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Pilot Trial: Pregabalin on Colonic Sensorimotor Functions in Irritable Bowel Syndrome

Johanna Iturrino, M.D.^{1,2}, Michael Camilleri, M.D.^{1,2}, Irene Busciglio, B.S.¹, Duane Burton, B.S.¹, and Alan R. Zinsmeister, Ph.D.³

¹Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), College of Medicine, Mayo Clinic, Rochester, MN

²Division of Gastroenterology and Hepatology, College of Medicine, Mayo Clinic, Rochester, MN

³Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, College of Medicine, Mayo Clinic, Rochester, MN

Abstract

Background—In prior studies, pregabalin reduced rectal or colonic pain in patients with irritable bowel syndrome (IBS) and healthy adults, suggesting reduction of afferent function.

Aim—To assess effects of pregabalin on colonic compliance, sensory and motor functions in patients with constipation-predominant IBS (IBS-C).

Methods—In a pilot, double-blind, placebo-controlled, parallel-group study, we tested oral pregabalin, 200mg, in 18 IBS-C adults. With a barostatically-controlled polyethylene balloon in the left colon, we assessed sensation thresholds and colonic compliance using ascending method of limits, sensation ratings over 4 levels of distension, fasting and postprandial colonic tone and phasic motility. ANCOVA (adjusted for the corresponding pre-drug response) was used to compare placebo and pregabalin. After 45% participants completed studies, we conducted an interim analysis to assess the conditional power to detect pre-specified treatment effects given the observed variation and treatment group differences based on the planned sample size for the trial.

Results—Pregabalin did not significantly affect colonic compliance, sensation thresholds, sensation ratings, fasting or postprandial tone or motility index. The study was stopped for futility to detect an effect on visceral pain with the planned design and sample size.

Conclusion—Pregabalin, 200mg, might not reduce distension-related colonic pain in IBS-C patients.

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Corresponding author: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First St. S.W., Rochester, MN 55905, camilleri.michael@mayo.edu, Tel: 507-266-2305.

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Keywords

colonic compliance; gas sensation; pain sensation; analgesia

Introduction

Irritable bowel syndrome (IBS) is a debilitating condition characterized by abdominal pain, diarrhea and/or constipation, which negatively impacts quality of life.¹⁻³ It is estimated that IBS affects about 15% of the U.S. and world populations^{4,5} and, despite better understanding of the pathophysiology of IBS,⁶ there are no effective medications approved for the treatment of abdominal pain associated with IBS. Nearly one-third of patients with IBS present with colon hypersensitivity (i.e. visceral pain) and/or gastrointestinal transit abnormalities;⁷ therefore, sensorimotor dysfunctions, which are readily measurable, constitute important targets for pharmacotherapy, although the dysfunctions are not present in all patients with IBS.

Treatment of abdominal pain in IBS has been predominantly centered on antidepressants, anxiolytics or analgesics; despite their extensive use and evidence of pharmacodynamic efficacy for some medications, the individual clinical trials have been generally unconvincing and the results of meta-analyses vary according to the trials included in the analyses, as summarized elsewhere.⁸

Pregabalin is approved by the FDA for the treatment of neuropathic pain; however, it has been proposed as a treatment for visceral pain, mostly based on its pharmacological actions and long-proven efficacy in neuropathic, somatic pain.^{9,10} Pregabalin binds potently to an auxiliary protein associated with voltage-gated calcium channels, reducing depolarization-induced calcium influx at the nerve terminal;¹⁰ consequently, pregabalin may reduce the release of several excitatory neurotransmitters including glutamate, noradrenaline, substance P, and calcitonin gene-related peptide (CGRP), which are involved in pain mechanisms.^{10,11}

Initially, animal models showed promising results for pregabalin as an effective visceral analgesic.¹²⁻¹⁴ Subsequently, a pharmacodynamic study in IBS patients suggested that it increased pain thresholds with a concomitant increase in rectal compliance.¹⁵ To clarify whether pregabalin is an effective visceral analgesic or simply increases colonic compliance reducing sensation of distension-induced pain, we embarked on a series of pharmacodynamic studies to understand the effects of pregabalin on colonic motor and sensory functions. We have previously reported that, in healthy adults, pregabalin did not affect colonic compliance, sensation thresholds, colonic fasting tone, or phasic motility index, but it did reduce colonic gas and pain sensation ratings in response to standardized isobaric colonic distensions.¹⁶ Based on these findings, our aim was to investigate the effects of pregabalin on colonic compliance, sensory and motor functions in IBS patients, with major interest in its potential as a medication for IBS-related pain.

