Scientific Research Publishing

Open Journal of Anesthesiology, 2025, 15(10), 231-241
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Evaluation of Acetaminophen Tramadol, Tefenol® Tablets in Acute Pain Real Life Study

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How to cite this paper: Gonzalez Yibirin, M., Rincón Matute, D. and Chirinos Cermeño, J. (2025) Evaluation of Acetaminophen Tramadol, Tefenol® Tablets in Acute Pain Real Life Study. *Open Journal of Anesthesiology*, **15**, 231-241.
https://doi.org/10.4236/ojanes.2025.1510018

Received: July 11, 2025
Accepted: October 12, 2025
Published: October 15, 2025

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Abstract

Pain is an unpleasant sensory and emotional experience associated with or similar to that associated with actual or potential tissue damage. Acute pain is a short-term physiological response to an adverse stimulus, associated with surgery, trauma or acute illness. The best intervention strategy is the one that achieves greater well-being with minimal adverse effects. The combined use of analgesics with different mechanisms of action achieves better analgesic efficacy with less toxicity. Objective: To evaluate the efficacy and tolerability of the combination Acetaminophen-Tramadol produced by LETI Laboratories, in the relief of acute pain of different etiology, in real-life conditions. Materials and methods: It was a prospective, observational, multicenter study, which included patients with acute pain of any etiology, or exacerbation of chronic pain, in whom the physician considered that the product was indicated for the short-term relief of that pain. Patients were instructed to take 1 tablet of Tramadol 37.5 mg and acetaminophen 325 mg (Tefenol® Tablets), orally, every 8 hours, at the same time of the day and to note the time of daily intake. Pain was assessed using a visual analogue scale (VAS) and pain relief was assessed using the PAIN RELIEF scale at times 0, 1, 2, 3, 4 and 5 days, every 24 hours, just before the first dose of the day. Results: There was a significant decrease in the VAS between each period analyzed until day 5 of treatment. The sums of the differences in Pain Intensity increased significantly at each of the assessment times. The sum of pain intensity relief increased significantly at each of the assessment times. Significant pain relief was observed on both scales in each evaluation period, indicating a progressive and constant effect throughout the evaluation period. Conclusions: Tramadol 37.5 mg and acetaminophen 325 mg (Tefenol® Tablets) is a useful association for the adequate management of acute pain and pain exacerbation in patients with chronic pain, with good tolerance.

Keywords

Pain, Visual Analogue Scale, Pain Relief, Tramadol, Acetaminophen

1. Introduction

Pain has been a concern throughout the history of medicine, as evidenced by Hippocrates' phrases: primum non nocere ("first do no harm") and divinum opus est sedare dolorem ("divine work is to relieve pain") [1]. Pain is the leading cause of medical consultation. The economic cost of pain is immense. In the United States alone, in 2010, total costs are estimated at between $560 and $635 billion [2].

In 1979, the International Association for the Study of Pain (IASP) defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

In 2020, the IASP proposed a new definition: Pain is an unpleasant sensory and emotional experience associated with or similar to that associated with actual or potential tissue damage. The following comments were made on this new definition:

- Pain is always a subjective experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena: the experience of pain cannot be reduced to the activity of sensory pathways.
- Through their life experiences, people learn the concept of pain and its applications.
- A person's account of an experience as pain should be accepted as such and respected.
- Although pain often serves an adaptive function, it can have adverse effects on social and psychological function and well-being.
- Verbal description is only one of various behaviors to express pain; the inability to communicate does not negate the possibility that a human being or non-human animal experiences pain [3].

Acute pain is a short-term physiological response to an adverse stimulus, associated with surgery, trauma, or acute illness. A correct assessment should always be made, collecting the measurement of intensity by simple, quick, and practical scales [4].

