)	0.6
Supplementary factors	Male sex, n (%)	8 (50)	9 (60)	0.7 (0.2–2.8)	0.6
	Age, y	57.9 ± 8.8	51.7 ± 11.8	1.1 (0.9–1.2)	0.1
	Alcoholic etiology, n (%)	9 (56)	6 (40)	1.9 (0.5–8.1)	0.4
	Continued alcohol consumption, n (%)	6 (38)	6 (40)	0.6 (0.1–2.7)	0.5
	Continued smoking, n (%)	12 (75)	10 (67)	1.5 (0.3–7.1)	0.6
	Clinical pain score (VAS)	4.1 ± 2.1	4.2 ± 2.4	1.0 (0.7–1.4)	0.9
	Variability of clinical pain score (CV)	0.4 ± 0.4	0.4 ± 0.4	1.1 (0.2–6.3)	0.9
	Previous surgery for CP, n (%)	3 (19)	3 (20)	0.9 (0.2–5.5)	0.9
	Exocrine pancreatic insufficiency, n (%)	7 (44)	6 (40)	1.2 (0.3–4.9)	0.8
	Diabetes, n (%)	7 (44)	3 (20)	3.1 (0.6–15.5)	0.2

the patient remained on that final dosage during the remainder of the study period. A minimum end dose of 300 mg/d was required; otherwise, the subject was withdrawn from the study.

Study Outcome

A daily pain score (ie, the intensity of pain for the last 24 hours) was collected by a pain diary based on a visual analog scale (VAS), where 0 = no pain and 10 = worst pain imaginable. The baseline pain score was calculated as the average daily pain score during the week prior to randomization (ie, no study medication), and the response to study medication was calculated as the average daily pain score during the last week of treatment. For the present study, a post hoc–defined clinical end point was used to stratify patients as responders or nonresponders to treatment (pregabalin or placebo). Hence, responders were defined as patients with a reduction in clinical pain score of 30% or more after 3 weeks of treatment compared with baseline recordings.[8,9]

Factors Associated With Treatment Outcome

Timing of Medical Therapy

Information on duration of CP and the use of pain medications including opioid equivalents was obtained from clinical interview at the baseline visit and through review of the individual patient records. These factors were previously shown to predict outcome of surgery for painful CP.[5]

Supplementary Factors

The following factors were included as supplementary features (not related to timing) in the prediction analysis: patient demographics (sex and age), etiology of CP, smoking and drinking habits, and diabetes. In addition, the baseline pain score (VAS) and its coefficient of variation (CV) were included as supplementary predictors of outcome as was exocrine pancreatic insufficiency. The latter was detected using the fecal elastase-1 concentration test, 72-hour fecal fat collection, and the ^{13}C-mixed triglyceride breath test according to the preferred local clinical practice.

Prediction Algorithm and Statistical Analysis

The prediction algorithm comprised a 2-step procedure. First, the predefined factors were analyzed using logistic regression models to determine the different factors capability to predict treatment outcome (ie, group-level analysis). The results of this analysis are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). Next, a linear support vector machine (SVM) was applied to explore the predefined factors predictive power of pregabalin and placebo treatment outcome for the individual patients (ie, individual-level analysis). Support vector machine is a machine learning technique based on statistical learning, which has been used in several previous studies, including a study from our group investigating the capability of sensory testing to predict treatment outcome in CP.[4] The basic principle of the SVM is to calculate an optimal decision boundary between 2 conditions (in our case responders and nonresponders) to obtain