Materials and Methods

Study Design, Randomization and Allocation to Treatment

A randomized, double-blind, placebo-controlled, parallel-group study of the effects of a single oral administration of pregabalin, 200mg, was conducted in a single center in 18 patients (out of an intended cohort of 40 patients) with IBS-C, aged 18 to 75 years. Prior to starting the study, the randomization schedule was generated in the Division of Biomedical Statistics and Informatics, Mayo Clinic, and was given to the research pharmacists. The study medications were prepared and dispensed by the Mayo Research Pharmacy. The

pregabalin and placebo were identical in appearance. The clinical investigators, study personnel, and participants were blinded to the treatment assignments until after the data were finalized for analysis. Allocation was concealed and medication was administered in double-blinded fashion.

Participants

Participants were enrolled by one study coordinator between March 2011 and May 2012. The study was approved by the Mayo Clinic Institutional Review Board and was registered on the [ClinicalTrials.gov](https://clinicaltrials.gov) website (NCT01331213). Data were collected in the Clinical Research Unit at Mayo Clinic in Rochester, Minnesota.

Adults with IBS-C were recruited from a preexisting database of approximately 200 IBS-C patients residing within 150 miles of Rochester, Minnesota, or through local advertisement. After informed consent was signed, candidates who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. All candidates were screened by means of the abridged Bowel Disease Questionnaire¹⁷ to insure diagnosis of IBS-C (by Rome III criteria) and by the Hospital Anxiety and Depression Questionnaire¹⁸ which was used to screen all volunteers for psychiatric comorbidities. We excluded those with prior abdominal surgery (other than appendectomy, cesarean section, laparoscopic cholecystectomy, vaginal or laparoscopic hysterectomy or tubal ligation), use of medications that could affect gastrointestinal motility, serum creatinine >1.5mg/dL, or history of uncontrolled hypertension, psychiatric or psychological dysfunction. A urine pregnancy test was performed in all women of childbearing potential within 48 hours of study drug administration and colonic intubation.

Pregabalin Pharmacokinetics

Pregabalin exhibits a highly predictable and linear pharmacokinetics. Absorption after oral administration is rapid and proportional to dosage. Time to maximal plasma (T_{max}) concentration is approximately 1 hour. Mean elimination half-life ($t_{1/2}$) is 6.3 hours, and excretion is virtually unchanged (<2% metabolism) by the kidneys. These characteristics reflect the observed onset of efficacy as early as day two in clinical trials.¹⁰

Given these pharmacokinetic characteristics, we conducted this study in patients with IBS-C using the same experimental design as in our previous study of pregabalin in healthy adults.¹⁶ Measurements were recorded before and again starting one hour after drug administration. All measurements of colonic compliance, tone and sensation were completed within 5 hours (Figure 1). “Stress arousal” symptoms (e.g. anxiety) pre- and post-treatment were assessed before conducting the sensation evaluations.

We used a single dose of 200mg pregabalin (Lyrica®, Pfizer, USA) capsules that were over-encapsulated with a blue gelatin capsule to mimic the blue placebo capsules. Testing of compliance and sensation was conducted pre- and 60 minutes post-dose.

Colonic Tube Placement

Colonic motility and sensation measured by the barostat method were assessed as previously described by our group.¹⁹ All subjects presented after an overnight bowel preparation with an oral colonic lavage solution (GoLYTELY, Braintree Laboratories, Inc., Braintree, MA) and a 12-hour fast. Flexible colonoscopy to the splenic flexure was performed without sedation by the same clinician investigator (M.C.) to evaluate the left side of the colon and to place a teflon-coated guidewire (Microvasive, Hobbs Medical, Stafford Springs, CT) into the colon. The colon was deflated as the colonoscope was withdrawn. The catheter, incorporating 6 manometric point sensors 5cm apart and a polyethylene balloon [10cm long

cylinder with a maximum volume of 600mL (MUI Scientific, Mississauga, ON, Canada)], was introduced into the colon over the guidewire and positioned under fluoroscopic control in the mid-descending or upper sigmoid colon. The catheter was connected to a rigid piston barostat (Mayo Rigid Barostat, Engineering Department, Mayo Clinic, Rochester, MN) by means of a double-lumen tube for balloon distension and intra-balloon pressure and volume measurements. Intracolonic balloon volumes were measured throughout the study.

