

## Web of Science Academy

### Peer Review Report Template for Co-reviewing with a Mentor

<b>Your name:</b> Soni Sunarso Sulistiawan	<b>Mentor's name:</b> Arie Utariani
<b>Manuscript/paper title:</b> Pregabalin in the reduction of pain and opioid consumption after burn injuries	<b>DOI (if published):</b> 10.1097/MD.0000000000015343
<b>Journal:</b> Medicine	<b>Review due date:</b> 19 August 2021

<b>Summary statement</b> of the article and its findings in your own words	There were no statistically significant differences in median pain scores and opioid consumption before IP administration between the 3 groups (pregabalin 300, pregabalin 600 and placebo).
<b>Major strengths</b> of the article and what <b>impact</b> it might have in your field	Significant strengths of the article are how they analyze their data, and they are honest about their limitation. The impact that may have in my field is that pregabalin is still considered an adjunct therapy in multimodal analgesia regimen for burn injuries, and opioids still are the first choice for pain treatment in burn injuries. The references displayed are varied and complete but need to be improved to use references less than 5 years old.
<b>Specific areas of improvement</b> needed in the article before it can be published	<p><b>Major points</b> (needs for clarification, re-analysis, re-writes and/or additional information and suggestions which would improve the article):</p> <ol style="list-style-type: none"> <li>1. Preliminary study A more detailed explanation of the exclusion criteria and possible gender bias is needed, as it is known that gender plays a role in a person's resilience to pain thresholds.</li> <li>2. Single centered</li> <li>3. Sample size it may be necessary to consider randomization by gender so that the distribution of sampling results can be more evenly distributed between genders</li> </ol> <p><b>Minor points</b> (inconsistencies, major typos)</p> <ol style="list-style-type: none"> <li>1. There are still many references that are over 5 years old.-</li> <li>2. -</li> <li>3. -</li> </ol>

<b>Confidential comments</b> to the editor (include your recommendation for publication here)	Even though there was not statistically significant, the research still has a bright future ahead, and there is still a long way to decide if pregabalin can not be effective for reducing pain and opioid consumption for pain in burn injuries.

## Web of Science Academy

### Peer Review Guidelines

Section	Ask yourself these questions while reviewing each section	Review comments and notes
<b>Introduction</b>	<ol style="list-style-type: none"> <li>1. Is it clear what is already known about this topic?</li> <li>2. Is the research question or aims clearly outlined?</li> <li>3. Is the research question justified given what is already known about the topic?</li> </ol>	The clarity of the topic is exceptionally qualified, the aims of the research have been met in the research results. The research content has also answered the research questions.
<b>Methodology</b>	<ol style="list-style-type: none"> <li>4. Is the study design appropriate to answer the aim?</li> <li>5. Are the study methods valid and reliable?</li> <li>6. Is there enough detail in order to replicate the study?</li> <li>7. If applicable, is the process of subject selection clear?</li> <li>8. Are the variables defined and measured appropriately?</li> </ol>	<b>The design is straightforward, including the inclusion and exclusion criteria • A prospective, randomized, double-blinded, single-centre, placebo-controlled trial • is necessary to consider the different varieties of pain scales for each person.</b>
<b>Results</b>	<ol style="list-style-type: none"> <li>9. Are the results stated clearly?</li> <li>10. Is the data presented in a clear and appropriate way?</li> </ol>	<ul style="list-style-type: none"> <li>• A total of 54 subjects were randomly assigned, and 51 were included in the data analysis. How do you explain the reason for dropping out?</li> </ul>
<b>Discussion and conclusions</b>	<ol style="list-style-type: none"> <li>11. Are the results discussed from multiple angles and placed into context without being overinterpreted?</li> <li>12. Do the conclusions answer the aims of the study?</li> <li>13. Are the conclusions supported by the results? If not, are they supported by references?</li> <li>14. Are the limitations of the study fatal or are they opportunities to inform future research?</li> </ol>	<p>the first and second limitations have almost the same meaning; which is the most significant limitation? Moreover, how to make sure these limitations are not biased? • Conclusion: Pregabalin could be part of an excellent multimodal analgesic regimen in the noncritical burn population•. This study, in principle, answers the aim • still needs a detailed explanation about the possibility of bias and the drop-out criteria or the mechanism of the drop-out. •.</p>
<b>References</b>	<ol style="list-style-type: none"> <li>15. Are the references relevant?</li> <li>16. Have key studies been referenced or is a key reference missing?</li> </ol>	The references used are relevant but there are still references over the age of 5 years.
<b>Title</b>	<ol style="list-style-type: none"> <li>17. Now that you know what the study is about, is the title informative and relevant?</li> </ol>	informative and relevant title and following the content of the research and valuable for the reader
<b>Abstract</b>	<ol style="list-style-type: none"> <li>18. Now that you've read the whole paper, does the abstract clearly summarise what the results and conclusions are and the methodology used?</li> </ol>	The aim is precise, according to the title • The Conclusion:: Pregabalin could be part of an excellent multimodal analgesic regimen in the noncritical burn

		population. The results of the study are also following the initial objectives of the study.
<b>Overall</b>	<ul style="list-style-type: none"> <li>19. What did this study add to what was already known on this topic?</li> <li>20. Is the article consistent within itself?</li> <li>21. Is there anything that stands out in the author or funder statement(s) that makes you question the objectivity of the study?</li> </ul>	The efficacy of pregabalin for post-burn pain management, This research is consistent and continuous with the initial objectives of the research.