TABLE 2. Placebo-Treated Patients

Factor		Responders (n = 12)	Nonresponders (n = 17)	OR (95% CI)	*P*
Timing of placebo treatment	Duration of CP, y	14.6 ± 9.7	8.1 ± 3.7	1.2 (1.0–1.4)	0.05
	Opioid equivalents (10 mg)	7.7 ± 7.7	10.8 ± 18.1	1.0 (0.9–1.0)	0.6
Supplementary factors	Male sex, n (%)	9 (75)	10 (59)	2.1 (0.4–10.7)	0.4
	Age, y	59.6 ± 9.5	56.3 ± 13.1	1.0 (0.9–1.1)	0.4
	Alcoholic etiology, n (%)	7 (58)	9 (75)	1.2 (0.3–5.5)	0.8
	Continued alcohol consumption, n (%)	2 (17)	4 (24)	0.6 (0.1–4.0)	0.6
	Continued smoking, n (%)	10 (83)	13 (76)	1.5 (0.2–10.2)	0.7
	Clinical pain score (VAS)	3.7 ± 2.1	4.0 ± 2.2	0.9 (0.7–1.3)	0.7
	Variability of clinical pain score (CV)	0.3 ± 0.3	0.3 ± 0.3	1.6 (0.1–22.8)	0.7
	Previous surgery for CP, n (%)	2 (17)	1 (6)	3.2 (0.3–40.1)	0.4
	Exocrine pancreatic insufficiency, n (%)	6 (50)	9 (53)	0.9 (0.2–3.9)	0.9
	Diabetes, n (%)	6 (50)	4 (24)	3.3 (0.7–16.0)	0.1

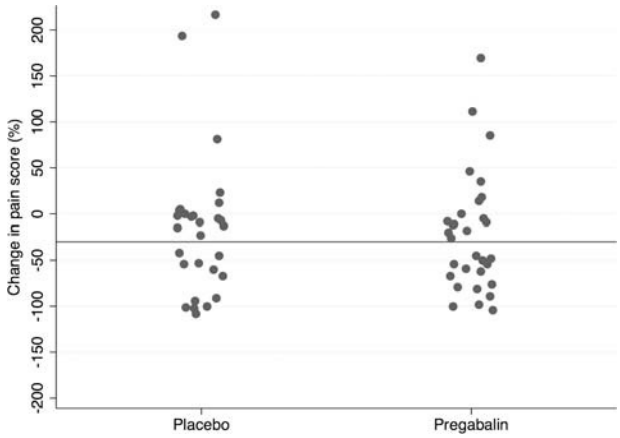

FIGURE 2. Individual patient outcomes to pregabalin or placebo treatment. A treatment responder was defined as a patient with a reduction in clinical pain score of 30% or more after 3 weeks of treatment compared with baseline recordings. There was no significant difference in the frequency of responders between pregabalin-treated (52%) and placebo-treated (42%) patients ($P = 0.5$).

maximum discrimination between the conditions.[10,11] In addition, if 1 patient is excluded from the calculation of the decision rule, it is possible to test the predicted response by this patient in a cross-validation scenario. If all patients are tested by this leave-one-out procedure, the predictive power for each independent factor on an individual basis can be assessed (see Fig. 1 for further explanation). The significance of the SVM discrimination for the different factors was analyzed by a χ^2 test or a Fisher exact test as appropriate. In case the predictive factor was a binary variable, these tests were used without preceding SVM analysis.

This study was a secondary analysis of a randomized clinical trial powered for a pre hoc–defined clinical primary end point, that is, change in clinical pain score. Consequently, a power calculation for the post hoc–defined clinical end point used in this study (ie, frequency of treatment responders) was not performed. All data were analyzed according to the per-protocol principle. Data are presented as means ± SD unless otherwise indicated. $P < 0.05$ was considered statistical significant. The analyses of supplementary predictive factors were adjusted by Bonferroni correction to account for multiple comparisons. The software package STATA version 11.2 (StataCorp LP, College Station, Tex) was used for statistical calculations. The utilized SVM was an in-house implementation in Matlab (Matlab 2012; The Mathworks Inc, Natick, Mass).