Experimental Protocol to Assess Colonic Motor and Sensory Functions

The experimental protocol is summarized in Figure 1. After inflating the balloon to 75ml to ensure unfolding of the balloon, a conditioning distension from 0 to 20mmHg, in increments of 4mmHg every 15 seconds, was performed over a period of 2 minutes. After an equilibration period of 10 minutes, a 100 cm visual analog scale (VAS) was used to assess the level of anxiety or stress experienced using the terms “peaceful” and “tense” and “worried” and “relaxed,” respectively by each subject because they are potentially significant covariates in the assessment of visceral sensation scores.¹⁹

Colonic compliance was then assessed using ascending methods of limits where the intra-balloon pressure is increased in ramp-like increments of 4mmHg at 60 second intervals. During the assessment of colonic compliance, participants were asked to report their thresholds for first perception, gas, and pain. After the assessment of compliance, the baseline operating pressure (BOP) was established by inflation to an intra-balloon pressure set 2mmHg above the minimal distention pressure at which respiratory excursions were recorded from the barostat tracing. After another 10-minute equilibration period, fasting colonic tone was measured at the operating pressure for a period of 30 minutes.^{19,20}

In order to measure sensation of gas and pain, randomized-order phasic distensions were applied at 16, 24, 30 and 36mm Hg above the operating pressure. Each distension lasted 1 minute and was followed by an equilibration period at the operating pressure for 2 minutes. During the distensions, participants also used the 100mm VAS to rate the intensity of gas and pain perception (anchored at the two ends with the words “Unnoticeable” and “Unbearable” at 30 seconds from the start of the distension.

Thus, colonic compliance, fasting tone, pressure thresholds for first perception, gas, and pain, and VAS scores of gas and pain during phasic distensions were measured before and 1 hour after drug administration (pregabalin, 200mg, or placebo) according to the randomization. After the post-drug assessment of compliance and sensation, baseline measurements of post-drug fasting colonic tone were conducted for 30 minutes, followed by ingestion of a standard liquid 1000kcal meal (750mL chocolate milkshake, 53% fat, 35% carbohydrate, 12% protein) to measure the colonic response to feeding over 60 minutes, with the main focus on the first 30 minutes.^{19,20} Thereafter, the balloon was deflated, and the tube was removed by gentle traction.

Data Analysis

Compliance—As previously validated,²¹ compliance was calculated by a computer-based linear interpolation method which estimates the pressure corresponding to specific volumes at 50% of maximum balloon distension. A higher value Pr50 corresponds to lower compliance, and vice-versa.

Colonic Motor Function—Colonic tone was measured as the intracolonic balloon volume measured at the operating pressure, as previously described.²² Tone was calculated by using the average of the colonic volumes measured throughout the period of interest during fasting or after the meal. Changes in colonic tone were calculated as absolute volume

changes in response to the study medication during fasting, and as symmetric percent changes in postprandial volume.²² High amplitude propagating contractions (HAPCs) were defined as increases in pressure of 75mmHg that propagated across a minimum of 3 leads (10cm) in the left colon.^{23,24}

Colonic Sensation—Sensation pressure thresholds for first sensation, gas, and pain were assessed during the measurement of colonic compliance. Sensation ratings for gas and pain were recorded on a 100mm VAS scale during randomized order phasic distensions at 16, 24, 30 and 36mmHg above the operating pressure.

Adverse Events—Adverse events were recorded by a single study technician while participants were undergoing colonic measurements and until the completion of the one day study.

Radiation Exposure—Radiation exposure in this study was minimal and only involved fluoroscopy (up to 1 rad) for the placement of the colonic motility tube. Endoscopic procedure, colonic tube placement and fluoroscopy were performed by a single endoscopist.

Statistical Considerations

Study Endpoints—The primary study endpoints were: 1) colonic compliance as the pressure at half-maximum volume (Pr50%); 2) postprandial colonic tone as the symmetric percent reduction in baseline colonic barostat balloon volume during the first 30 minutes postprandially corrected for the preprandial (30 minute) tone (symmetric percent change=100*log[fasting/PP]); 3) post-treatment sensory thresholds for pain; 4) post-treatment sensory ratings in response to 30 and 36 mmHg distensions.

The secondary endpoints were: 1) fasting colonic tone; 2) phasic motor function as the first 30-minute postprandial motility index ($MI = \log_e[\text{sum of amplitudes} * \# \text{ of contractions}] + 1$), and the preprandial MI; 3) post-treatment sensory thresholds for first sensation and gas; 4) post-treatment sensory ratings in response to 16 and 24mmHg distensions.