# Pregabalin in the reduction of pain and opioid consumption after burn injuries

## A preliminary, randomized, double-blind, placebo-controlled study

Larry M. Jones, MD<sup>a</sup>, Alberto A. Uribe, MD<sup>b,\*</sup>, Rebecca Coffey, CNP, PhD<sup>a</sup>, Erika G. Puente, MD<sup>b</sup>, Mahmoud Abdel-Rasoul, MS, MPH<sup>c</sup>, Claire V. Murphy, PharmD<sup>d</sup>, Sergio D. Bergese, MD<sup>b,e</sup>

### Abstract

**Background:** The primary objective of the study was to evaluate the efficacy of 300 milligrams (mg) and 600 mg of pregabalin compared to placebo in the reduction of pain in patients with noncritical partial and full thickness burn injuries.

**Methods:** A prospective, randomized, double-blinded, single center, placebo-controlled trial was conducted. Simple randomization method was used in this trial. After subjects met all the inclusion and none of the exclusion criteria, they were randomized and assigned to 1 of the 3 18-day treatments groups: Pregabalin 300 group, Pregabalin 600 group, or Placebo group. Demographics and clinical characteristics were recorded. The severity of pain was assessed by using the visual analog scale for pain intensity at baseline on day 3, day 9±3, day 25±7, day 90±6, and day 180±12.

**Results:** A total of 54 subjects were randomly assigned, and 51 were included in the data analysis. Demographics and clinical characteristics did not differ significantly between the 3 groups. There was a statistically significant difference in pain between the Pregabalin 300 and Pregabalin 600 groups ( $P$ -value = .0260). The Pregabalin 300 group had 17.93 units (95% confidence interval: 1.83–34.04) higher pain scores on average than the Pregabalin 600 group, regardless of time. The adjusted  $P$ -value comparing 0 to 300 was .1618, while the adjusted  $P$ -value for 0 versus 600 was .5304. There was an overall difference in pain across time regardless of study group ( $P$ -value = <.0001). An overall difference in opioid consumption ( $P$ -value = .0003) and BSHS ( $P$ -value = .0013) across time regardless of study group was noted.

**Conclusions:** Pregabalin could be part of a promising multimodal analgesic regimen in noncritical burn population. Future placebo-controlled studies assessing the use of pregabalin in burn victim patients may further endorse our findings.

**Abbreviations:** BID = bi-daily, BSHS = burn-specific health scale, CONSORT = consolidated standards of reporting trials, IP = investigational product, IR = immediate release, mg = milligrams, TBSA = total body surface area, VAS = visual analog scale.

**Keywords:** burn, full thickness, opioid consumption, partial thickness, pregabalin

## 1. Introduction

Burns are a common injury requiring medical attention in the US. Of 500,000 burn cases per year, 40,000 require hospitalization.<sup>[1]</sup> One of the major challenges of burn injuries is managing

pain, which presents itself in different forms: a background nociceptive pain, procedural pain, and neuropathic pain.<sup>[2,3]</sup> The type of pain experienced by burn survivors changes after the healing process, and this residual pain is akin to the neuropathic pain described by patients with diabetes or postherpetic neuralgia.<sup>[4]</sup> While neuropathic pain is produced by a disease or injury of the peripheral somatosensory nervous system, nociceptive pain is caused by the stimulation of nociceptors due to non-neural tissue harm.<sup>[5]</sup> The incidence of chronic neuropathic pain in burn patients reported by the literature is as high as 52%, and is mostly described in patients that have experienced considerably higher intensities of acute pain, extensive body surface area burns, and those requiring skin grafting.<sup>[3,6,7]</sup> There are several mechanisms by which burn scarring could lead to neuropathic pain, but the most relevant of these are nerve entrapment by nearby scar tissue and neuroma formation.<sup>[3]</sup> Neuropathic pain is usually reported 4.3±0.5 months following the burn injuries and can persist for years.<sup>[4]</sup> Patients commonly describe the pain as a stabbing, itching, burning, electric shock-like, pins and needles, and/or shooting sensation.<sup>[2,4,7,8]</sup> Managing burn-related neuropathic pain is challenging, and it usually continues after traditional or scar modulation therapies.<sup>[3]</sup> The pain experienced by burn patients is typically treated on a daily basis with a multimodal regimen of narcotics, antipruritics, anticonvulsants, and/or antidepressants that often compromise patients' quality of life due to side effects of such a regimen.<sup>[3,9]</sup>

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Additionally, opioids are currently the most frequently used medications for the treatment of intense pain in burn patients. One of the most notable challenges burn injuries carry is a pain-related decrease in functional ability and quality of life.<sup>[7]</sup> Consequently, post-burn heat sensitivity hinders an individual's ability to participate in outdoor activities, and this lack of physical movement and/or exercise can indirectly lead to further decline on quality of life, including the onset of symptoms of depression.<sup>[10]</sup>