RESULTS

Sixty-four patients with painful CP were randomized to receive pregabalin or matching placebo. Detailed information on patient enrolment and randomization is provided by Olesen et al.[7] Four patients had incomplete pain diary data at follow-up and were excluded from further analysis, as they could not be classified as responders or nonresponders. Hence, 60 patients were included in the per-protocol analysis. In the placebo-treated group, the etiologies of CP were toxic (alcoholic) for 16 patients (55%), idiopathic for 10 patients (34%), and obstructive for 2 patients (7%), and a single patient (3%) had recurrent acute pancreatitis. In the pregabalin-treated group, 15 patients (48%) had toxic CP, 10 patients (32%) had idiopathic CP, 2 patients (6%) had genetic CP, 1 patient (3%) had autoimmune pancreatitis, 2 patients (6%) had recurrent acute pancreatitis, and 1 patient (3%) had an obstructive etiology. No significant difference was seen in the frequency distribution of etiologies between groups ($P = 0.8$). Clinical and demographic characteristics of patients are provided in Table 1 (pregabalin group) and Table 2 (placebo group). Pregabalin- and placebo-treated patients (data reported in Olesen et al[7]), as well as responders and nonresponders in the 2 treatment groups (Tables 1 and 2), were comparable with respect to demographic characteristics, clinical data, and clinical pain scores (all $P > 0.05$).

Response to Pregabalin and Placebo Treatment

Sixteen (52%) of 31 patients were classified as responders in the pregabalin-treated group compared with 12 (42%) of 29 patients in the placebo group ($P = 0.5$; Fig. 2). A complete analysis of the clinical end points was previously reported.[7]

Prediction of Pregabalin Response

First, the prespecified factors were tested for their ability to predict pain relief (ie, group-level analysis). Duration of CP (OR, 0.9; 95% CI, 0.8–1.1; $P = 0.3$) and opioid consumption prior to treatment (OR, 1.0; 95% CI, 0.9–1.1; $P = 0.6$) were not associated with pain relief. In addition, none of the supplementary factors were associated with pregabalin responses (all $P > 0.1$; Table 1). Next, individual patient data were used to train the SVM to determine the optimal thresholds to separate pregabalin responders from nonresponders (ie, individual-level analysis). The optimal separation threshold for duration of CP was 134 months. When testing the predictive power of this factor, only 15 of 31 patients were correctly classified, which corresponded to an accuracy of 48.4% ($P = 0.8$; Fig. 3). Similar findings were evident for opioid consumption, where the optimal separation threshold was 102 mg morphine equivalents per day. Once again, when testing the predictive power in a leave-one-out scenario, the correct treatment response was identified in only 15 of 31 patients, corresponding to an accuracy of 48.4% ($P = 0.8$; Fig. 3). Classification accuracies for the supplementary factors are reported in Table 3.

TABLE 3. Classification Accuracies of Supplementary Predictive Factors

	Pregabalin (n = 31)		Placebo (n = 29)	
Factor	Classification Accuracy, %	P*	Classification Accuracy, %	P*
Male sex	45.2	0.6	55.2	0.4
Age	51.6	0.8	41.4	0.4
Alcoholic etiology	48.4	0.4	51.7	0.8
Continued alcohol consumption	58.1	0.9	51.7	0.7
Continued smoking	58.1	0.5	48.3	0.7
Clinical pain score	48.4	0.9	55.2	0.6
Variability of clinical pain score	54.8	0.6	41.4	0.2
Previous surgery for CP	48.4	0.9	62.1	0.4
Exocrine pancreatic insufficiency	51.6	0.8	48.3	0.9
Diabetes	61.3	0.2	65.5	0.1

*Compared with chance level.

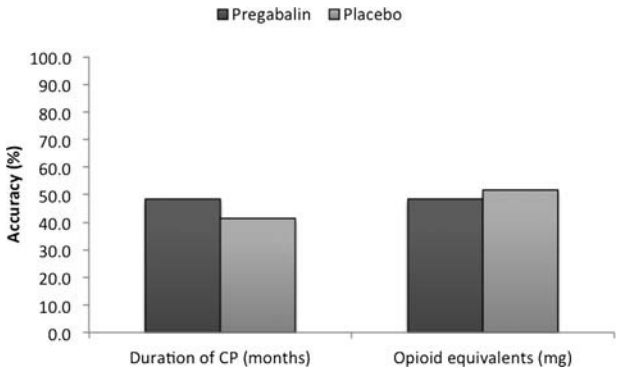

FIGURE 3. Predictive power of treatment outcome for factors associated with timing of treatment. The SVM was used to screen disease duration and opioid consumption for their predictive power of analgesic response to pregabalin and placebo treatments. None of the factors reached classification accuracies greater than chance level (71.0%).

