Efficacy and Safety of Pregabalin in the Treatment of Postoperative Pain Following Inguinal Herniorrhaphy

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INTRODUCTION

- Inguinal herniorrhaphy is one of the most common procedures in general surgery[1]
- The estimated incidence of chronic pain post inguinal hernia repair is 5% to 50%[2]
- Postsurgical pain often mimics neuropathic pain and may be caused by the entrapment of ilioinguinal, iliohypogastric, or genital branches of the genitofemoral nerves, suture material, staples or tacks, perineural fibrosis, prosthetic material, and iatrogenic nerve damage[3-6]
- Perioperative pregabalin administration has been shown to reduce the incidence of chronic neuropathic pain after total knee arthroplasty[7]
- Because pregabalin is indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia, and not approved for the treatment of postoperative pain (US Food and Drug Administration Investigational New Drug No. 53, 763),[8-10] this study was designed to further assess the use of pregabalin in postoperative pain

OBJECTIVE

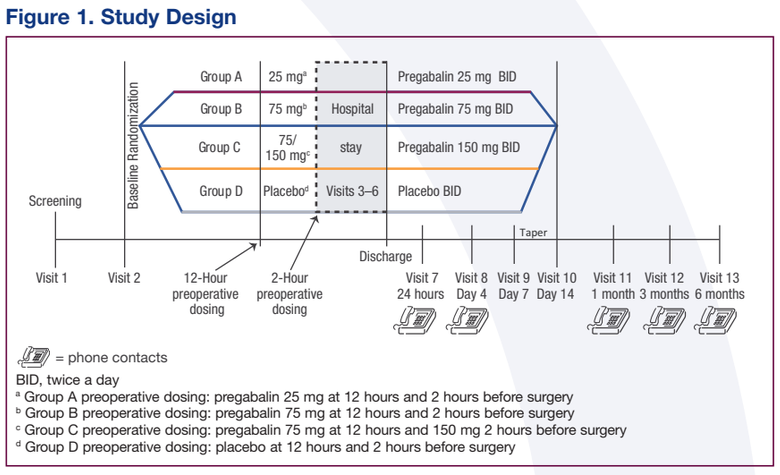
- To evaluate the efficacy and safety of pregabalin compared with placebo in the adjunctive treatment of postsurgical pain following primary inguinal hernia repair

METHODS

Study Design and Population

- Multicenter, randomized, double-blind, placebo-controlled study conducted at 35 sites in Australia, Canada, India, Spain, Sweden, and the United States (ClinicalTrials.gov identifier: NCT00551135)
- The study adhered to the International Conference on Harmonization Good Clinical Practice Guidelines and was approved by Institutional Review Boards at participating sites. Written informed consent was obtained prior to participation in the trial
- The study design (**Figure 1**) consisted of:
  - A screening visit 2 weeks prior to surgery
  - A baseline visit 12 hours prior to surgery
    - Patients were randomized to receive pregabalin 25 mg, 75 mg, 150 mg, or placebo at 12 and 2 hours before surgery followed by pregabalin 50 mg/d twice a day (BID), 150 mg/d BID, 300 mg/d BID, or placebo BID for 1 week after surgery and 1 week taper
    - Patients were hospitalized for 1 day
- Each site was asked to use the same anesthesia and analgesia regimen for all patients enrolled at that site
- Rescue medications:
  - Naproxen, ketorolac, ketoprofen, morphine, fentanyl, sufentanil, tramadol, paracetamol, and oxycodone
- Postdischarge clinic or phone visits occurred on postoperative days 2, 4, 7, and 14
- Follow-up phone calls were completed at 1, 3, and 6 months

Figure 1. Study Design



BID, twice a day
[a] Group A preoperative dosing: pregabalin 25 mg at 12 hours and 2 hours before surgery
[b] Group B preoperative dosing: pregabalin 75 mg at 12 hours and 2 hours before surgery
[c] Group C preoperative dosing: pregabalin 75 mg at 12 hours and 150 mg 2 hours before surgery
[d] Group D preoperative dosing: placebo at 12 hours and 2 hours before surgery