The best intervention strategy is the one that achieves the greatest well-being with the least adverse effects. The proposal must take into account the risk profile and comorbidity. In mild pain, the first option is paracetamol (acetaminophen). When the pain is moderate, NSAIDs alone or in combination with minor opioids are effective, and, if they must be avoided, the combination of paracetamol with minor opioids is a valid alternative. The combined use of analgesics with different mechanisms of action achieves better analgesic efficacy with less toxicity. Two NSAIDs should not be combined, due to the greater frequency of adverse effects. When the pain is intense, the greatest analgesic efficacy is achieved with potent

opioids. Analgesic escalation prolongs the patient's suffering. When the pain is colic-like, metamizole or NSAIDs such as diclofenac or ketorolac can be used. In severe pain, it may be useful to introduce potent opioids, alone or in combination with paracetamol, metamizole or NSAIDs [4].

The proposal should take into account the age, type of pain, intensity, risk profile and comorbidity. In many cases, a single drug may be sufficient. In others, the use of two or more drugs will be necessary in order to achieve maximum patient well-being [4]. The addition of NSAIDs or acetaminophen to opioid analgesics can achieve a "sparing effect", such that a lower dose of opioids can relieve pain with fewer side effects [5] (**Figure 1**).

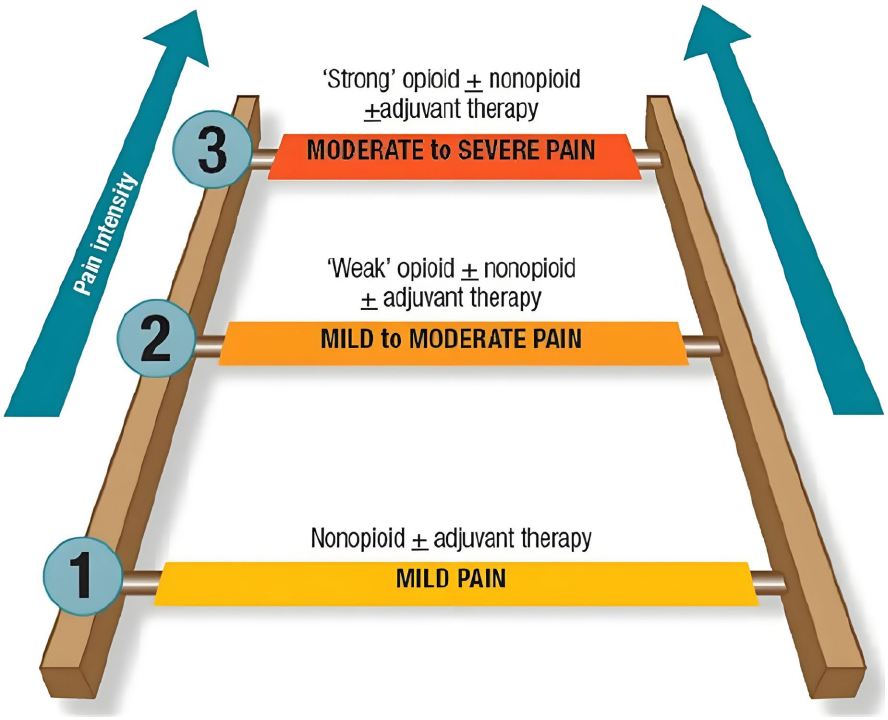

Figure 1. WHO analgesic ladder [6].

Tramadol is an opioid analgesic that acts on the central nervous system. It is a non-selective pure agonist of the mu (μ), delta (δ) and kappa (κ) opioid receptors, with a greater affinity for the μ receptors, exerting its analgesic action by a dual mechanism: binding to the opioid receptors (mainly μ), and blocking the reuptake of noradrenaline and increasing the release of serotonin.

Acetaminophen (paracetamol) has an analgesic and antipyretic action, with very little or no anti-inflammatory activity. Its mechanism of action is at the level of the central nervous system and this action is related to the inhibition of the production of prostaglandins by blocking cyclooxygenases (specifically COX-3). It also stimulates the descending serotonergic pathways that block the transmission of nociceptive signals to the spinal cord from peripheral tissues; and its antipyretic action relates to the inhibition of prostaglandin E1 (PGE1) synthesis at the hypothalamic level.