As for the factors related to timing of treatment, none of these factors reached classification accuracies greater than chance level (all $P \geq 0.2$).

Prediction of Placebo Response

A similar approach as for the pregabalin group was used to test the prespecified factors in the placebo group for their capability to predict placebo-induced pain relief. The corresponding ORs are provided in Table 2. None of the factors were associated with placebo effect (all $P \geq 0.1$). Also, none of the factors reached classification accuracies greater than chance level in the individual-level analysis (all $P \geq 0.1$; Fig. 3 and Table 3).

DISCUSSION

We investigated the link between timing of pregabalin or placebo treatment and clinical outcome in patients with painful CP. Duration of CP and pretreatment opioid consumption (ie, factors associated with timing of therapy) were not associated with the analgesic effect of pregabalin. Furthermore, a predefined battery of secondary predictors (not related to timing), among others, including pretreatment clinical pain scores and their variability, diabetes, and exocrine pancreatic insufficiency, was not associated with pregabalin effect. In line with the results from pregabalin-treated patients, none of the aforementioned parameters were associated with placebo analgesia.

Timing of Pregabalin Treatment and Its Relation to Outcome

The rationale for the present study was based on findings in surgically treated patients with painful CP, where the timing of surgery was found to be associated with clinical outcome.[5,12–14] Hence, in a recent retrospective study, patients undergoing early surgery (arbitrarily defined as surgery within 3 years from symptom onset) had significantly better pain relief and delayed loss of exocrine and endocrine pancreatic function compared with patients operated on at a later phase of their disease.[5] The results in surgical series with regard to the effect of the timing of surgery have, however, been inconsistent, and other studies found no clear association, which is in agreement with the findings from the present study.[15]

The improved pain-relieving effect of early surgery is based on the hypothesis that ongoing pain results in pathological changes of central pain processing, which at a certain time point become independent of the peripheral nociceptive drive. From this point, the patient may develop a central autonomous pain syndrome no longer treatable by removing the initial pain trigger (ie, the pancreas).[3] From a neurobiological point of view, such aberrant central pain processing has been well characterized, and the phenomenon is known as *central sensitization*.[16] This refers to an increased synaptic efficacy established in sensory neurons in the dorsal horn of the spinal cord and brain following intense peripheral noxious stimuli, tissue injury, or nerve damage as seen in CP.[16–18] It has been speculated that early treatment prevents the evolution of central sensitization. This is compatible with findings from a previous study where a more progressive disease stage of CP was associated with more widespread hyperalgesia (a clinical manifestation of central sensitization).[6] Interestingly, widespread hyperalgesia was also reported to be associated with a poor clinical outcome to surgery and splanchnic denervation, which are both treatments that target the pancreatic source of pain.[19,20] In addition to effects on central sensitization, early and effective treatment would also mean shorter exposure to opioids and hence less chance of opioid-induced hyperalgesia.[21]

In the present study, we used pregabalin to treat pain associated with CP. This drug specifically targets a well-defined receptor in the pain system (the $\alpha 2\delta$ subunit of voltage-dependent calcium channels), whereby it blocks the influx of calcium into presynaptic nerve terminals and reduces release of excitatory neurotransmitters.[22,23] Hence, in contrast to surgery and other treatments targeted against the peripheral nociceptive source, pregabalin targets central sensitization per se. Consequently, the effect of pregabalin is probably more likely to be associated with hyperalgesia and other manifestations of central sensitization rather than factors related to the temporal course of the disease. This is in line with the current study and with findings from a previous study from our group, where pregabalin was found to reduce the hyperalgesia associated with CP.[24] Furthermore, segmental hyperalgesia of the pancreatic viscerotome (a biomarker of spinal sensitization) was previously shown to be a clinical useful predictor of pregabalin efficacy.[4]