Pregabalin is an analog of gamma aminobutyric acid.<sup>[9,11]</sup> Pregabalin decreases the synaptic release of multiple neurotransmitters (glutamate, noradrenaline, serotonin, dopamine, and Substance P) by binding to the  $\alpha 2\delta$ -subunits of the presynaptic voltage-dependent calcium channels.<sup>[9,12]</sup> As a result, the drug inhibits neuronal excitability, especially in the central nervous system.<sup>[12–14]</sup> Pregabalin has been shown in multiple studies to be an effective analgesic agent in both peripheral and central neuropathic pain, and it is particularly effective in reducing post-burn pain.<sup>[4,9,13,15–17]</sup>

We hypothesized that pregabalin is effective in reducing pain in noncritical recovering burn patients. Secondarily, pregabalin for pain management will improve patient quality of life with a significant reduction of opioid consumption.

## 2. Methods

This study has been described according to the consolidated standards of reporting trials (CONSORT) guidelines for the presentation of clinical trials.<sup>[18]</sup> A prospective, randomized, double-blinded, single center, placebo-controlled trial was conducted. After obtaining institutional review board (Office of Responsible Research Practices-The Ohio State University) approval (Protocol Number 2009H167, approved on January 22, 2010), subjects with noncritical partial and full thickness burn injuries that required hospitalization to manage pain control, social issues or support with personal daily activities at The Ohio State University Wexner Medical Center were approached and provided their written informed consent and completed essential study procedures required to analyze the data between April 2010 and November 2014. This trial was not registered in ClinicalTrials.gov or any other publicly accessible registry because it was not a requirement from institutional guidelines at the moment of IRB approval and enrollment period.

Study inclusion criteria consisted of burn patients with noncritical partial and full thickness burn injuries whose ages ranged from 18 to 85 years, referring moderate-to-severe pain requiring pain management lasting a minimum of 18 days and able to receive oral medication. Subjects with clinically significant renal impairment (defined as a creatinine clearance of  $\leq 60$  ml/min), history of allergy to any anti-epileptic medication, pregabalin or gabapentin, history of cognitive impairment condition, prior consumption of pregabalin or gabapentin (7 days prior of enrollment), current pregnant or breastfeeding, or history of seizure were excluded from the study.

Demographics including age, height, weight, body mass index, race, and gender were collected before randomization. Additionally, clinical characteristics such as total body surface area (TBSA), duration of hospital stay, mean number of treatment days, mean number of total doses administered, and mean numbers of hours from admission time to first investigational product (IP) of the 3 groups were recorded.

After subjects met all of the inclusion and none of the exclusion criteria, a subject identification number from the randomization

list was assigned, and consequently the unblinded pharmacist prepared and dispensed IP. Study medication administration started usually right after subjects were assessed as clinically stable and transferred to the floor through the emergency department.

The 18-day oral pregabalin administration regimen consisted of a tapering-up period (day 1–2), maintenance period (day 3–16), and tapering-down period (day 17–18) in accordance with the following schedule:

- Pregabalin 300 group received 150 mg bi-daily (BID) during the maintenance period, with a dose of 50 mg BID on day 1 and 18, and 100 mg BID for day 2 and 17 during initial and last tapering periods respectively.
- Pregabalin 600 group received 300 mg BID during the maintenance period, with a dose of 75 mg BID on day 1 and 18, and 150 mg BID for day 2 and 17 during initial and last tapering periods respectively.
- The placebo group received matching placebo tablets BID for the duration of the treatment period.

Our institutional standard regimen for pain control consisted of either intravenous morphine preservative-free 2 mg every 2 hours as needed or hydromorphone injection 0.5 mg every 2 hours as needed for severe pain and oxycodone (immediate release) tablet 5 mg every 6 hours as needed for moderate pain. Subjects received intravenous and/or oral opioid medication as pain rescue during hospitalization and subsequently, opioid consumption during hospitalization was collected and converted to oral morphine units for data analysis purposes.

Subjects were discharged home with the remaining drug regimen pertinent to this study. In addition to the IP, subjects received a prescription for standard burn oral pain medication (oral opioids) for use during the time between discharge from the hospital and their next scheduled follow-up visit.

### 2.1. Outcome measurement

The primary objective of the study was to evaluate the efficacy of 300 mg and 600 mg of pregabalin compared to placebo in the reduction of pain in patients with noncritical partial and full thickness burn injuries. The severity of pain was assessed by using the visual analog scale (VAS) for pain intensity; it consisted of a 100 mm long line with 2 descriptors at each end representing pain intensities (no pain and extreme pain). Subjects were asked to mark their pain intensity somewhere on the line, then the VAS score was assessed by measuring the distance from the “no pain” end to the mark placed by the subject. VAS pain assessments were performed at baseline, on day 3, day  $9 \pm 3$ , day  $25 \pm 7$ , day  $90 \pm 6$ , and day  $180 \pm 12$ .