Statistical Analysis—The interim analysis used analysis of covariance (ANCOVA) models to assess treatment effects on colonic tone, compliance, sensation VAS ratings at 36 mmHg, phasic motor function, and stress-arousal scores in all randomized subjects. These were per protocol analyses with no imputation of missing data. The covariate included in the ANCOVA models was the corresponding baseline (pretreatment) response value. The associations between compliance, sensation (VAS) ratings, and stress-arousal scores were estimated using (Pearson) correlation coefficients.

Each primary and secondary endpoint measurement addressed a different biological variable (colonic compliance, sensory thresholds and ratings, and motor function) in patients with IBS. Additionally, we took the precaution to pre-specify the precise stimulus level for the sensation ratings in order to avoid multiple comparisons. Therefore, each of the endpoints was assessed at $\alpha=0.05$.

Sample Size Assessment—Prior to the study, the effect size demonstrable, based on 20 participants per group, was estimated based on the previously observed^{25,26} coefficients of variation (defined as standard deviation divided by mean value) for the main endpoints of interest, as measured in our laboratory using the same methods (Table 1). The choice of sample number was based on the assessment that the effect size demonstrable was clinically relevant.

Results

Demographics (Figure 2)

A total of 18 participants with IBS-C were recruited out of an intended total recruitment cohort of 40, when an interim analysis was conducted to assess the conditional power to detect pre-specified treatment effects given the observed variation and treatment group differences based on the planned sample size for the trial.

Seventeen of the participants were females. One participant was excluded from the pregabalin group due to balloon leak during the barostat distension procedure (Table 2). The demographics, baseline BMI, and baseline operating pressures of intracolonic balloon data of all 18 participants are summarized in Table 2, according to the randomization group (pregabalin, 200mg, or placebo). No clinically important differences among treatment groups were noted.

Colonic Compliance, Sensation Ratings for Gas and Pain, Sensation Thresholds, Colonic Motility and Tone

Tables 2 and 3 show the data in the two treatment groups. There were no appreciable numerical differences in all the primary and secondary endpoints.

Adverse Events

The most common adverse events were dizziness observed in 28% of the participants, 5/8 with pregabalin, 200mg, and 0/10 placebo; and drowsiness in 28% of participants, 4/8 with pregabalin, 200mg, and 1/10 with placebo. Headaches occurred in 22% of the participants, 1/8 with pregabalin, 200mg, and 4/10 with placebo. One participant withdrew from the study due to balloon leak during colonic distension. No participant withdrew from the study due to a treatment-related adverse event.

Prospective Assessment of Study Power and Determination of Futility

Table 4 contrasts the coefficient of variation (COV) used prior to the study that predicted an effect size of ~22 to 50% in primary endpoints demonstrable with n=20 per treatment arm. The interim analysis demonstrated somewhat higher than expected (~10% higher) coefficients of variation. Anticipating a total sample size of 20 per treatment arm, the conditional power at the interim analysis to detect clinically important differences based on the observed variation and treatment group differences was very low for each of the primary endpoints. The study was, therefore, terminated.

Discussion

In this randomized, double-blind, placebo-controlled, pilot study, we sought to address the effects of pregabalin on colonic sensation and motor functions in patients with IBS-C. Although the study was conducted with the same dose, design and methods that previously had proven efficacious in healthy adults,¹⁶ the interim analysis implied greater variability in the endpoints than expected, and the conditional power to detect the protocol specified effects was very low. This is evident from analysis of the information in Table 4, which shows that the observed COV was higher in the patients with IBS-C exposed to placebo than the COV of healthy participants exposed to pregabalin, 200mg, except for pain rating at 30mmHg distension and postprandial colonic tone. Thus, the interim analysis indicated typically higher than expected COV and small observed differences between treatments for all endpoints except the postprandial motility index, which was one of the secondary endpoints. Indeed, even if we had planned our study based on the COV for the healthy participants exposed to pregabalin, 200mg, the planned sample size of 20 per treatment arm

would have sufficed to demonstrate a clinically relevant effect of the drug in IBS-C patients, such as an ~30% change in colonic compliance, postprandial tone or pain sensation threshold, but not pain ratings at 30mmHg distension (which would have had to change by 72% to be demonstrable). In fact, the observed differences lacked clinical relevance (e.g. 1% change in pain ratings on 30mmHg distension, 12-14% change in pain threshold or colonic compliance, or 3% change in colonic tone in response to meal ingestion), and it was concluded that it would be futile and potentially unethical to continue to expose more patients to the potential study harms (e.g. colonoscopy, colonic tube placement, exposure to fluoroscopy) with knowledge of the limited potential benefit for these patients or IBS-C patients in general. Hence, the study was stopped early.