Major Inclusion Criteria

- Study participants were men 18 to 75 years of age with mild to moderate systemic disease with or without functional limitations prior to the primary elective inguinal herniorrhaphy

Major Exclusion Criteria

- Patients with emergency surgery, hernia incarceration, and those undergoing additional procedures at the time of the total inguinal herniorrhaphy were excluded

Efficacy and Safety Assessments

- The primary end point was the mean worst pain score at 24 hours reported by participants using the worst pain item (question 1) of the modified Brief Pain Inventory–short form (mBPI-sf)
- Secondary end points:
  - Movement-related pain measured by the numeric rating scale (NRS; 0 = no pain to 10 = pain as bad as you can imagine)
    - Pain caused by sitting, walking, and coughing
  - Total opioid consumption
  - Average pain (NRS)
  - Current pain at rest (NRS)
  - Pain Interference Index scores
  - Pain-related sleep interference scale scores (NRS)
  - Anxiety visual analog scale (VAS) scores
- Safety was assessed by examining the incidence and intensity of adverse events

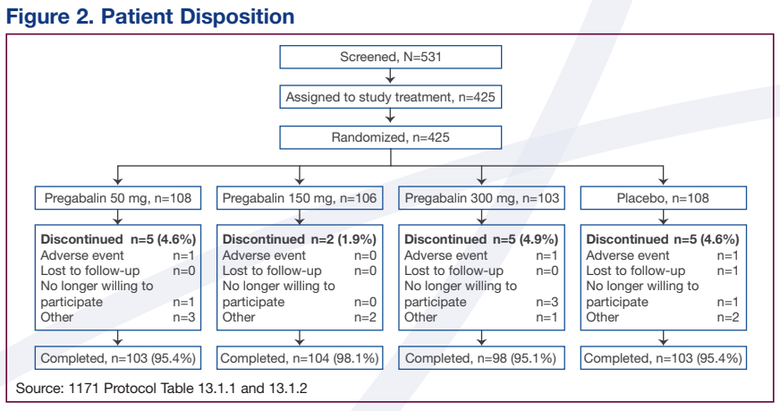
Statistical Analysis

- A sample size of 100 per group was estimated to provide 90% power (α=0.05) to detect a treatment effect of 1.0, assuming a 2-sided comparison and a standard deviation of 2.2
- Efficacy analyses were carried out using a modified intent-to-treat population defined as all randomized patients who were administered ≥1 dose of the double-blind medication for whom ≥1 postbaseline safety evaluation was obtained, for whom the presurgery study medication was taken, and no complication occurred during the herniorrhaphy
  - Multiple comparisons adjustment for the primary efficacy end point was done using a step-down procedure
- Analysis of variance (ANOVA) with model terms of treatment and study center was used to compare the primary end point in the pregabalin and placebo groups
- ANOVA, Cochran-Mantel-Haenszel test, Kaplan-Meier method, and log-rank test were used to evaluate secondary efficacy end points
- Descriptive statistics summarized the safety analysis

RESULTS

- Of the 531 patients screened, 425 patients were enrolled in the study; patient disposition is described in **Figure 2**
- Patient demographics are summarized in **Table 1**

Figure 2. Patient Disposition



Source: 1171 Protocol Table 13.1.1 and 13.1.2

Table 1. Patient Characteristics

Number (%) of Patients	Pregabalin 50 mg/d	Pregabalin 150 mg/d	Pregabalin 300 mg/d	Placebo
Age, y				
18–44	43 (39.8)	37 (34.9)	40 (38.8)	46 (42.6)
45–64	48 (44.4)	58 (54.7)	52 (50.5)	47(43.5)
≥65	17 (15.7)	11 (10.4)	11 (10.7)	15 (13.9)
Mean (SD)	48.4 (13.7)	48.8 (13.6)	48.4 (13.8)	47.2 (14.5)
Race				
White	82 (75.9)	89 (84.0)	85 (82.5)	84 (77.8)
Black	6 (5.6)	2 (1.9)	6 (5.8)	6 (5.6)
Asian	13 (12.0)	7 (6.6)	9 (8.7)	13 (12.0)
Other	7 (6.5)	8 (7.5)	3 (2.9)	5 (4.6)
Years diagnosed with inguinal hernia				
Mean	1.0	1.4	1.2	1.4
Range	0–12.2	0–21.0	0–21.1	0–21.2

