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Review Article

Postoperative Nausea and Vomiting With NALDEBAIN®: A Retrospective Review

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Background: NALDEBAIN® (dinalbuphine sebacate, 150 mg/2 mL) is an extended-release analgesic with κ-opioid agonist and μ-opioid antagonist activity. It has been approved in Taiwan since 2017 for managing post-operative pain. Its distinct pharmacologic profile may provide advantages over conventional opioids, particularly in reducing opioid-related adverse events such as postoperative nausea and vomiting (PONV), a common complication that may impede recovery. Although NALDEBAIN® is increasingly used in a variety of surgical procedures, the relationship with PONV is poorly understood. This retrospective review aims to assess the incidence, clinical features, and potential risk factors for PONV associated with NALDEBAIN® using clinical trial data and pharmacovigilance reports.
Methods: We reviewed data from 14 published clinical trials involving 569 patients treated with NALDEBAIN® and 47 pharmacovigilance case reports submitted to the Taiwan Adverse Drug Reaction Center between 2017 and 2025, which reported 65 adverse events. Reports were assessed for PONV-related outcomes such as nausea and vomiting. Incidence rates were calculated quantitatively, but intensity and causality were evaluated qualitatively. A comparative analysis was performed on trial data and pharmacovigilance reports, accounting for reporting variability.
Results: PONV rates varied across clinical trials, with nausea ranging from 1.8% to 45.0%, and vomiting ranging from 2.8% to 33.3%, with higher rates observed in laparoscopic procedures. The majority of cases were mild and manageable. Among 65 pharmacovigilance-reported adverse events, 15 (23%) were PONV-related and primarily affected female patients.
Conclusion: Current evidence suggests that NALDEBAIN® is not associated with an elevated risk of PONV. Reported incidences appear within expected ranges, though further confirmation is warranted.

Keywords: *analgesic, extended-release, nalbuphine, opioid receptor antagonist, PONV*

Introduction

Postoperative nausea and vomiting (PONV) is a common complication of surgical procedures affecting up to 35% of patients, especially in those receiving opioid-based analgesia [1]. Nalbuphine, a mixed opioid agonist-antagonist that acts as a κ-opioid receptor agonist and partial μ-opioid receptor antagonist, has received increased attention due to its favorable analgesic profile and potentially lower risk of common opioid side effects [2]. NALDEBAIN® (dinalbuphine sebacate [DS], 150 mg/2 mL), an ex-

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tended-release formulation of nalbuphine, was developed to provide prolonged postoperative pain relief with a unique pharmacologic profile that may offer advantages in perioperative care [3,4].

Despite its increasing clinical use, concerns about PONV associated with NALDEBAIN® persist, particularly in surgeries with high emetogenic potential, such as laparoscopic procedures [5]. Although early clinical data suggested a relatively benign side effect profile, more recent findings from clinical trials and pharmacovigilance reports have highlighted inconsistencies in the reported incidence of PONV and raised questions about the potential influence of surgical variables and patient-specific risk factors [6]. Reported rates of nausea and vomiting following NALDEBAIN® have ranged widely, from under 5% in hemorrhoidectomy and gynecologic surgeries to over 30% in laparoscopic cholecystectomy and ileostomy reversal [7-12]. However, the variability in study design and reporting standards across trials makes it difficult to determine a definitive incidence pattern.

The etiology of PONV is multifactorial. Well-established patient-related risk factors include female sex, nonsmoking status, history of motion sickness or prior PONV, use of volatile anesthetics, nitrous oxide, and perioperative opioid administration [6]. Certain surgical procedures, such as laparoscopic and gynecologic operations, are also associated with increased emetogenic potential. Furthermore, the interaction between anesthetic technique, postoperative pain control methods, and antiemetic prophylaxis can significantly influence PONV outcomes.

In light of these complexities, a systematic evaluation of PONV incidence following NALDEBAIN® administration across both clinical trials and real-world pharmacovigilance data is warranted. This study aims to characterize the frequency and severity of PONV associated with NALDEBAIN®, explore procedure-specific trends, and assess the consistency of adverse event reporting to inform safer and more effective postoperative pain management strategies.