Differences in sensory mechanisms and pain perception in patients with IBS compared to healthy adults might explain the discrepancy in the COV between healthy adults and patients with IBS when addressing pain sensations. These findings are contrary to the COV in patients with IBS undergoing gastrointestinal transit studies, where the COV seem to be almost the same as the COV in healthy individuals and appear to be predictive of results in the diseased population, as has been extensively validated by our group.^{27,28} The discrepancy might be explained by potential introduction of response bias in the assessment of sensation thresholds for gas and pain by ramp-like distensions (ascending methods of limits) since participants respond to distension at increasing pressure levels. In addition, sensation thresholds in human rectum and colon are associated with relatively greater coefficients of variation.^{20,29}

On the other hand, assessments of sensation ratings by phasic random distensions are expected to be less prone to bias because the distensions are delivered in random order and the COV are smaller. However, our interim analysis showed that the observed COV was higher than that observed in healthy adults. It is also known that studies with parallel-group design need somewhat greater sample sizes than crossover trials to show similar magnitude of differences in sensation thresholds.²⁹ However, disadvantages of a crossover design include the carryover effect and potential for dropouts from the study, especially in studies that involve invasive procedures.

Ultimately, the effects of pregabalin on abdominal pain or discomfort and adequate relief of symptoms in IBS patients by using escalating doses of pregabalin for 12 weeks are currently being evaluated in a formal clinical trial (NCT00977197). This trial might answer the question whether the use of escalating doses of pregabalin would be efficacious in relief of visceral pain as opposed to a single dose design used in the current study. However, the mechanism of action of this drug in the management of visceral hypersensitivity is still unknown. It is conceivable that escalating doses of pregabalin and maintaining treatment for a prolonged time might be beneficial; thus, the results of the clinical trial are eagerly awaited. There are currently no approved medications for the management of visceral hypersensitivity in patients with IBS. It is clear that there is unmet clinical need for management of visceral hypersensitivity in IBS patients and, due to the burden of disease, we encourage the development of more drugs for the management of visceral hypersensitivity.

Our study is relevant to middle-aged, predominantly female Caucasians with IBS-C. The extent to which these results apply to other populations requires further study. Pregabalin showed a favorable safety profile, with dizziness and drowsiness as the most common side effects. As has been previously described in multiple studies,³⁰ this finding is consistent with some central effects and implies ability of pregabalin to cross the blood-brain barrier. It is likely that our approach of administering a high dose of pregabalin to pregabalin-naïve patients was responsible for some of the side effects encountered, and the adverse effects

could have been attenuated by starting at a lower dose and gradually increasing it. Our main interest in this study was the acute effects of pregabalin and not the effects of a gradual introduction to pregabalin. The latter approach, including dose escalation, represents an area for future research in the field.

The strengths of this study include the use of a dose of pregabalin that has been shown to be effective in healthy adults compared to placebo, the participation of patients with IBS-C which decreases heterogeneity of the IBS spectrum, and the use of a standardized barostat distension protocol performed and analyzed by experienced investigators.

In summary, we concluded that pregabalin, 200mg, might not be an effective treatment for acute, distension-related colonic pain in patients with IBS-C. Future studies should assess both the potential role of new drugs in the treatment of visceral hypersensitivity in IBS patients, as well as the relationship of their effects on pain perception and colonic compliance. Such studies may enhance understanding of the pathophysiology of chronic abdominal pain in IBS.

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Figure 1. Experimental Protocol

Participants were enrolled in a 1 day study. Participants were randomized to the study medication or placebo. After overnight fasting and bowel preparation a limited colonoscopy was done with tube placement in the left side of the colon. Barostat tracings for baseline colonic tone, compliance and sensation were performed. Sixty minutes after drug administration, post-drug colonic tone, compliance and sensation was addressed. Postprandial tone was addressed after a 1000 Kcal meal. All measurements were recorded in 5 hours, before the study medication reached its have life.

Figure 2. Study Flow Chart

The study flow chart shows numbers assessed for eligibility to participate, participants excluded and allocated to intervention and analysis. Note there was one drop-out from the study due to barostat malfunction. All participants' data were included in the intent-to-treat analysis.