SD, standard deviation

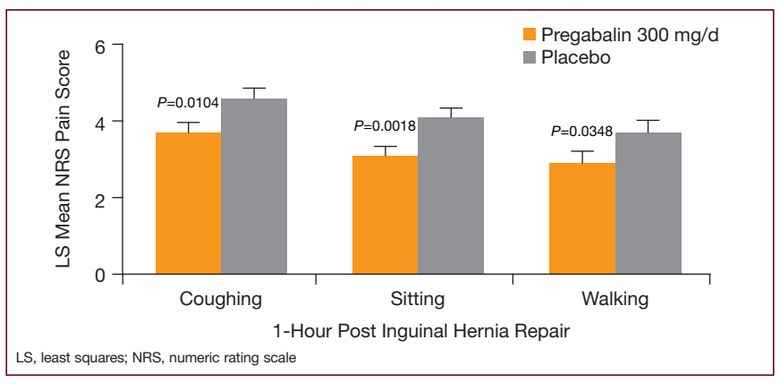
Primary End Point

- Pregabalin 300 mg reduced least squares (LS) mean worst pain scores at 24 hours post surgery; however, after multiple comparisons adjustment, this reduction in pain was not statistically significant compared with placebo (LS mean difference: –0.7 [unadjusted 95% confidence interval (CI), (–1.4 to –0.1)]; Hochberg adjusted *P*=0.0668; nominal *P*=0.0334)
- There were no significant differences compared with placebo in LS mean worst pain scores in the pregabalin 50-mg/d and 150-mg/d treatment groups

Secondary End Points

- Compared with placebo, patients in the pregabalin 300-mg group reported lower LS mean NRS pain scores 1 hour post surgery for pain caused by coughing, sitting, and walking (**Figure 3**)

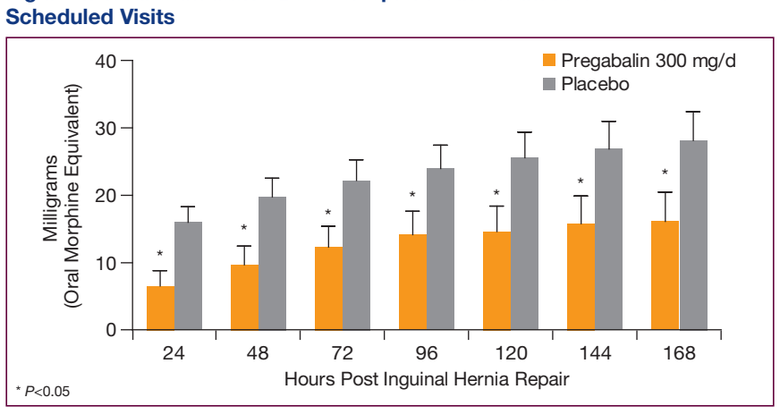
Figure 3. Pain Caused by Coughing, Sitting, and Walking (NRS)



LS, least squares; NRS, numeric rating scale

- Patients in the pregabalin 300-mg/d group reported lower total opioid consumption during the first 7 days post inguinal hernia repair compared with placebo (*P*<0.05; **Figure 4**)

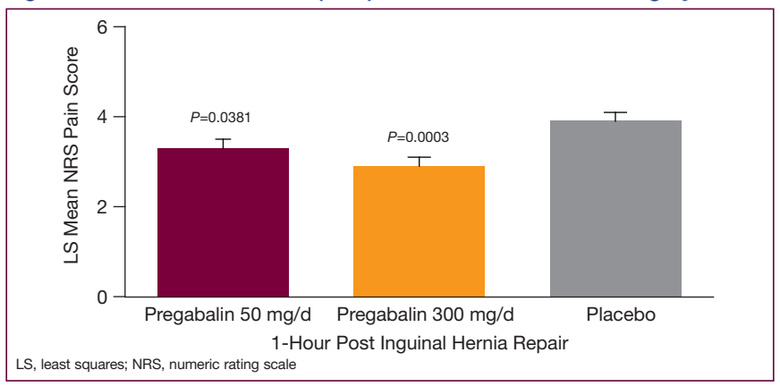
Figure 4. Total Cumulative Dose of Opioids and Tramadol Used at Scheduled Visits