As secondary outcomes, opioid consumption measurement and quality of life assessments were made at different time points throughout the study for comparison. Opioid consumption (oral morphine per day) before first dose of IP until hospital discharge or day 3 (whichever occurs first) was recorded. A Quality of Life questionnaire – the Burn Specific Health Scale (BSHS)<sup>[19]</sup> – was administered to all study groups at baseline, on day  $25 \pm 7$ , day  $90 \pm 6$ , and day  $180 \pm 12$ .

Side effects, if reported, were collected immediately after first dose of IP and during each study visit. Complete blood count with differential, electrolytes, and liver function tests at baseline day  $25 \pm 7$  were collected and assessed by a licensed physician acting as a sub-investigator

## 2.2. Sample size

A sample size of 33 per group, with an 80% power to detect significant differences in pain levels of at least 17 mm on the VAS for pain between the treatment groups and placebo group at any of the evaluated time points was calculated. A conservative standard deviation of 20 was assumed for this calculation. Also, we had 80% power to detect at least an effect size of 0.85 in opioid consumption between the 2 treatment groups and control groups at discharge. A 1 sided 2-sample *t* test with an alpha of 0.006 (0.05/8) was assumed in this calculation to account for 2 comparisons at each of the 3-time points for pain score, and 2 comparisons at discharge for opioid consumption. A total of 40 patients per group was planned to be enrolled into the study to account for drop-outs or lost to follow-up patients. However, due to a high incidence of loss of follow up during the last period of the study and an unanticipated change of institutional standard of care for burn patients (use the application of long-acting Silver dressing for 7 days for partial thickness burns and early discharge [24–36 hours after its application] instead of topical antibiotics and daily dressing changes), the investigators decided to close study enrollment and conduct the data analysis with the available 51 subjects in order to be proceed with this publication as a preliminary study.

The randomization method utilized in this study was simple randomization; before enrollment activities, an unblinded research pharmacist generated a randomization list (using an online random list generator <http://randomization.com>) and allocated each listed subject to 1 of the 3 treatments groups: Pregabalin 300 group, Pregabalin 600 group, or Placebo group.

The blinding process was maintained by using placebo tablets identical to the active tablets with different doses. Subjects, health care providers, and research personnel were blinded throughout the study. Only the research pharmacist, who prepared the IP following randomization allocation, was aware of the specifics of each patient's drug regimen.

## 2.3. Statistical methods

Continuous demographic and clinical variables were compared between treatment groups using analysis of variance or nonparametric Kruskal–Wallis tests where relevant. Categorical variables were compared using chi-square or Fisher exact tests where relevant. A linear mixed effects model was fit to estimate and compare the primary pain longitudinal outcome and included main effects and an interaction term for study group and time. The model also included random intercepts to account for repeated measures within patient. Multiple hypotheses testing between study groups were adjusted for using the Bonferroni–Holm step down method to control the overall type 1 error rate at 5%. A similar mixed effect model was fit to assess the BSHS secondary endpoint. Kruskal–Wallis nonparametric tests were used to test differences in opioid consumption between study groups during hospitalization before and after IP administration, respectively. The data were analyzed using SAS, version 9.4 (SAS Institute Inc, Cary, NC). Adjusted *P*-values <.05 were considered to be statistically significant.

## 3. Results

The flow diagram of this clinical trial according to the CONSORT 2010 is shown in Figure 1.<sup>[18]</sup> Over a 55-month period (April 2010 to November 2014), a total of 316 subjects

with acute burn injury were assessed as potential candidates for this study after admission. After the eligibility assessment of each subject, 262 were considered ineligible or refused to participate in the initial phase of this trial. The remaining 54 subjects underwent screening procedures and were consequently enrolled into the study. However, 3 subjects were considered early termination after randomization; 2 subjects withdrew from the study after receiving the first dose due to adverse events that they related to IP, including nausea and dizziness, and 1 subject withdrew from the study before receiving the study medication was started. After removal of the blind, 19 subjects were allocated to the Placebo group, 18 to the Pregabalin group and 14 to the Pregabalin 600 group. Therefore, data analysis of 51 subjects was conducted using an intention-to-treat manner.

There were no significant differences in demographics and clinical characteristics, duration of hospital stay, mean number of treatment days, mean number of total doses administered, mean number of hours from admission time to first IP among the 3 groups) among the 3 groups (Table 1).

The primary outcome measured pain scores over day 9, day 22, day 90, and day 180. There were no statistically significant differences in median pain scores between the 3 groups at any of the time points (Table 2). Additionally, the rate of change of pain scores did not differ between study groups (interaction term *P*-value=.9060) (Fig. 2).

In addition, there was no statistically significant difference in opioid consumption before IP administration (oral morphine, milligrams per day [mg/d]) among all the groups (*P*-value=.8789). In addition, there was no statistically significant difference in opioid consumption before discharge (oral morphine, mg/d) among all the groups after IP initiation (*P*-value=.3064). (Table 3 and Fig. 3)

Pro re nata opioid medication most commonly used during hospitalization were as follows: intravenous fentanyl, intravenous morphine, intravenous hydromorphone, oral oxycodone, oral methadone, oral hydrocodone, and oral tramadol.

There was no statistically significant difference in BSHS between the groups (*P*-value=.6411); however, an overall difference in BSHS across time regardless of study group (*P*-value=.0013) was noted.