Long-term opioid use has repeatedly been shown to negatively affect the response to total pancreatectomy and other invasive treatments of pain in CP.[5,25,26] This association is presumably due to central sensitization and pain chronification as discussed previously. Hence, the lack of effect of opioid treatment on the responses to pregabalin treatment in the present study was an unexpected finding because pregabalin targets central sensitization. However, various mechanisms have been associated with central sensitisation, which comprises 2 temporal phases: (1) an early phosphorylation-dependent and transcription-independent phase, which results mainly from rapid changes in glutamate receptor and ion channel properties; and (2) a later, longer-lasting, transcription-dependent phase, which drives synthesis of the new proteins responsible for the longer-lasting form of central sensitisation observed in several pathological conditions.[17,27,28] It could be speculated that pregabalin prevents the evolution of early to late phase of sensitization and thereby reverses the condition before it becomes independent of the peripheral nociceptive drive, while it is less effective when the later phase of central sensitization is established. In addition, long-term opioid therapy may be harmful because of mechanisms such as opioid-induced hyperalgesia and potential effects on the immune system.[29] Finally, adverse effects—where there is often no tolerance—may also play a role, including opioid-induced bowel dysfunction, which may be painful itself.[30] These factors will be independent of pregabalin effects and taken together may explain why opioid therapy was not related to treatment outcome.

Supplementary Factors and Their Relation to Outcome

None of the supplementary factors were associated with pregabalin or placebo outcome. A high variability of clinical pain scores compared with a stable pain profile was previously shown to be associated with a better treatment outcome in a population of neuropathic pain patients.[31] The authors suggested that low pain variability was an indication of a rigid and fully manifested chronic pain process with severe central plastic changes unresponsive to therapy. These findings were not reproduced in the present study where pain scores and their variability were not associated with outcome. This may relate to a relatively short baseline pain registration (1 week) in our study, which may not give a reliable assessment of clinical pain variability in the individual patient.

From a theoretical point of view, pancreatic insufficiency (endocrine and exocrine) could interfere with pregabalin absorption and thereby influence its analgesic potency. Hence, abnormal gut motility, bacterial overgrowth, and changes in the intestinal milieu are well-known complications of pancreatic insufficiency.[32–34] However, no association between pregabalin response and pancreatic insufficiency was found.

Pregabalin was previously shown to be effective for the treatment of diabetic neuropathy.[35] Consequently, we included diabetes as a supplementary predictor of pregabalin efficacy, but no association was found. This is likely explained by the clinical phenotype of patients with diabetes, as they were generally well treated and importantly had no complaints of peripheral or autonomic neuropathies.

Study Strengths and Limitations

The main strengths of our study are the prospective design and analysis of individual patient data. The prospective design ensured a rigorous and exact definition of "treatment responder," which is an advantage compared with previous retrospective studies lacking registration of clinical pain scores prior to intervention and consequently using arbitrary definitions of treatment outcome.[5] Also, retrospective studies are generally prone to recall bias, making inferences and conclusions challenging. In addition to conventional statistics, which typically identify predictors of treatment outcome based on differences between groups (ie, group-level analysis), prediction studies should be based on supplementary analysis and classification of individual patient responses. Consequently, we utilized a prediction algorithm based on individual patient data as a supplement to conventional statistics. A limitation to our study is the limited number of patients and the relatively short follow-up period. However, in most previous studies of pregabalin for different neuropathic pain conditions, a maximal analgesic response was typically seen within 2 weeks of treatment.[7,35,36] Hence, we do not consider the short follow-up period to be a major bias of the present study, and we find the classification of treatment response after 3 weeks appropriate.

CONCLUSIONS

Our study shows that timing of pregabalin treatment is not associated with analgesic outcome in painful CP. Pregabalin can be introduced as an adjuvant analgesic at any time point during the disease course, and its effect is most likely related to sensitization of central pain pathways.