The combination of two agents such as tramadol and paracetamol, with com-

plementary mechanisms of action and multiple therapeutic targets, could be more effective in the treatment of various types of pain

2. Objective of the Study

To evaluate the efficacy and tolerability of the active combination of Acetaminophen Tramadol produced by LETI Laboratories, in the relief of acute pain of different etiology, in real-life conditions.

3. Materials and Methods

It was a prospective observational, multicenter study, which included patients with acute pain of any etiology, or exacerbation of chronic pain and in whom the physician considered the product was indicated for the short-term relief of that pain, could be entered into the study.

The study was approved by the Autonomous Health Oversight Service, which is part of the Ministry of People's Power for Health of the Government of the Bolivarian Republic of Venezuela.

It included patients, male or female, between 18 and 70 years of age, after having read and signed the informed consent of the subject.

Patients were not included if patients had used ibuprofen, acetaminophen (paracetamol), or aspirin within 6 hours before the first dose of study medication, or if patients had used any other prescription or over-the-counter pain medication within 24 hours before the first dose of study medication.

Patients who had used medications for epilepsy or depression within the past 3 weeks, steroids within 3 months before study entry, or any other long-term treatment with steroids, tramadol, tramadol hydrochloride/acetaminophen, or any other oral opioid or opioid combination during the course of the current episode of acute pain were also excluded. Patients who had used transcutaneous electrical nerve stimulation (TENS) within 2 weeks of study entry were excluded.

Other exclusion criteria were patients who had used an investigational drug within the past 30 days, patients with significant medical conditions, uncontrolled high blood pressure or diabetes, pregnancy, or breastfeeding. Patients with any condition that may affect the way the body absorbs or processes the study drug, history of suicidal thoughts or suicide attempts in the past 2 years, history of a major psychiatric disorder in the past 6 months, history of drug or alcohol abuse or dependence. Patients with a history of allergy or hypersensitivity to tramadol or acetaminophen (paracetamol). Patients with ASA IV status, or higher, from the American Society of Anesthesiologists and Physical Status Classification.

Each patient was given a box containing 20 tablets of Tramadol 37.5 mg and acetaminophen 325 mg (Tefenol® Tablets) with instructions to take it orally every 8 hours, always at the same time of day, during 5 days, and to write down the time of daily intake.

The main effectiveness variables were: the level of pain at the beginning, using a VAS pain scale where 0 means no pain and 10 the maximum possible pain; pain

relief was evaluated using the PAIN RELIEF scale at times 0, 1, 2, 3, 4 and 5 days every 24 h just before the first dose of the day.

The sum of pain intensity differences, SPID, in the context of pain, refers to the sum of the differences in pain intensity from baseline, weighted by the time since the last measurement [7] and total pain relief, TOPAR is a measure used to quantify the extent of pain relief experienced by a patient over a specific period. It is a time-weighted measure, often calculated by summing the pain relief scores recorded at different time points. A higher TOPAR score indicates greater overall pain relief, at times 1, 2, 3, 4 and 5 days were also calculated [8].

The presence of adverse effects was evaluated by direct questioning of the patient.

The variables VAS, PAIN RELIEF, SPID and TOPAR at 0-1-2-3-4-5 days were analyzed using a non-parametric test, Wilcoxon Rank Test. (SPSS IBM Statistics V 26)

An analysis was performed by intention to treat, that is, those patients who received at least one dose of the product under evaluation and had a post-treatment evaluation in the first 5 days of its start were included in the analysis.

4. Results

Four hundred and forty-three patients entered the study and 383 patients were analyzed by ITT.

Table 1 shows that the patients had an average age of 54.2 years with extremes of 14 and 92 years, with a tendency to be overweight and normal blood pressures. Table 2 lists the main diagnosis of the patients included in the study.