Adverse events related to study drug were uncommon with no difference among all groups and no serious adverse events were reported throughout the study (Table 4).

## 4. Discussion

A few limitations during the conduction of the study are important to mention. The first limitation involves an attrition bias; the investigators experienced a high incidence of lack of follow-ups once subjects were discharged from the hospital. The second limitation was the lack of post-hospital discharge opioid consumption data collection due to the aforementioned follow-up gapping and accuracy of information provided by the subjects. A third limitation that disrupted the enrollment rate and the completion of the study was the aforementioned unanticipated change of institutional standard of care of burn patients, the implementation of conservative management of burn wounds led to a reduction of hospital admissions or length of stay in the burn population at our institution. As a result of these important limitations, the investigators decided to close study enrollment early and run an unplanned data analysis with the available data of 51 subjects of the 120 planned subjects, to be presented in this publication.

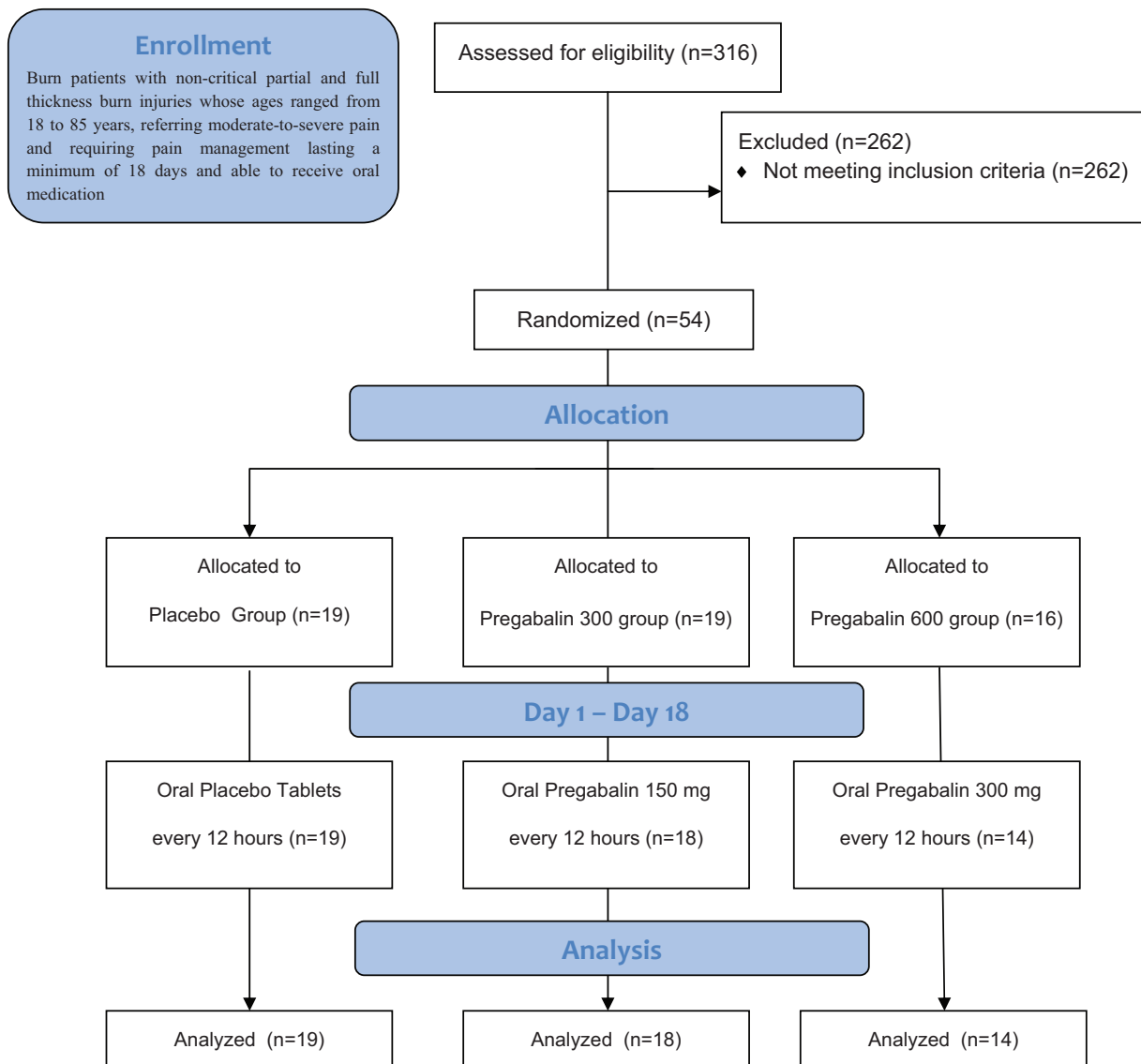


Figure 1. Trial profile according to CONSORT guidelines. CONSORT = consolidated standards of reporting trials.

Table 1

Demographics and clinical characteristics.