Table 1
Estimated effect sizes predicted to be demonstrable in primary sensory, compliance, and motility endpoints with 20 participants per group

	COV, %	Effect size [†] (%)
Pain threshold	46	42
Pain sensation at 30mmHg distension	59	54
Compliance Pr 50	41	37
Postprandial colon tone (symmetric % change)	47	43
Postprandial colon motility index	24	22

[†] Effect size is the difference in group means as a result of the treatment that could be detected using 20 participants per group with the coefficient of variation (COV) [SD/mean] calculated from prior studies using the same methods in our laboratory.^{25,26}

Table 2
Participant demographics, baseline characteristics, and effects of pregabalin on colonic compliance, sensation thresholds and sensation ratings for gas and pain

Parameter	Placebo, n=10	Pregabalin 200mg, n=8
Total #/Female#	10/9 (90%)	8/8 (100%)
Age, years	44.1 ± 11.5	44.0 ± 5.9
BMI, kg/m ²	27.1 ± 5.1	25.9 ± 3.2
BOP, mmHg	18.4 ± 14.4	18.5 ± 9.5
Pre-drug compliance Pr50%	16.9 ± 9.0	19.0 ± 4.8
Mean pre-drug gas sensation ratings	35.3 ± 28.3	34.1 ± 19.5
Mean pre-drug pain sensation ratings	32.5 ± 31.1	28.5 ± 16.1
Compliance Pr 50%, mmHg	15.7 ± 7.9	16.0 ± 6.4
Gas threshold, mmHg [§]	29.4 ± 21.8	36.3 ± 17.3
Pain threshold, mmHg [§]	31.9 ± 22.6	32.1 ± 22.7
Gas sensation ratings at 30mmHg	50.6 ± 25.8	68.9 ± 21.4
Gas sensation ratings at 36mmHg	53.5 ± 30.8	65.9 ± 15.2
Pain sensation ratings at 30mmHg	60.3 ± 25.0	64.0 ± 26.1
Pain sensation ratings at 36mmHg	53.7 ± 33.5	59.0 ± 21.9

Data show mean ± SD.

[§] ignores censoring; BOP = baseline operating pressure; BMI = body mass index. All p > 0.05

Table 3
Effects of pregabalin on motility and tone

Parameter	Placebo, n=10	Pregabalin 200mg, n=8
Colon tone fasting, mL	116.8 ± 24.8	120.4 ± 12.8
Colon tone fed, mL	92.4 ± 17.2	98.1 ± 16.3
Postprandial % Δ colonic tone, first 30 min. PP/fasting 30 min. *	22.8 ± 11.4	21.3 ± 13.5
Colon motility index fasting	8.0 ± 1.6	10.5 ± 3.2
Colon motility index fed	11.2 ± 2.6	12.7 ± 1.1

Data show mean±SD. PP = postprandial;

* overall P=0.10; all P>0.05

Table 4
Effect sizes that could have been detected with 80% power (2-sided α of 0.05) based on a two-sample t-test with n=20 per group using the COV actually observed in this study

This table contrasts the COV used prior to the study that predicted an effect size of ~10-70% in primary endpoints detectable with n=20 per treatment arm. The interim analysis indicated typically higher than expected coefficients of variation and small observed differences between treatments.

	Mean $\pm$ SD (Health, 200mg pregabalin) [†]	COV (%) (Health, 200mg pregabalin)	Observed COV% (pre-drug)	Observed COV% (post- placebo)	Effect size ^{α} (%) (Health, 200mg pregabalin)	Current observed difference ^{$\S$} (%)
Pain threshold	46.7 $\pm$ 13.9	30	46	55	27	14
Pain rating with 30mmHg	36.1 $\pm$ 28.4	79	48	41	72	1
Compliance Pr _{50%}	19.1 $\pm$ 4.6	24	43	50	33	12
Postprandial colon tone (30 min. avg.)	74.1 $\pm$ 25.4	34	ND	21	32	3
Postprandial colon motility index	11.4 $\pm$ 1.4	12	ND	20	8	7

COV = coefficient of variation;

ND = not done; postprandial measurements were not done pre-drug

[†] From reference 16;

^{α} Effect size detectable is the difference in group means divided by mean used for COV% (based on responses of healthy subjects who received 200mg pregabalin in prior study)

^{$\S$} Based on difference in LSMEANS from an ANCOVA model