* *P*<0.05

- There were no significant differences compared with placebo in LS mean average pain scores (mBPI-sf) at 24 hours, 72 hours, and end of treatment
- Compared with placebo, patients in the pregabalin 50-mg/d and 300-mg/d group reported lower current pain (NRS) scores at 1 hour post surgery (**Figure 5**)

Figure 5. Current Pain at Rest (NRS) Scores at 1 Hour Post Surgery



LS, least squares; NRS, numeric rating scale

- Pain Interference Index scores at 24 hours post inguinal hernia repair were lower in each treatment group compared with placebo (**Table 2**)

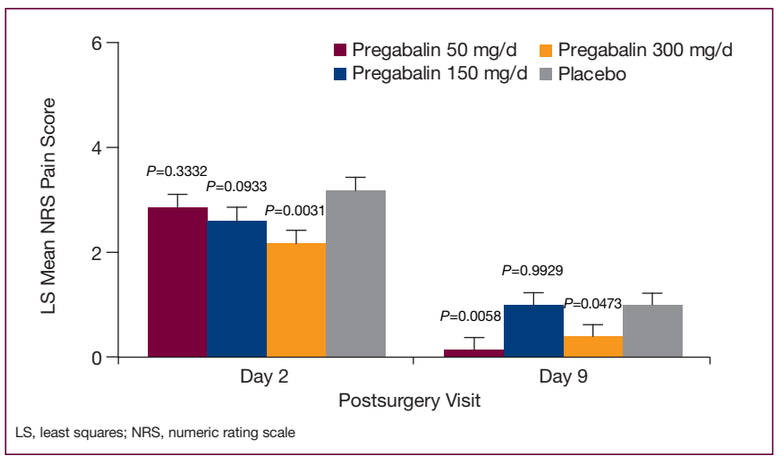
Table 2. Pain Interference Index Scores at 24 Hours Post Surgery

	Pain Interference Index Score (mBPI-sf)		Contrast of Treatment vs Placebo		
Treatment	n	LS Mean (SE)	Difference (SE)	95% CI	*P* Value
Pregabalin 50 mg	102	3.04 (0.204)	–0.61 (0.276)	–1.15 to –0.07	0.0278
Pregabalin 150 mg	99	3.02 (0.210)	–0.62 (0.280)	–1.17 to –0.07	0.0268
Pregabalin 300 mg	101	2.82 (0.205)	–0.82 (0.278)	–1.37 to –0.28	0.0033
Placebo	101	3.65 (0.204)			

mBPI-sf, modified Brief Pain Inventory–short form; n, modified intent-to-treat population; LS, least squares; SE, standard error; CI, confidence interval

- Compared with placebo, patients in the pregabalin 300-mg group reported lower LS mean pain-related sleep interference scores at days 2 and 9 post surgery (**Figure 6**)

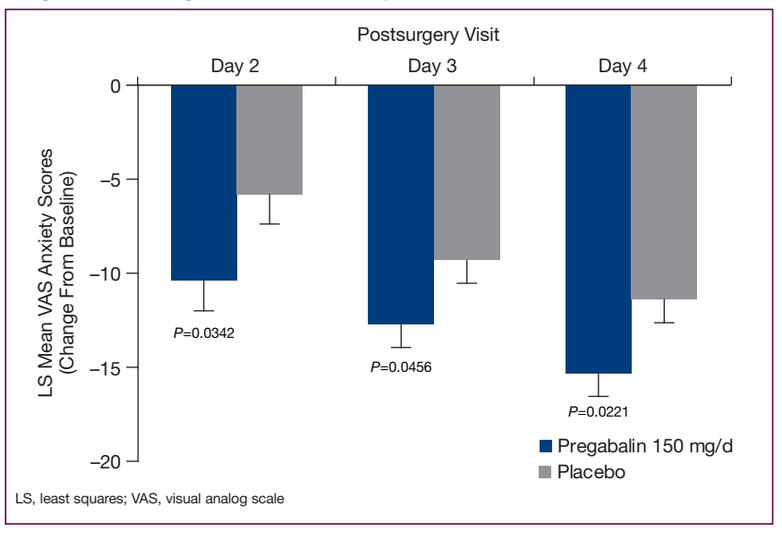
Figure 6. Pain-Related Sleep Interference Scores Postsurgery: Pregabalin Versus Placebo