Demographics and clinical characteristics	Placebo group n=19	Pregabalin 300 group n=18	Pregabalin 600 group n=14	P-value
Age in years, mean (SD)	37.5 (±12)	36 (±11.4)	42.6 (±14.1)	.3146
Weight in kg, mean (SD)	84.3 (±15.5)	87.5 (±15.6)	91.2 (±23.8)	.5586
Height in cm, mean (SD)	173.6 (±9.0)	175.0 (±11.0)	171.1 (±14.1)	.6212
BMI, mean (SD)	27.9 (±4.9)	28.6 (±5.1)	31.3 (±8.6)	.2817
Race-White	14 (74)	13 (72)	11 (79)	>.999
Male	17 (89)	15 (83)	9 (64)	.1974
TBSA %, median (IQR)	6.17 (±4.55)	6.14 (±4.43)	6.00 (±4.75)	.8575
Trunk burn coverage %, mean (SD)	1.11 (±2.85)	0.31 (±0.79)	1.27 (±3.45)	.4809
Genitalia burn coverage %, mean (SD)	0.05 (±0.23)	0.06 (±0.24)	0 (±0.00)	.679
Head and neck coverage %, mean (SD)	1.03 (±1.33)	0.94 (±1.23)	0.82 (±1.42)	.7515
Upper extremities coverage %, mean (SD)	3.07 (±2.46)	2.61 (±2.77)	2.21 (±2.76)	.5076
Lower extremities coverage %, mean (SD)	0.92 (±2.07)	2.49 (±4.13)	1.70 (±2.16)	.1846
Duration of total hospital stay, mean (SD), days	2.21 (±1.28)	2.70 (±2.00)	4.70 (±4.95)	.213
Number of treatment days, mean (SD)	12.36 (±7.0)	10.3 (±7.3)	10.8 (±7.6)	.6207
Number of doses, mean (SD)	24.56 (±13.84)	20.5 (±14.7)	21.2 (±14.5)	.6854
Hours from admission to first IP dose, mean (SD)	24.3 (±12.8)	31.5 (±24.9)	33.2 (±15.9)	.3369

Unless otherwise indicated values are presented as number of cases (%).

% = percentage, cm = centimeter, IP = investigational product, kg = kilogram, n = number of cases, SD = standard deviation.

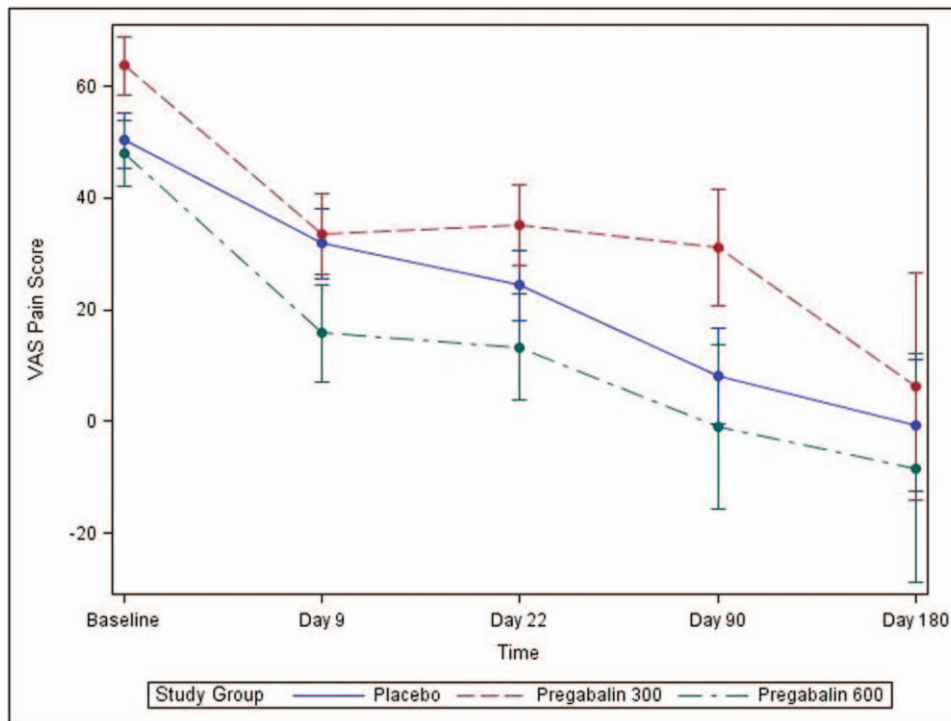


**Table 2**

**Pain throughout study time points.**

Time points	Placebo group n=19	Pregabalin 300 group n=18	Pregabalin 600 group n=14	P-value Pregabalin 300 versus Placebo	P-value Pregabalin 600 versus Placebo	P-value Pregabalin 300 versus Pregabalin 600
Baseline	50.3 (40.3, 60.3)	63.7 (53.4, 74.0)	47.9 (36.3, 59.6)	.93	>.99	.7
Day 9, median (IQR)	31.9 (19.6, 44.2)	33.5 (19.4, 47.7)	15.8 (0.0, 33.1)	>.99	>.99	>.99
Day 22, median (IQR)	24.4 (12.0, 36.7)	35.2 (21.0, 49.4)	13.3 (0.0, 32.2)	>.99	>.99	.93
Day 90, median (IQR)	8.2 (0.0, 25.1)	31.2 (10.6, 51.8)	0.0 (0.0, 28.1)	.99	>.99	.93
Day 180, median (IQR)	0.0 (0.0, 22.7)	6.1 (0.0, 46.6)	0.0 (0.0, 32.3)	>.99	>.99	>.99

IQR=interquartile range, n=number of cases.



