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Suzetrigine Versus Tramadol for Acute Postoperative Pain: Systematic Review and Meta-Analysis

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Abstract

Opioids remain the backbone for postoperative analgesia, but adverse effects and misuse remain major concerns. Suzetrigine (VX-548), a selective NaV1.8 inhibitor, is an FDA-approved non-opioid analgesic for moderate-to-severe acute pain. This PRISMA-guided systematic review and meta-analysis evaluated the efficacy and adverse effects of suzetrigine versus tramadol following bunionectomy or abdominoplasty. PubMed, Scopus, Cochrane CENTRAL, Ovid, ClinicalTrials.gov, and medRxiv were searched. Six randomized clinical trials involving 2,136 participants (1,289 treatment; 847 placebo) were included. Placebo-adjusted treatment effects were compared using random-effects meta-regression with placebo as the common comparator. Suzetrigine was associated with significantly lower SPID24 than intravenous tramadol after adjustment for surgery type (β = −7.46; 95% CI, −12.52 to −2.40; p = 0.0184), indicating greater analgesic efficacy with tramadol at 24 hours. No significant difference was observed at 48 hours (β = −2.49; 95% CI, −24.83 to 19.84; p = 0.75). Suzetrigine demonstrated significantly lower odds of nausea (p = 0.003) and vomiting (p = 0.010) than tramadol, with no significant differences in constipation or headache. GRADE assessment determined the certainty of evidence to be very low for the efficacy outcomes, constipation, and headache, and low for nausea and vomiting. Direct comparative trials are necessary to confirm suzetrigine's relative efficacy and adverse-effect profile versus tramadol.

Introduction

Postoperative pain management is a critical component of patient care following surgery. The prevalence of moderate-to-severe postoperative pain has been reported to be as high as 31% on the first postoperative day and as high as 58% two weeks after surgery in a large number of patients[1]. Inadequate pain control can impair recovery, delay rehabilitation, and reduce overall quality of life, particularly in outpatient surgical procedures such as abdominoplasty and bunionectomy. Currently, postoperative pain is managed with opioids due to their effectiveness. However, concerns about adverse effects, as well as the risk of dependence and misuse, have driven the search for safer alternatives[2]. Common opioid-associated complications include nausea, vomiting, constipation, sedation, respiratory depression, and the potential for addiction, particularly among opioid-naive patients[3-4]. The continued prevalence of postoperative pain despite available treatments highlights the need for effective analgesics that provide adequate pain relief with minimal opioid-related risks. Tramadol and suzetrigine represent two distinct pharmacologic approaches for postoperative pain management.

Tramadol is a weak centrally acting opioid. It can produce analgesia by binding to the μ-opioid receptor and inhibiting serotonin and norepinephrine reuptake, intensifying descending inhibitory pain pathways[5]. Tramadol was developed as an alternative to traditional opioids, which have a higher risk of tolerance and dependence among patients[6]. However, the potential for tramadol abuse has been observed, and the risk of misuse or dependence cannot be eliminated[5-6]. Tramadol was chosen for comparison with suzetrigine in this systematic review because both drugs have been studied in placebo-controlled abdominoplasty and bunionectomy trials, making it possible for indirect comparisons within the same surgical models.

In January 2025, suzetrigine (VX-548; Journavx®) became the first selective NaV1.8 inhibitor approved for the treatment of moderate-to-severe acute pain. This sodium voltage-gated channel is primarily expressed on peripheral nociceptive neurons, where it plays a key role in pain signal transmission[7]. By selectively inhibiting this channel, suzetrigine reduces peripheral pain signaling without directly activating μ receptors, potentially minimizing opioid-related effects[8]. Clinical trials in patients undergoing bunionectomy and abdominoplasty have demonstrated significant reductions in postoperative pain with a favorable adverse effects profile, supporting its potential as a non-opioid alternative for acute surgical pain[9].

Bunionectomies and abdominoplasties are well-established clinical models to evaluate postoperative pain and are commonly used in randomized trials to evaluate analgesic efficacy. Both procedures produce moderate to severe postoperative pain during the first 24-48 hours[9-10]. A bunionectomy corrects hallux valgus deformities and is associated with moderate-to-severe postoperative pain because of osseous and soft tissue manipulation[11]. Similarly, abdominoplasties involve abdominal soft tissue dissection and repair, which leads to significant postoperative pain that usually requires multimodal analgesia[12].