Table 1. Anthropometric variables.

Variable	Mean Values	Deviation
Age (years)	54,2	14-92
Sex (F/M)	243/137	
Weight	75,0	16,5
Height	1,7	0,1
BMI	27,2	5,5
SBP	123,1	12,7
DBP	77,8	11,4

Table 2. Main diagnosis.

Diagnosis	N°	%
Acute or chronic low back pain, lumbar disc disease	90	26,1
Acute cervical pain, chronic cervical disc disease	40	11,6
Arthritis and osteoarthritis	59	17,1
Fractures and trauma	59	17,1
Tendinitis, bursitis	37	10,7
Neuritis, neuropathic pain	20	5,8
Others	40	11,6

There was a significant decrease in the Pain scale measured by a Visual Analogue scale of 0 - 10 between each period analyzed until day 5 of treatment (Wilcoxon Rank Test) (Figure 2).

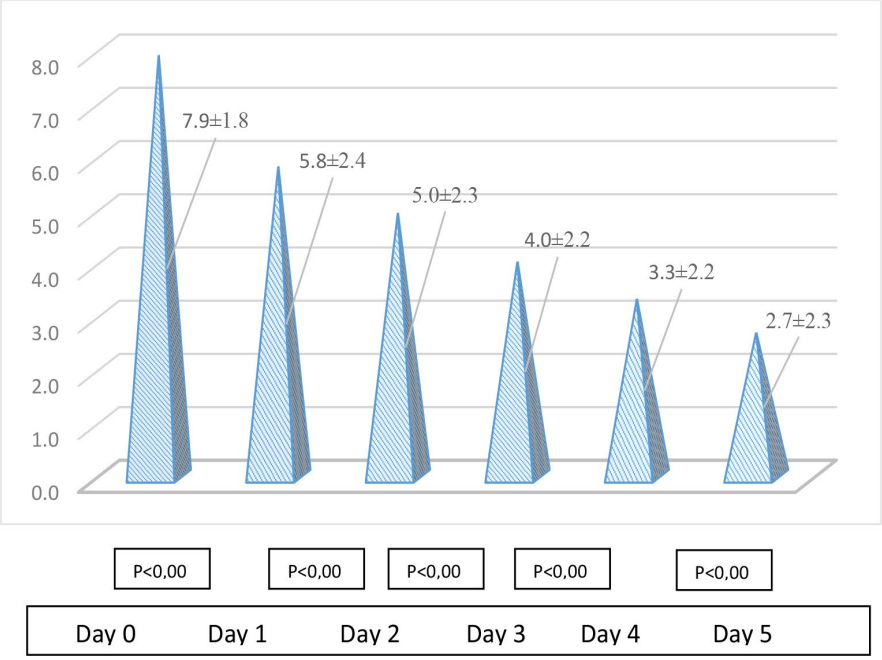

Figure 2. Evolution of the VAS 0 - 10 Pain scale.

The sums of the differences in Pain Intensity increased significantly at each of the evaluation times (Wilcoxon Rank Test) (Figure 3).