**Figure 2.** Pain throughout study time points (VAS for pain intensity). VAS = visual analog scale.

This prospective, randomized, double-blinded, single center, placebo-controlled trial demonstrated that dosing 600 mg of oral pregabalin per day provides superior pain control in patients with both noncritical partial and full thickness burn injuries as compared to dosing oral 300 mg pregabalin per day. A substantial reduction of pain relief was observed in the Pregabalin 600 group when compared to the Pregabalin 300 group ( $P < .260$ ). In

addition, no statistically significant degree of pain relief was revealed in the Pregabalin 300 group and Pregabalin 600 group when compared to the placebo group ( $P < .5304$ ). However, there was an overall difference in pain and opioid consumption across time regardless of study group ( $P\text{-value} = < .0001$ ); indicating that subjects had lower pain values and consume less opioid medication on average as the treatment period progressed. These facts could

**Table 3**

**Opioid consumption, prior and after investigational product administration (oral morphine, mg/day).**

Time points	Placebo group n=19	Pregabalin 300 group n=18	Pregabalin 600 group n=14	P-value Pregabalin 300 versus Placebo	P-value Pregabalin 600 versus Placebo	P-value Pregabalin 300 versus Pregabalin 600
Opioid consumption (mg/d), before IP administration, median (IQR)	140.0 [102.3, 230.6]	169.5 [83.9, 288.4]	163.5 [92.0, 259.0]	.93	.97	.89
Opioid consumption (mg/d), after IP administration, median (IQR)	73.3 [0, 141.3]	116.9 [80.7, 207.5]	60.35 [4.61, 147.95]	.38	.99	.4

IP=investigational product, IQR=interquartile range, Legend=number of cases, mg/d=milligrams per day.

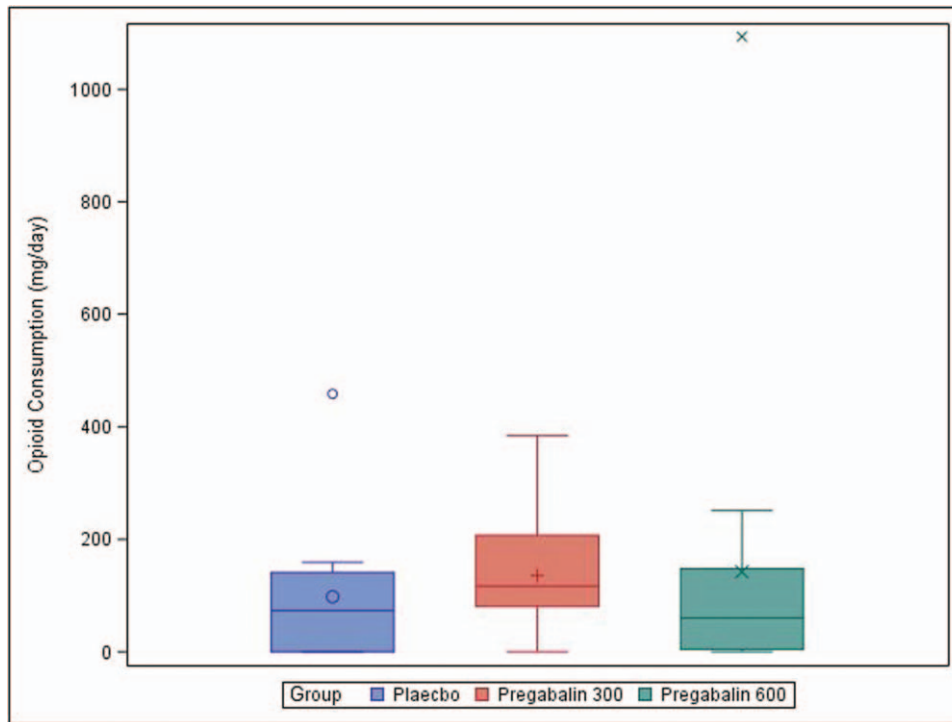


Figure 3. Opioid consumption throughout study time points (oral morphine, mg/day).

suggest that the dosage amount of pregabalin could be essential for adequate pain management in burn patients. Finally, there was an overall difference in BSHS across time regardless of study group ( $P$ -value = .0013); this indicated that people had higher average BSHS scores as recovery time progressed, but this did not differ by study group. Therefore, quality of life did not differ significantly between study groups but improved on average over time regardless of study group. These facts could suggest that the dosage amount of pregabalin could be essential for adequate pain management in burn patients. Previous to our study, only 3 other published clinical trials have assessed the efficacy of pregabalin in the management of post-burn pain.<sup>[2,4]</sup>

Pregabalin is an anti-epileptic drug, as well as a gabapentinoid, with a chemical structure similar to gabapentin.<sup>[9,14]</sup> Commonly described side effects of pregabalin include dizziness, somnolence, peripheral edema, weight gain, and asthenia.<sup>[13]</sup> The recommended dose of pregabalin for pain management is 100 mg 3 times per day (300 mg/d), with an initial titration period of 50 mg 3 times per day (150 mg/d) during the first week.<sup>[20]</sup> Both pregabalin and gabapentin have been shown to be a well-tolerated and effective for neuropathic pain disorders; however, pregabalin has demonstrated equivalent efficacy in comparison to gabapentin while requiring lower doses.<sup>[4,20,21]</sup> Pregabalin has linear pharmacokinetics, undergoes minimal metabolism, and

Table 4

Adverse events.