Postoperative pain management for bunionectomies and abdominoplasties includes a two-phase multimodal analgesic approach. Current practice involves acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy for pain relief. When pain persists beyond these measures, stronger analgesics, such as opioids like hydrocodone, morphine, and tramadol, are utilized[13-14]. Since both procedures have similar postoperative pain trajectories, they serve as reliable clinical models for evaluating the efficacy and adverse effects of novel analgesics.

The objectives of this systematic review and meta-analysis are two-fold. One includes an analysis of the clinical trial evidence comparing suzetrigine and tramadol for the management of acute postoperative pain following bunionectomy and abdominoplasty. While both drugs have been evaluated in randomized clinical trials after these procedures, direct comparative studies comparing suzetrigine and tramadol are lacking. Therefore, a comparison across studies will provide insight into their relative efficacy and adverse effects. The second goal is to examine patterns across the included studies to identify consistent findings or remaining gaps in the literature. Since suzetrigine is the first selective NaV1.8 inhibitor for moderate-to-severe acute pain in adults, analyzing available evidence alongside tramadol may provide insight into its potential role in postoperative analgesia.

Methods

Study Design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A protocol was registered with the Open Science Framework (OSF) Registries (DOI: 10.17605/OSF.IO/2EJ46)[15]. A medical librarian developed and conducted the search strategy. Peer-reviewed articles and grey literature were compiled for screening using electronic databases available to the researchers at the institution, including Medline via Ovid, Scopus via Elsevier, PubMed, Cochrane Central Register of Controlled Trials via EBSCO, ClinicalTrials.gov, and medRxiv. These databases were searched until April 6, 2026. The following search strategy was inputted into PubMed and adjusted for each database as necessary using database-specific logic and wildcards: ("suzetrigine" [Supplementary Concept] OR "Tramadol"[Mesh] OR tramadol[tw] OR suzetrigine[tw] OR vx-548[tw] OR journavx[tw]) AND ("Bunion/surgery"[Mesh] OR "Abdominoplasty"[Mesh] OR bunion*[tiab] OR abdom*[tiab] OR feet[tw] OR foot[tw] OR pannicu* OR osteotom*). The term "hallux valgus" was not included within the search strategy as it did not yield results that were not already included. The complete search strategy can be found in the Supplementary Materials.

Inclusion and Exclusion Criteria

Studies were included for analysis if they evaluated suzetrigine or tramadol for postoperative pain following bunionectomy or abdominoplasty in adult patients (≥18 years). Eligible studies also utilized a validated pain scale, were written in English, and employed a relevant study design (i.e., controlled clinical trials, controlled observational studies, prospective clinical trials, or clinical trials). Studies reporting sufficient data for prespecified efficacy and/or safety outcomes were included in the corresponding analyses.

Studies were excluded if they were literature reviews,

reported insufficient outcome data, included pediatric populations, involved *in vitro*, preclinical, or animal studies, were not written or translated into English, or evaluated patients who underwent procedures other than bunionectomy or abdominoplasty.

Data Extraction

The articles were uploaded to Zotero and Rayyan for deduplication. All four researchers (PP, RP, BK, and MAP) then independently screened titles and abstracts, followed by full-text review, against the inclusion and exclusion criteria. Conflicts were resolved through discussion; if conflicts remained, the Principal Investigator (MAP) made the final decision. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

For data extraction, a standardized table was developed, and all four researchers independently extracted data from each eligible article. The following data were extracted: author, year, title, registry number, study period, intervention, dosage, route of administration, procedure, sample size, participant characteristics, pain scale, primary outcome, rescue medication, perioperative anesthetic protocol, adverse event counts, AE ascertainment window, and the placebo-adjusted Sum of Pain Intensity Differences over 24 hours (SPID24) and 48 hours (SPID48) (Table 1). Extracted data were compared across reviewers, and discrepancies were resolved through discussion and consensus; any unresolved disagreements were adjudicated by the Principal Investigator (MAP). All numerical values used in the analyses, including SPID24, SPID48, sample sizes, and adverse event counts, were then jointly verified by all four researchers against the original source publications and regulatory documents before analysis.