LS, least squares; NRS, numeric rating scale

- Patients in the pregabalin 150-mg/d group reported lower VAS anxiety scores compared with placebo at days 2 to 4 post surgery (**Figure 7**)

Figure 7. Change From Baseline VAS Anxiety Scores in the Pregabalin 150 mg/d Treatment Group



LS, least squares; VAS, visual analog scale

- Worst pain scores in the pregabalin treatment arms did not differ from placebo at 1, 3, and 6 months post surgery

Safety

- The incidence of treatment-emergent adverse events is summarized in **Table 3**

Table 3. Incidence of All-Causality Treatment-Emergent Adverse Events

	Pregabalin 50 mg (n=108)	Pregabalin 150 mg (n=106)	Pregabalin 300 mg (n=103)	Placebo (n=108)
Somnolence	24 (22.2)	25 (23.6)	25 (24.3)	28 (25.9)
Fatigue	24 (22.2)	18 (17.0)	23 (22.3)	23 (21.3)
Constipation	21 (19.4)	22 (20.8)	27 (26.2)	27 (25.0)
Nausea	21 (19.4)	18 (17.0)	14 (13.6)	22 (20.4)
Dizziness	15 (13.9)	20 (18.9)	29 (28.2)	16 (14.8)
Disturbance in attention	11 (10.2)	11 (10.4)	15 (14.6)	16 (14.8)
Dysuria	10 (9.3)	6 (5.7)	10 (9.7)	10 (9.3)
Pruritus	9 (8.3)	7 (6.6)	4 (3.9)	6 (5.6)
Hypotension	7 (6.5)	3 (2.8)	4 (3.9)	2 (1.9)
Confusional state	6 (5.6)	3 (2.8)	8 (7.8)	6 (5.6)
Headache	5 (4.6)	3 (2.8)	1 (1.0)	3 (2.8)
Vomiting	2 (1.9)	7 (6.6)	1 (1.0)	7 (6.5)

Source: Tables 13.6.2.2 and 13.6.2.3

DISCUSSION

- Variability in perioperative anesthetics and analgesics, types of mesh, size of defects, and surgical techniques across study sites may have confounded pain evaluations[11-13]
- Pregabalin did not demonstrate statistically significant reductions in postoperative pain following inguinal hernia repair compared with placebo; however, the opioid-sparing effects, decreased sleep interference, and improved function post surgery establish the benefit of the perioperative use of pregabalin
- Future research is needed to demonstrate the efficacy and safety of pregabalin in the treatment of postoperative pain following inguinal hernia repair

References: **1.** Erhan Y, et al. *Can J Surg*. 2008;51(5):383–387. **2.** Kehlet H, Rathmell JP. *Anesthesiology*. 2010;112(3):514–515. **3.** Aasvang EK, et al. *Hernia*. 2006;10(4):316–321. **4.** Loos MJ, et al. *World J Surg*. 2007;31(9):1760–1765; discussion 1766–1767. **5.** Massaron S, et al. *Hernia*. 2007;11(6):517–525. **6.** Mikkelsen T, et al. *Anesth Analg*. 2004;99(1):146–151. **7.** Buvanendran A, et al. *Anesth Analg*. 2010;110(1):199–207. **8.** Crofford LJ, et al; Pregabalin 1008-105 Study Group. *Arthritis Rheum*. 2005;52(4):1264–1273. **9.** Stacey BR, et al. *J Pain*. 2008;9(11):1006–1017. **10.** Tölle T, et al. *Eur J Pain*. 2008;12(2):203–213. **11.** Katz J, et al. *Neurology*. 2008;70(4):263–272. **12.** Katz N. *Neurology*. 2005;65(12 Suppl 4):S32–S49. **13.** Kehlet H, et al. *Lancet*. 2006;367(9522):1618–1625.

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