Methods

This retrospective review assessed data from two primary sources: published clinical trials and pharmacovigilance reports, to assess PONV associated with NALDEBAIN® use from 2017 to 2025.

Clinical studies were identified through a literature search of peer-reviewed publications related to NALDEBAIN® and postoperative adverse events. Studies were screened for relevance based on title and abstract, followed by full-text review to determine eligibility. Inclusion criteria required reports of NALDEBAIN® use in postoperative pain management and explicit documentation of PONV-related events. Studies without adverse event data or unrelated to NALDEBAIN® were excluded. The selection process is summarized in the PRISMA flow diagram (Figure 1). A qualitative assessment of study quality was conducted based on three criteria: study design (randomized vs. non-randomized), clarity of adverse event reporting, and sample size.

Sixty-five adverse event reports from the Taiwan Adverse Drug Reaction Center were screened. Reports were included if NALDEBAIN® was listed as the suspect drug and the event was categorized under gastrointestinal symptoms consistent with PONV. Cases unrelated to PONV were excluded from the analysis.

From clinical trials, the following data were extracted: surgery type, sample size, incidence of nausea and vomiting, and adverse event intensity when available. Pharmacovigilance reports were reviewed for patient sex, event type (nausea, vomiting, procedural nausea/vomiting), severity, outcome, and causality assessment ("Probable/Likely," "Possible," or "Unlikely").

Results

PONV Data From Clinical Trials

Across the 14 clinical trial publications, PONV was reported in several studies involving NALDEBAIN® for postoperative pain management and summarized in Table 1 [7-20]. Among these, 9 were randomized controlled trials, 3 were retrospective studies, and 2 were case reports. Several studies involved laparoscopic or minimally invasive procedures, including laparoscopic cholecystectomy, bariatric surgery, and gynecologic or thoracic operations, which are associated with a higher baseline risk of PONV. The heterogeneity of study designs and surgical types was taken into account when interpreting the reported PONV incidence. In total, 569 patients were exposed to NALDEBAIN® across studies with detailed adverse event data. The incidence of nausea ranged from 1.8% to 45.0%, and vomiting from 2.8% to 33.3%, varying by surgery type and study design (Figure 2). For hemorrhoidectomy, nausea occurred in