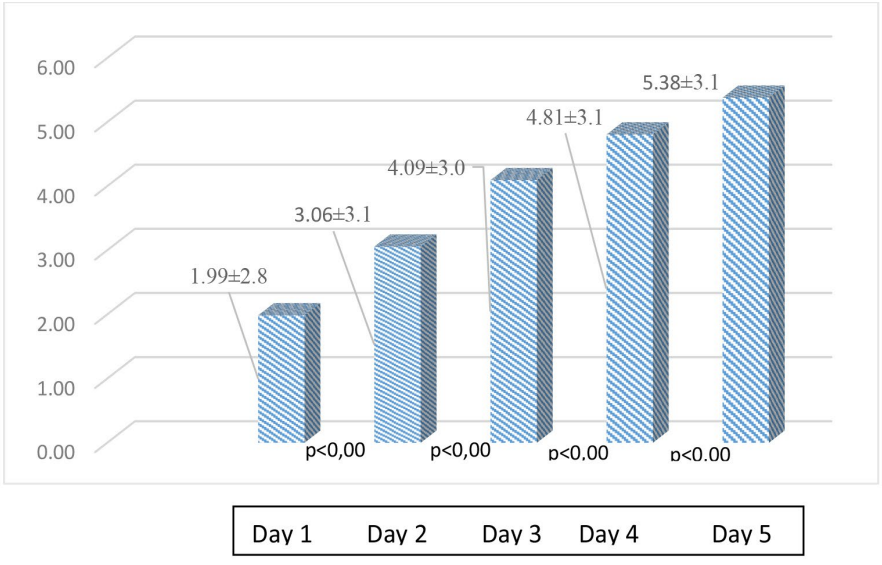

Figure 3. Evolution of the differences in pain intensity SPID Scale.

The relief of pain intensity increased significantly at each of the evaluation times (Wilcoxon Rank Test) (Figure 4).

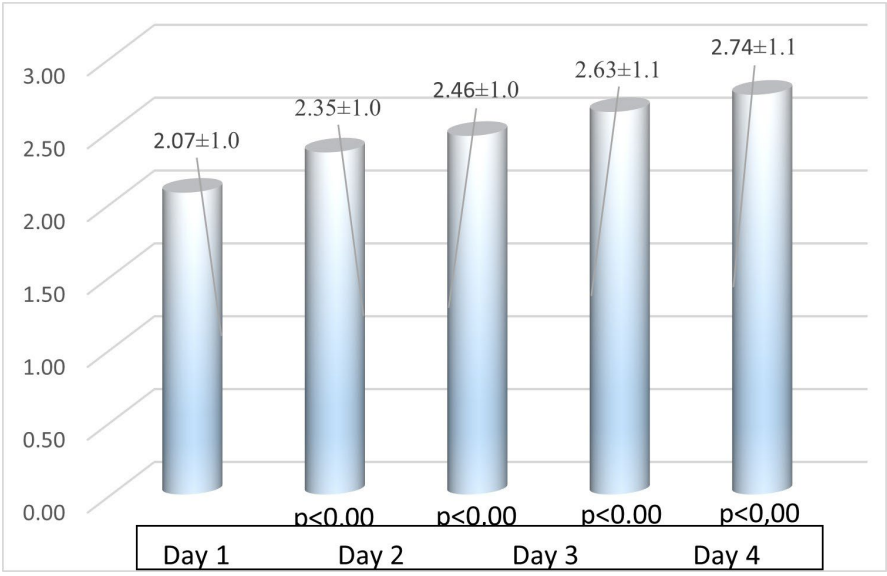

Figure 4. Evolution of the Pain Relief Scale. PAIN RELIEF.

The sum of pain intensity relief increased significantly at each evaluation time point (Wilcoxon Rank Test) (**Figure 5**).