Pain intensity was measured by the Numeric Pain Rating Scale (NPRS), a patient-reported measurement ranging from 0 ("no pain") to 10 ("worst pain imaginable")[16]. In the original trials, serial NPRS measurements were used to derive the Summed Pain Intensity Difference over 24 hours (SPID24) and 48 hours (SPID48), reflecting cumulative pain relief over the respective time periods[17].

If prespecified trial characteristics were not reported in the primary publication, publicly available regulatory documents were consulted to supplement missing

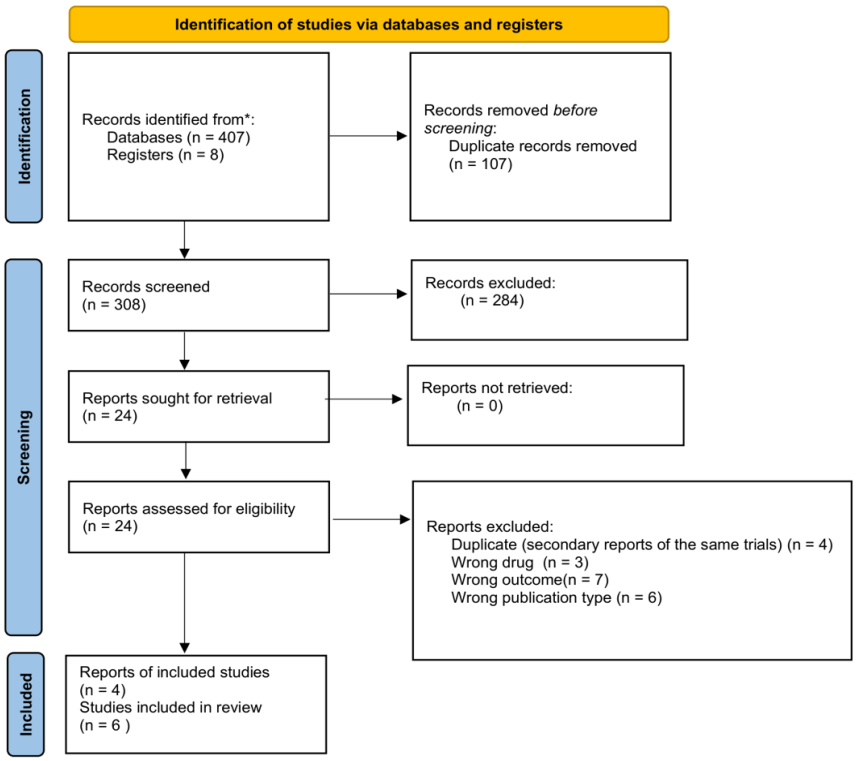

Figure 1: PRISMA flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies in the systematic review.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
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information. Specifically, rescue-medication dosing details for the Singla et al. and Minkowitz et al. trials were not fully reported in the primary publications and were obtained from the corresponding FDA briefing document (Table 1)[18]. When trials included multiple active-treatment arms, only treatment arms relevant to the comparison of suzetrigine and intravenous tramadol were extracted. Because dosing regimens varied across the included trials, the regimens with the greatest amount of available data across eligible studies were selected for analysis. For suzetrigine, the 100-mg loading dose followed by 50 mg every 12 hours was selected, while lower-dose regimens (60-mg loading dose followed by 30 mg every 12 hours and 20-mg loading dose followed by 10 mg every 12 hours) were excluded. For tramadol, the 50-mg IV regimen was selected, while the 25-mg IV regimen was excluded. Active-comparator arms other than tramadol and suzetrigine were excluded, including the 4-mg IV morphine arm in Minkowitz et al. and the hydrocodone-acetaminophen arms in the suzetrigine trials[9,10,12].

To assess the plausibility of the transitivity assumption underlying the indirect comparison, trial-level characteristics that could modify postoperative analgesic responses were systematically compared across all studies, including the following possible confounds: age, sex distribution, pain eligibility criteria, baseline pain severity, study period, treatment regimen, route of administration, rescue medication, and perioperative anesthetic protocols (Table 1).