Adverse events	Placebo group (N=19)		Pregabalin group 300 (N=18)		Pregabalin group 600 (N=14)	
	N subjects	N events	N subjects 2	N events 3	N subjects 4	N events 2
At least 1 AE, n (%)	2 (10.5%)	2	2 (11.1%)	6	2 (14.3%)	5
Any SAE	0	0	0	0	0	0
Any event leading to study withdrawal, n (%)	1 (5.3%)	1	1 (5.6%)	1	1 (7.14%)	1
List of Adverse Events, n (%)						
Wound burn swelling	0	0	1 (5.6%)	1	0	0
Chest tightness	0	0	1 (5.6%)	1	0	0
Dizziness	0	0	1 (5.6%)	1	1 (7.14%)	1
Cooper taste	0	0	1 (5.6%)	1	0	0
Edema low extremity	0	0	1 (5.6%)	1	0	0
Itching	0	0	1 (5.6%)	1	0	0
Flushing	0	0	0	0	1 (7.14%)	1
Insomnia	0	0	0	0	1 (7.14%)	1
Hypertension	1 (5.3%)	1	0	0	0	0
Nausea	1 (5.3%)	1	0	0	0	0

% = percentage, AE = adverse events, N = number, SAE = serious adverse events.

98% of the absorbed dose is renally excreted unaffected.<sup>[20]</sup> Thus, its mean elimination half-life of 5.5 to 6.7 hours.<sup>[20]</sup>

A retrospective review study published in 2009 by Wong et al reported their experience administering pregabalin (up to 600 mg) to 13 subjects that referred subjective symptoms of post-burn neuropathic pain in an outpatient setting.<sup>[4]</sup> This study showed a pain score reduction on 69% of the treated subjects and a proficient tolerability profile of pregabalin.<sup>[4]</sup>

In 2010, a randomized, double-blinded, placebo-controlled trial with 90 inpatients with 5% or greater TBSA burn injury and treated with pregabalin for 28 days; Gray et al demonstrated that hot ( $P=.01$ ) and sharp ( $P=.04$ ) pain could be significantly reduced following a pregabalin regimen of progressively increasing doses starting at 75 mg twice per day to a maximum of 300 mg twice per day.<sup>[2]</sup> There was no statistical difference in adverse events, opioid consumption, length of stay, or pain at 6 months between the treatment groups.<sup>[2]</sup> In addition, secondary outcome measures of itch, unpleasantness, surface pain, and procedural pain were significantly lower ( $P<.05$ ) in the pregabalin group compared to the placebo group.<sup>[2]</sup> In Gray's study, the greatest improvement in pain scores was seen in the cohorts of patients with greater TBSA.<sup>[2]</sup> However, Gray et al discussed their exclusion subjects with  $\leq 5\%$  TBSA as a limitation of their study and suggested that future studies include patients with burn areas of less than 5%.<sup>[2]</sup> We consider that our study addressed this limitation, since our study population had a median TBSA of 5.0% (3.0%–9.00%) with suitable pain reduction after pregabalin regimens.

Another retrospective study conducted in 2017 assessed the efficacy of gabapentin versus pregabalin and gabapentin in the treatment of post-burn neuropathic pain and itching in 136 subjects under 20 years of age.<sup>[9]</sup> Out of these 136 subjects, only 24 received both pregabalin and gabapentin; where 88.2% of the subjects expressed a satisfactory response for management of pain and pruritus.<sup>[9]</sup>

In conclusion, this is another prospective, randomized, double-blinded, single center, placebo-controlled trial study that assessed the use of pregabalin on post-burn pain in an acute setting. The primary goal of this 3-armed study was to compare the efficacy of 300 mg pregabalin versus 600 mg pregabalin versus a placebo for post-burn pain management. The different doses of pregabalin in this study were well tolerated. However, our results in conjunction with other published clinical trials demonstrated that future placebo-controlled studies assessing the use of pregabalin in non-critical burn population may be needed in order to have a better understanding of the role of pregabalin as part of a multimodal analgesia approach and other related post-burn clinical outcomes. A search for funding to support the implementation of future placebo-controlled studies assessing the use of pregabalin in noncritical burn victims as part of a multimodal analgesia approach for the management of post-burn neuropathic pain and other related post-burn clinical outcomes will be conducted to further endorse our findings.

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LJ participated in methodology, data collection, and manuscript editing. SB, AU, EP, and RC participated in literature search, study design, methodology, data collection, data analysis, and manuscript editing. MA participated in data analysis and manuscript editing. CM participated in study design, methodology, data collection, and manuscript editing

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