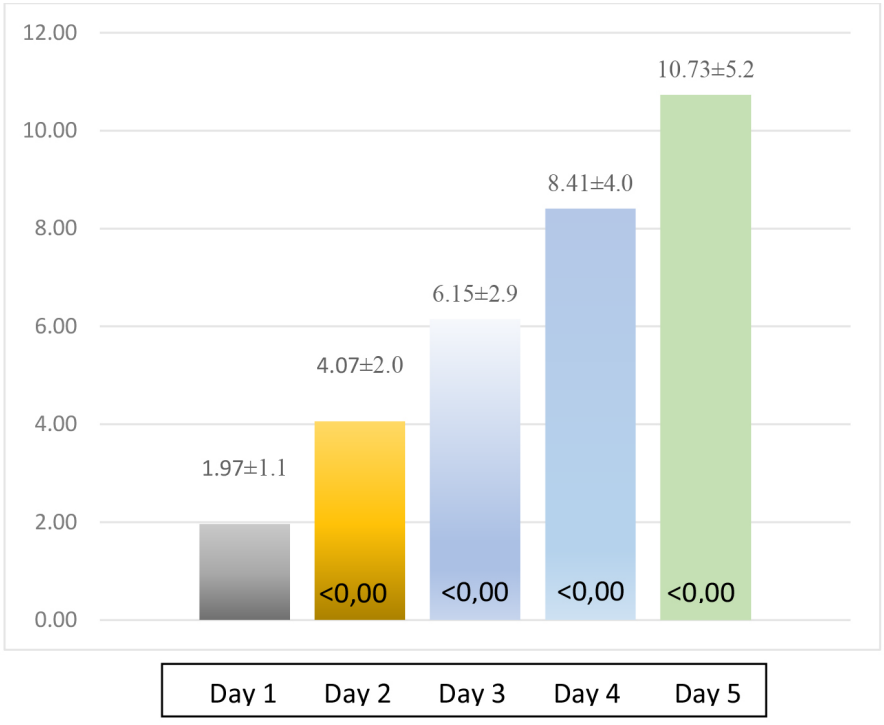

Figure 5. Summation of the pain relief scale TOPAR Scale.

Power Calculation for the Comparison of Two Means vas 0 - 10 Day 0 to day 5.

Power calculation for a study comparing the mean value of two independent groups.

Mean value in the first group 7.92 (VAS initial).

Mean value in the second group 2.71 (VAS Final).

Minimum difference to be detected 1.

Standard deviation in the reference group 1.8.

Sample size in each group 383.

Confidence level 0.95.

Statistical power one-sided approach 100.00%, two-sided approach 100.00%.

Eighty-one (81, 20%) adverse effects (AE) were reported; the most frequent AE was drowsiness in 23 patients (6%), followed by dizziness in 14 patients (3.7%), nausea in 5 patients (1.3%). The rest of the AE were: low blood pressure in 4 patients, headache in 4 patients, 2 cases of gastric discomfort, vomiting: 2, fainting: 2, diarrhea: 1, dehydration: 1, flatulence: 1, dermatitis: 1 and sweating: 1.

Fifty-six patients required rescue medication, that is, 14.6% of the patients, which was done with Ibuprofen, Ketorolac, Meloxicam, Ketoprofen, Diclofenac, Etoricoxib, Pregabalin, and steroids.

5. Discussion

Pain control is essential to quality of life. Pain prevents people from doing normal activities of daily living, whether work or pleasure, and can affect mood and the ability to think, i.e., decrease productivity.

The combination of acetaminophen and tramadol has been used successfully in the treatment of acute pain and in the exacerbation of chronic pain [9].

In chronic pain, such as patients with osteoarthritis, the combination of Tramadol 37.5 mg, Acetaminophen 325 mg was found to be as effective as the combination of codeine 30 mg, Acetaminophen 300 mg and with better tolerability [10].

Another study reported that the combination of Tramadol-Acetaminophen is effective as an adjunctive therapy with a selective inhibitor of cyclooxygenase-2 (COX-2, celecoxib or rofecoxib) in the treatment of pain in osteoarthritis [11].

A multicenter, double-blind study evaluated the efficacy and tolerability of the combination tablet formulation of Tramadol 37.5 mg, Acetaminophen 325 mg as adjunctive therapy, in subjects with rheumatoid arthritis with uncontrolled pain on NSAIDs. The combination Tramadol-Acetaminophen as adjunctive therapy was associated with significantly improved pain relief and a significant reduction in pain intensity compared to placebo [12].