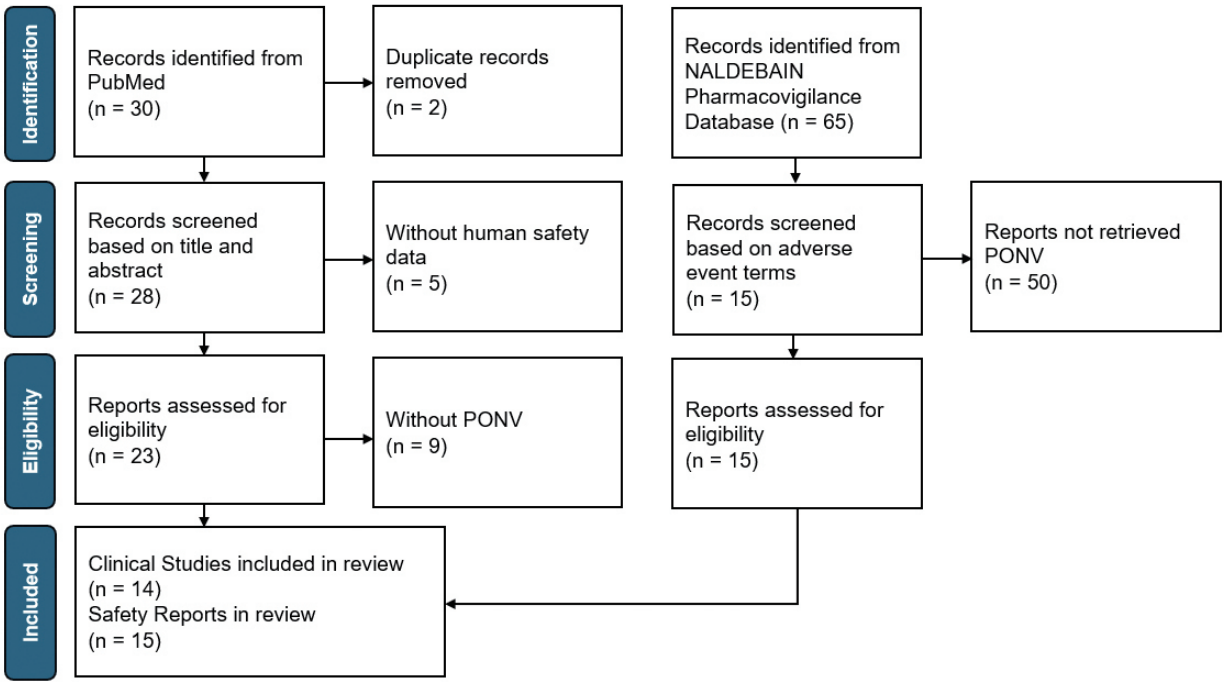

Figure 1. PRISMA Flow Diagram
Abbreviation: PONV, postoperative nausea and vomiting.

2/109 (1.8%) and vomiting in 3/109 (2.8%). Gynecologic surgery showed nausea in 2/52 (3.8%), vomiting in 1/52 (1.9%), and upper extremity trauma showed nausea in 1/49 (2.0%). There were no PONV reports for thoracoscopic wedge resection, colorectal surgery, cesarean section, bariatric surgery, or shoulder rotator cuff surgery. In contrast, laparoscopic cholecystectomy studies reported higher rates: Lee et al. [9] reported nausea in 6/21 (28.6%) and vomiting in 7/21 (33.3%), whereas Lee et al. [10] reported nausea in 18/40 (45.0%). Nausea was reported in 11/30 (36.7%) cases of laparoscopic bariatric surgery, 5/30 (16.7%) cases of mammoplasty, and 6/20 (30.0%) cases of ileostomy reversal, with vomiting in 3/20 (15.0%). When comparing NALDEBAIN® to morphine or fentanyl through patient-controlled analgesia, PONV rates were generally comparable or lower, though control group data were frequently reported inconsistently. Across all studies, the majority of PONV events were mild and manageable.

PONV Data From Pharmacovigilance Reports

From 2017 to January 2025, 65 adverse events were reported in 47 individual cases involving NALDEBAIN® (Figure 3). Fifteen of these (23.1%) were classified as PONV-related, including 10 instances of procedural vomiting, 2 of nausea, 2 of procedural nausea, and 1 of vomiting. Of the 15 patients, 13 were female, and 2 were male. An increase in reporting was observed, with 5 cases in 2017, 2 in 2018, and a peak of 8 events in 2022. In terms of intensity, 3 cases were classified as mild, 3 as moderate, and one as severe. Only 4 (26.7%) cases had outcome data available, and all of them were resolved; the remaining 11 (73.3%) cases had unknown outcomes from the last follow-up. PONV events were reported following a variety of surgeries, including hemorrhoidectomy, cesarean section, and gynecologic procedures. Due to the small sample size, no procedure-specific trends could be identified.

Causality Comparison From Clinical Trials and Pharmacovigilance

Among the 15 pharmacovigilance cases involving PONV, causality was assessed as "Probable/Likely" in one case and "Possible" in 13 cases (86.7%), with one case deemed "Unlikely". Despite the scarcity of causality data from clinical trials, PONV is listed as a known adverse reaction on the NALDEBAIN® product labeling, indicating a possible association. Potential confounding factors, such as concomitant medications, anesthesia type, and surgical technique,