Risk of Bias Methodology

Risk of bias was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials[19]. The assessment

Table 1: Summary of Baseline Characteristics, Interventions, and Efficacy Outcomes of the Included Clinical Trials.
**For Singla et al. and Minkowitz et al., rescue-medication dosing details not fully reported in the primary publications were obtained from the FDA briefing document.[18]*

Study	Singla, 2020 (bunionectomy)	Bertoch, 2025 (bunionectomy)	Jones, 2023 (bunionectomy)	Minkowitz, 2020 (abdominoplasty)	Bertoch, 2025 (abdominoplasty)	Jones, 2023 (abdominoplasty)
Registry	NCT03290378	NCT05553366	NCT04977336	NCT03774836	NCT05558410	NCT05034952
Study Period	Sep 2017-Apr 2018	Oct 2022-Dec 2023	Jul 2021-Mar 2022	Dec 2018-Jun 2019	Oct 2022-Sep 2023	Aug-Dec 2021
Age (years), mean (SD)	45.5 (13.45)	48.0 (13.0)	47.7 (13.6)	40.1 (8.72)	42.0 (8.7)	42.8 (9.6)
Female, *n* (%)	233 (84.7)	553 (86.1)	102 (85.7)	274 (98.9)	657 (98.1)	151 (98.7)
Sample Size	275	642	119	277	670	153
Treatment (n)	Tramadol, 50 mg at 0, 2, and 4h, then q4h through hour 44 (139)	VX-548, 100 mg loading dose, then 50 mg q12h (426)	VX-548, 100 mg loading dose, then 50 mg q12h (60)	Tramadol, 50 mg at 0, 2, and 4h, then q4h through hour 44 (141)	VX-548, 100 mg loading dose, then 50 mg q12h (447)	VX-548, 100 mg loading dose, then 50 mg q12h (76)
Route of Administration	IV	Oral	Oral	IV	Oral	Oral
Placebo (n)	136	216	59	136	223	77
NPRS Eligibility	Moderate/severe pain; ≥5	Moderate/ severe pain; ≥4	Moderate/ severe pain; ≥4	Moderate/severe pain; ≥5	Moderate/severe pain; ≥4	Moderate/severe pain; ≥4
Baseline qualifying NPRS, mean ± SD	6.8 ± 1.6	6.7 ± 1.8	6.8 ± 1.7	6.5 ± 1.4	7.4 ± 1.7	7.3 ± 1.6
Placebo-adjusted SPID24 treatment difference, mean ± SE (95% CI)	17.80 ± 4.50 (8.98, 26.62)	10.70 ± 3.65 (3.55, 17.85)	13.70 ± 7.80 (-1.59, 28.99)	31.30 ± 4.71 (22.07, 40.53)	23.80 ± 3.42 (17.10, 30.50)	19.60 ± 6.70 (6.47, 32.73)
Placebo-adjusted SPID48 treatment difference, mean ± SE (95% CI)	25.00 ± 8.81 (7.73, 42.27)	29.30 ± 7.81 (13.99, 44.61)	36.80 ± 11.50 (14.26, 59.34)	59.70 ± 9.97 (40.16, 79.24)	48.40 ± 7.53 (33.64, 63.16)	37.80 ± 14.50 (9.38, 66.22)
Rescue Medication	Ibuprofen 400 mg PO q4h PRN (maximum 2,400 mg/day)*	Ibuprofen 400 mg PO q6h PRN	Ibuprofen 400 mg PO q6h	Ibuprofen 400 mg PO q4h PRN (maximum 2,400 mg/day)*	Ibuprofen 400 mg PO q6h PRN	Ibuprofen 400 mg PO q6h PRN
Anesthetic/ Perioperative Protocol	Popliteal and Mayo blocks; ropivacaine/ lidocaine; IV sedation	Popliteal and Mayo blocks; ropivacaine; IV sedation	Popliteal and Mayo blocks; ropivacaine/ lidocaine; IV sedation	Standardized anesthetic protocol; agents NR	General anesthesia with propofol/fentanyl	General anesthesia with propofol/ fentanyl

utilized five domains to determine the overall judgement of efficacy reporting: bias from the randomization, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement outcomes, and bias in the selection of reported results. Each domain was rated as "low risk," "some concerns," or "high risk of bias" according to RoB 2 guidelines with an overall risk of bias judgement assigned to each study. Disagreements between reviewers were resolved through discussion and consensus. RoB 2 assessments were also applied to the adverse-event outcomes (nausea, vomiting, constipation, and headache), and these judgments were used to address the risk-of-bias domain in the GRADE assessment for both efficacy and safety outcomes.