Another study compared the analgesic efficacy of tramadol/acetaminophen (APAP) (total dose 75 mg/650 mg) and tramadol (total dose 100 mg) for pain control after oral surgery. A total of 456 patients with moderate to severe pain within 5 h after extraction of two or more third molars were randomized to receive two identical encapsulated tablets containing tramadol/APAP 37.5 mg/325 mg, tramadol 50 mg, or placebo. Tramadol/APAP was superior to tramadol ($P < 0.001$) or placebo ($P < 0.001$) on all efficacy measures. The most common adverse events with active treatment were nausea, dizziness, and vomiting; these events occurred more frequently in the tramadol group than in the tramadol/APAP

group. This study established the superiority of tramadol/APAP 75 mg/650 mg over tramadol 100 mg in the treatment of acute pain after oral surgery [13].

For a drug to be approved by health authorities, it must go through a complex and lengthy process of clinical research and development before reaching the scientific community and patients in general. However, what happens once this drug is on the market? Does drug research end once the health authorities have approved it?

The answer is no, and it is essential to know how a drug works in real-life conditions. Once the authorization has been obtained, when a drug is integrated into the therapeutic arsenal of health professionals, its use expands and becomes available to all types of patients, not selected, in real clinical practice. That is why after the approval of a drug, observational studies of real life or Real World Evidence are carried out.

These studies aim to learn more about aspects of safety, as well as to observe what people experience in "real life" when they have a disease and are being treated with the drug. In simple terms, it is about obtaining all the available data on a larger group of patients than those included in clinical studies.

6. Conclusion

In this study, the analgesic effect of the combination was evaluated in everyday office conditions in patients with different types of acute pain, such as trauma, acute and postoperative low back pain, and chronic pain, such as chronic low back pain, arthritis, and osteoarthritis. They were given a dose of the combination of Tramadol 37.5 mg and acetaminophen 325 mg for 5 days, and pain was measured using a VAS score from 0 to 10 and the Pain Relief scale for five days. Significant pain relief was observed on both scales during each evaluation period, indicating a progressive and constant effect throughout the evaluation period, making it a useful combination for the proper management of acute pain and worsening pain in patients with chronic pain, with good tolerance.

Collaborating Physicians

Regalado, Julio; Oliveros, Ali; Peña, Daniel; Palomo, Damarys; Schumuck, Delia; Barríos, Yelitza; Di Giacomo, Salvatore; Kurusis, Stefany; Pacheco, Carmen; Pino, Yadira; Chami, Antoine; González, Clary; Ramos, Elisa; La Rosa, Enrique; Ojeda, Gilberto; Ríos, Ricardo; Arias, Lord; Gomez, Alida; Contreras, Asdrubal; Nobrega, Mary; Rodríguez, Reinaldo; Chapon, Carlana; Neeter, Daniel; Figueroa, Dayana; Urbina, German; Padrón, Hiram; Loroño, Neiramar; Vera, Omaira; Vasquez, Rafael; Arape, Rodolfo; Tucci, Alberto; Peralta, Carlos; Saturno, Darío; Aponte, Juan Pablo; Aponte, Laura; Pinto, Leonardo; Forero, Olga; Hernandez, Petra; Finol, Yetiza; Gutierrez, Ylse; Coropa, Yusbely; Garoffalo, Anamaría; Jiménez, Alessandra; Salazar, Arelyz; Hernandez, Carlos; Morillo, Francisco; Martinez, Johanna; Valles, Juan; Castro , Katherine; Bonetti, María; Arcia, Rafael; Guillén, Rómulo; Apóstol, Saúl; García, Williams; Lezama, Yurima; Roa, Dévora; Recabal,

Erica; Favrin, Jorge; Villegas, José; León, Katherine; ; Debirmer; Ledezma, Douglas; Celis, Fernando; Gomez, Flor; Herrera, Freddy; Hernandez, Ithamar; Acuña, Lourdes; Conde, Luis; Parada, Luis; Cazas, Marcel; Soler, Mariely; Barranco, Marisela; Lopez, Nelson; Llovera, Pedro; Zamora, Raúl; Mendoza, Rolando; Isturiz, Samantha; Febres, Yadeley.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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