Table 1. PONV Outcomes With Risk of Bias

Study	Surgery type	Study design/patient number	Nausea n (%)	Vomiting n (%)	Risk of bias[a]
Yeh et al. [7], 2017	Hemorrhoidectomy	RCT, NALDEBAIN® vs. placebo (n = 103 vs. n = 106)	2 (1.8)	3 (2.8)	Low
Huang et al. [13], 2020	Shoulder Rotator Cuff Surgery	Case report, NALDEBAIN® + nerve block (n = 1)	0 (0.0)	0 (0.0)	High
Wong et al. [14], 2020	Mixed	Observational, NALDEBAIN® + parecoxib (n = 10)	2 (20.0)	1 (10.0)	High
Lee et al. [9], 2020	Laparoscopic cholecystectomy	RCT, NALDEBAIN® vs. morphine (n = 21 vs. n = 22)	6 (28.6)	7 (33.3)	Low
Chang et al. [15], 2020	Colorectal laparotomy	RCT, NALDEBAIN® vs. fentanyl PCA (n = 55 vs. n = 52)	0 (0.0)	0 (0.0)	Low
Liu et al. [16], 2021	Bariatric surgery	Case report, NALDEBAIN® + TAP block (n = 1)	0 (0.0)	0 (0.0)	High
Chang et al. [8], 2021	Gynecologic laparotomy	Retrospective, NALDEBAIN® vs. PCA vs. conventional (n = 52 vs. n = 55 vs. n = 30)	2 (3.8)	1 (1.9)	Moderate
Zheng et al. [17], 2022	Upper extremity trauma surgery	Retrospective, NALDEBAIN® + MMA vs. conventional analgesia (n = 49 vs. n = 60)	1 (2.0)	0 (0.0)	Moderate
Lee et al. [10], 2023	Bariatric surgery	RCT, NALDEBAIN® + MMA vs. placebo + MMA (n = 30 vs. n = 30)	11 (36.7)	0 (0.0)	Low
Lee et al. [12], 2023	Laparoscopic cholecystectomy	RCT, NALDEBAIN® + MMA vs. placebo + MMA (n = 38 vs. n = 40)	18 (45.0)	0 (0.0)	Low
Li et al. [18], 2023	Video-assisted thoracoscopic surgery	Retrospective, NALDEBAIN® vs. conventional analgesia (n = 139 vs. n = 618)	0 (0.0)	0 (0.0)	Moderate
Chen et al. [11], 2023	Ileostomy Reversal	RCT, NALDEBAIN® vs. control (n = 20 vs. n = 18)	6 (30.0)	3 (15.0)	Low
Tang et al. [19], 2024	Cesarean Section	Milk pharmacokinetics (n = 20)	0 (0.0)	0 (0.0)	Moderate
Dmytriiev et al. [20], 2024	Mammoplasty	RCT, NALDEBAIN® vs. multimodal analgesia (n = 30 vs. n = 30)	5 (16.7)	0 (0.0)	Low
Total[b]		569	53	15	

Abbreviations: MMA, multimodal analgesia; PCA, patient-controlled analgesia; RCT, randomized controlled trial; TAP, transversus abdominis plane.
[a]A risk of bias was assessed based on study design, adverse event reporting clarity, and sample size.
[b]Total number includes only patients who received NALDEBAIN®, excluding control arms.