Statistical Methodology

Since no clinical trial directly compared tramadol and suzetrigine, we used a network meta-analytic framework[20]. Given that each of the studies compared its respective treatment to a control, the goal of the network meta-analytic framework was to treat the control group as a common 'node' among all the studies and model the indirect comparison between the treatments via the common control. To estimate the indirect comparative effect of VX-548 versus tramadol, we estimated the difference between the treatment effects of VX-548 versus control and tramadol versus control. This difference accounts for the common control under the assumption of transitivity, yielding an estimate of the relative effect of VX-548 versus tramadol. Transitivity requires that the included studies be sufficiently comparable with respect to characteristics that may modify relative treatment effects. Based on the study characteristics presented in Table 1, including patient populations, eligibility criteria, and treatment regimens (for a fixed drug), the transitivity assumption was considered plausible. Surgery type varied within treatment groups and was therefore included as a fixed-effect moderator in the meta-regression to account for potential differences in postoperative pain responses. Lastly, although the analysis was conducted within a network meta-analytic framework, the statistical modeling procedure is equivalent to a random-effects meta-regression when comparing only two treatments indirectly[20,21].

The random-effects meta-regression model was fitted to SPID24 and SPID48 using treatment type (VX-548 or Tramadol) and surgery type (bunionectomy or abdominoplasty) as categorical covariates using the *metafor* R package[22]. The model was fitted using a restricted maximum likelihood procedure (REML) and confidence intervals were generated using a Hartung-Knapp adjustment. To harmonize the direction of SPID outcomes across studies, estimates reported using an inverse SPID convention were multiplied by −1 so that positive values uniformly indicated greater cumulative pain reduction. Specifically, estimates from Minkowitz et al. (2020) and Singla et al. (2020) were adjusted because they reported SPID using the inverse convention.

The Hartung-Knapp adjustment was used because it has been shown to help maintain type I error control of confidence intervals when the number of studies is small[23]. After restricting to studies within the same treatment, there was no missingness to be handled. While Jones (2023) and Bertoch (2025) both have bunionectomy and abdominoplasty studies per paper, both authors conducted independent clinical trials with randomization within each surgical group. Consequently, each trial within each publication was considered an independent study used to fit the meta-regression.

For the adverse event outcomes, the log odds ratio versus placebo and its sampling variance were calculated for each trial from the 2×2 event counts (Supplementary Table S1). A continuity correction of 0.5 was added to all four cells of any trial with a zero cell in either arm[22].

Beyond the covariate analysis of treatment type and surgery type, with confidence intervals generated using the Hartung-Knapp adjustment, an omnibus test of moderators was also performed, and residual heterogeneity was assessed using I^2. The former investigates the significance of treatment type and surgery type on SPID, while the latter assesses between-study variability after accounting for the moderators and sampling error. While useful, these analyses are substantially underpowered given the small number of included studies, and the absence of statistical significance should be interpreted cautiously. Lastly, no statistical analysis of publication bias was undertaken. Because only six studies were included, statistical methods for assessing publication bias would have been substantially underpowered.

Certainty of Evidence Methodology (GRADE)

The certainty of evidence for efficacy and safety outcomes was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework[24]. Certainty was assessed across the pain and adverse effect outcomes based on the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. Randomized evidence was initially considered high certainty and was downgraded based on concerns within these domains. The overall certainty of evidence for each outcome was classified as high, moderate, low, or very low. Assessments were performed independently by two reviewers, with disagreements resolved through discussion and consensus.

Results

Selected Study Results

Six randomized controlled trials involving 2,136

participants were included in the analysis (Table 1). Two trials evaluated intravenous tramadol, including one bunionectomy and one abdominoplasty trial, while four trials evaluated oral suzetrigine (VX-548), comprising two bunionectomy and two abdominoplasty trials. Across the included studies, participants experienced moderate-to-severe postoperative pain, although trials differed in pain eligibility thresholds, study periods, perioperative anesthetic protocols, and treatment routes. Study characteristics, including treatment regimens, baseline pain measures, rescue medication use, and placebo-adjusted SPID24 and SPID48 outcomes, are summarized in Table 1.