REFERENCES

1. Lieb JG 2nd, Forsmark CE. Review article: pain and chronic pancreatitis. *Aliment Pharmacol Ther*. 2009;29:706–719.
2. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology*. 1994;107:1481–1487.
3. Poulsen JL, Olesen SS, Malver LP, et al. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. *World J Gastroenterol*. 2013;19:7282–7291.
4. Olesen SS, Graversen C, Bouwense SA, et al. Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. *PLoS One*. 2013;8:e57963.
5. Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH, et al. Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief. *Arch Surg*. 2012;147:925–932.
6. Bouwense SA, Olesen SS, Drewes AM, et al. Is altered central pain processing related to disease stage in chronic pancreatitis patients with pain? An exploratory study. *PLoS One*. 2013;8:e55460.
7. Olesen SS, Bouwense SA, Wilder-Smith OH, et al. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. *Gastroenterology*. 2011;141:536–543.
8. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.
9. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.
10. Lee Y. Support vector machines for classification: a statistical portrait. *Methods Mol Biol*. 2010;620:347–368.
11. Rojas J, Fernandez I, Pastor JC, et al. Development of predictive models of proliferative vitreoretinopathy based on genetic variables: the Retina 4 project. *Invest Ophthalmol Vis Sci*. 2009;50:2384–2390.
12. Lamme B, Boermeester MA, Straatsburg IH, et al. Early versus late surgical drainage for obstructive pancreatitis in an experimental model. *Br J Surg*. 2007;94:849–854.
13. Maartense S, Ledeboer M, Bemelman WA, et al. Effect of surgery for chronic pancreatitis on pancreatic function: pancreatico-jejunostomy and duodenum-preserving resection of the head of the pancreas. *Surgery*. 2004;135:125–130.
14. Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified Puestow procedure. *Ann Surg*. 1993;217:458–466; discussion 466–468.
15. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology*. 1999;116:1132–1140.
16. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in Pain. *Science*. 2000;288:1765–1769.
17. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(suppl 3):S2–S15.
18. Ceyhan GO, Bergmann F, Kadihasanoglu M, et al. Pancreatic neuropathy and neuropathic pain—a comprehensive pathomorphological study of 546 cases. *Gastroenterology*. 2009;136:177–186.
19. Bouwense SA, Ahmed Ali U, ten Broek RP, et al. Altered central pain processing after pancreatic surgery for chronic pancreatitis. *Br J Surg*. 2013;100:1797–1804.
20. Bouwense SA, Buscher HC, van Goor H, et al. Has central sensitization become independent of nociceptive input in chronic pancreatitis patients who fail thoracoscopic splanchnicectomy? *Reg Anesth Pain Med*. 2011;36:531–536.
21. Simonnet G, Rivat C. Opioid-induced hyperalgesia: abnormal or normal pain? *Neuroreport*. 2003;14:1–7.
22. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology*. 2002;42:229–236.

23. Houghton LA, Fell C, Whorwell PJ, et al. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut*. 2007;56:1218–1225.
24. Bouwense SA, Olesen SS, Drewes AM, et al. Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial. *PLoS One*. 2012;7:e42096.
25. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg*. 2012;214:409–424; discussion 424–426.
26. Bellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology*. 2014;14:27–35.
27. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895–926.
28. Willert RP, Woolf CJ, Hobson AR, et al. The development and maintenance of human visceral pain hypersensitivity is dependent on the *N*-methyl-D-aspartate receptor. *Gastroenterology*. 2004;126:683–692.
29. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113–130.
30. Brock C, Olesen SS, Olesen AE, et al. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;72:1847–1865.
31. Martini CH, Yassen A, Krebs-Brown A, et al. A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia. *Eur J Pain*. 2013;17:1491–1501.
32. Layer P, von der Ohe MR, Holst JJ, et al. Altered postprandial motility in chronic pancreatitis: role of malabsorption. *Gastroenterology*. 1997;112:1624–1634.
33. Kumar K, Ghoshal UC, Srivastava D, et al. Small intestinal bacterial overgrowth is common both among patients with alcoholic and idiopathic chronic pancreatitis. *Pancreatology*. 2014;14:280–283.
34. Andersen DK. Mechanisms and emerging treatments of the metabolic complications of chronic pancreatitis. *Pancreas*. 2007;35:1–15.
35. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110:628–638.
36. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain*. 2008;136:150–157.