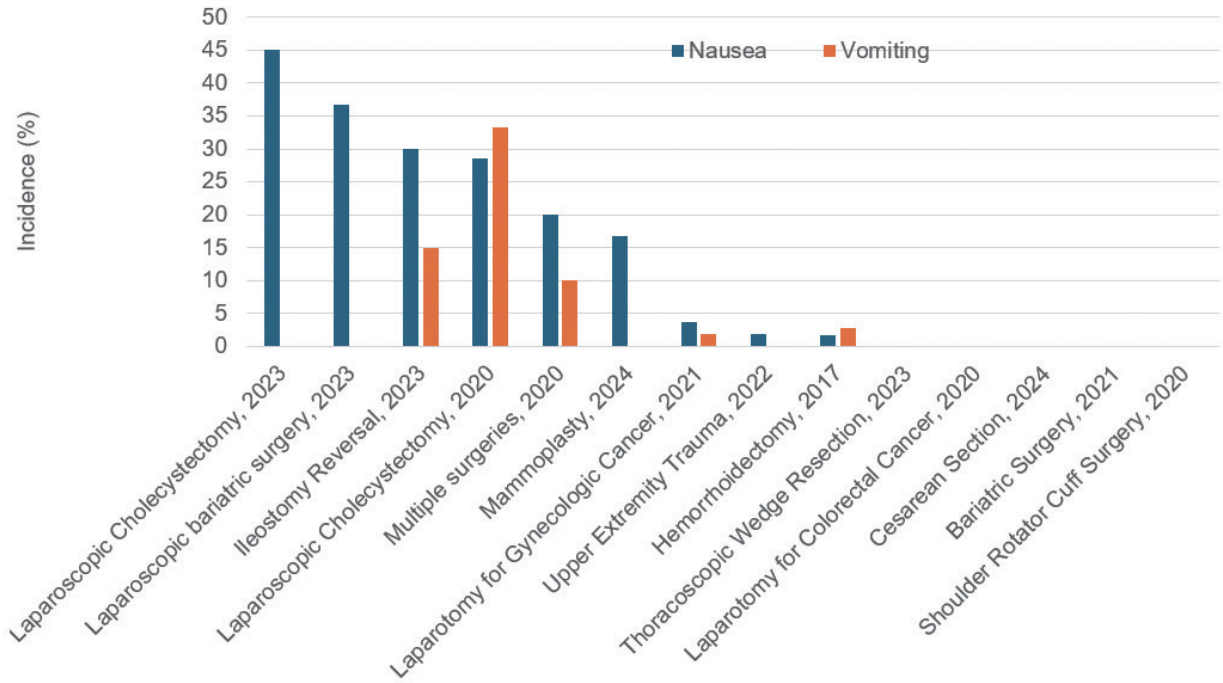

Figure 2. Postoperative Nausea and Vomiting Incidence Across Clinical Trials by Surgery Type

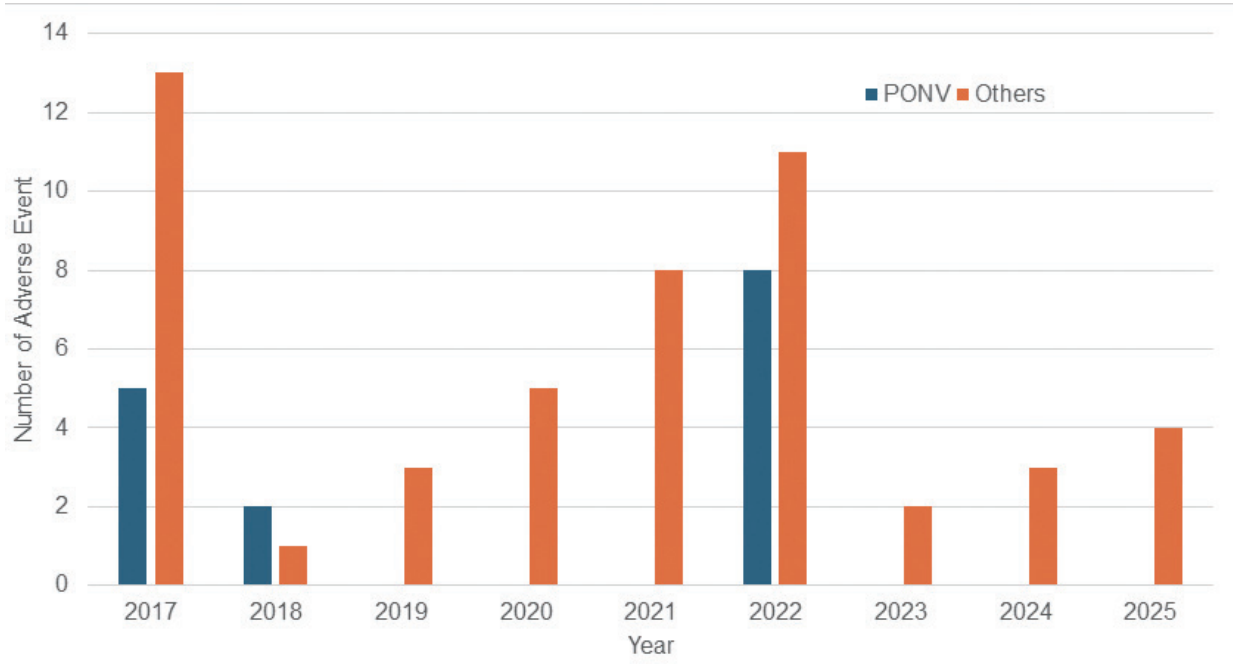

Figure 3. Trend of Postoperative Nausea and Vomiting (PONV) Reporting in Pharmacovigilance Data (2017-2025)

were not thoroughly described. Overall, laparoscopic surgery showed higher PONV rates in clinical trials than in pharmacovigilance data.

Discussion

This study aimed to characterize the incidence and nature of PONV associated with NALDEBAIN® across published clinical trials and pharmacovigilance

data. Our findings suggest that, while PONV is associated with NALDEBAIN®, the observed patterns are more consistent with known procedural and patient-related risk factors rather than with the pharmacologic characteristics of the active ingredient.

Across clinical trials involving 569 patients, PONV incidence varied substantially by surgery type. As expected, higher rates of nausea and vomiting were reported after laparoscopic procedures, notably cholecystectomy and bariatric surgery, where nausea reached up to 45.0% and vomiting 33.3%. In contrast, procedures such as hemorrhoidectomy, gynecologic surgery, and upper extremity trauma demonstrated much lower PONV rates, typically under 5% [7, 8,17]. These results align with established literature that identifies laparoscopic surgery as an independent predictor of PONV, attributed to physiological mechanisms such as pneumoperitoneum, vagal stimulation, and CO_2 retention [6]. From a real-world clinical perspective, NALDEBAIN®-related symptoms were generally mild and transient. Mild dizziness was occasionally observed beginning 12 to 24 hours after NALDEBAIN® administration, typically lasting no more than 24 to 48 hours. When nausea or vomiting occurred, symptoms were uncommon and generally mild in severity. These findings are consistent with a recent randomized trial in video-assisted thoracoscopic surgery patients, which found that while mild dizziness occurred more frequently in the DS group during the first 72 hours, the incidence of PONV remained comparable to placebo [21]. This suggests that mild, transient central symptoms may occur during DS absorption peaks but are not consistently associated with increased PONV risk.

PONV reports from the pharmacovigilance database followed a similar trend, with most cases occurring in female patients and across a range of surgical indications. Although limited by small case numbers, the predominance of the female sex among PONV reports supports previous evidence that women are inherently at higher risk—most likely due to hormonal modulation of central emetogenic pathways [22]. Importantly, only one case was judged as "probable/likely" related to NALDEBAIN®, while most were classified as "possible," reflecting the multifactorial etiology of PONV and the challenge of establishing causality in real-world settings.

From the pharmacologic view, NALDEBAIN®'s dual mechanism as a κ-opioid receptor agonist and μ-opioid receptor antagonist theoretically suggests a lower emetogenic potential compared to full μ-agonists like fentanyl. Some comparative trials have reported comparable or lower PONV rates with NALDEBAIN® [8,15]. However, its extended-release formulation maintains systemic opioid levels over several days, which may sustain low-level emetic stimulation in susceptible individuals.

Several limitations temper the results. Pharmacovigilance data lack detailed information, including anesthesia type, perioperative antiemetic use, and concurrent medications, which limits causal inference. Due to a lack of individual patient data, subgroup statistical analyses across surgical types or patient characteristics were not feasible. While clinical trials are more controlled, they vary in sample size, surgery type, and rigor of adverse event reporting, resulting in heterogeneity. Pharmacovigilance reports are subject to underreporting and may be biased by clinician awareness or reporting practices. The lack of standardized PONV definitions makes comparisons challenging. Furthermore, anesthetic techniques, use of antiemetic prophylaxis, and perioperative opioid co-administration are major determinants of PONV but were inconsistently reported across studies, limiting our ability to adjust for these confounders, potentially masking the real PONV contribution from NALDEBAIN® administration.

Nonetheless, the available data indicate that NALDEBAIN® does not significantly increase PONV risk above what is expected from known patient and procedure-related factors. The relatively low incidence across various surgical settings, as well as the generally mild severity of events, support the continued use of extended-release NALDEBAIN® as part of multimodal analgesia protocols—particularly when combined with appropriate antiemetic prophylaxis [23]. Given the intricate interactions between anesthesia, surgical factors, and postoperative opioids, future prospective studies should use standardized methods to determine whether PONV is caused by intraoperative anesthetic techniques or the use of NALDEBAIN®.

Conclusion

Across 14 studies and pharmacovigilance data, NALDEBAIN® did not show a clear signal of increased PONV risk. These findings support its safety profile, but further validation in controlled trials is recommended.

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Author Contribution

SO Lee wrote the manuscript. WZ Sun reviewed the manuscript and provided critical opinions. The authors analyzed the data and approved the article.

Conflict of Interest

The authors have no conflicts of interest to declare.

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