Risk of Bias Assessment

All six trial datasets were judged to have some concerns overall, with no trial judged to be at high risk of bias. Concerns were primarily related to missing pain-intensity outcome data, including the reporting of observations following rescue analgesia. Additional concerns regarding the selection of the reported results were identified for the Bertoch (2025) bunionectomy and abdominoplasty trials. The Minkowitz (2020) trial also raised some concerns regarding the randomization process because of insufficient reporting of sequence generation and allocation concealment (Figure 2).

Pain Outcome Analysis

Pain intensity was measured by the Numeric Pain Rating Scale (NPRS), a patient-reported measurement ranging from 0 ("no pain") to 10 ("worst pain imaginable")[16]. SPID was calculated by the original trial investigators as the time-weighted sum of pain intensity differences from baseline over the evaluation period, corresponding to the trapezoidal area under the pain intensity difference–time curve over 24 hours (SPID24) or 48 hours (SPID48)[17]. For the present meta-analysis, reported SPID24 and SPID48 estimates were extracted directly from the original trial reports and were not reconstructed from serial NPRS measurements.

SPID24 Analysis

The SPID24 analysis included six independent studies evaluating two active treatments: intravenous tramadol in two studies and oral suzetrigine (VX-548) in four studies across bunionectomy and abdominoplasty surgical models (Table 1). Overall, the analysis included 2,136 participants (1,289 treated and 847 controls). Tramadol was evaluated in one bunionectomy and one abdominoplasty study, while suzetrigine was evaluated in two studies of each surgical model. The 95% CI for the placebo-adjusted SPID24 estimate in the Jones (2023) bunionectomy trial crossed zero (95% CI, −1.59 to 28.99); however, the trial was retained in the analysis based on the prespecified eligibility criteria to avoid selective inclusion based on statistical significance.

A random-effects meta-regression model was used to estimate the indirect comparative effect of treatment on SPID24 while accounting for surgical model as a moderator (Figure 3, Table 2). Since no study directly compared tramadol and suzetrigine, their effects were compared indirectly under the assumption of transitivity, meaning that the distribution of potential effect modifiers was sufficiently similar across trials, apart from the treatment being investigated. Consequently, the comparative treatment effect should be interpreted as an indirect effect

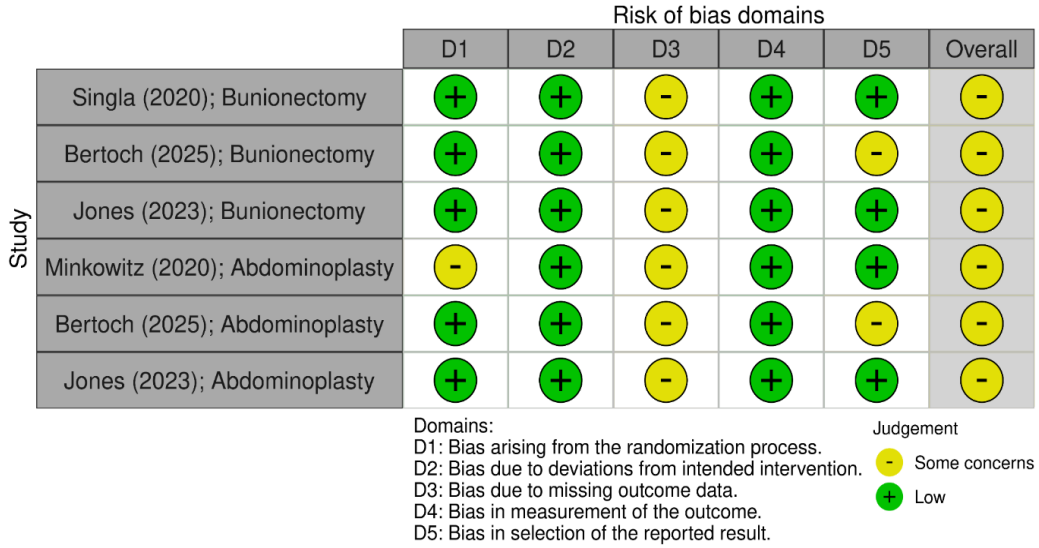

Figure 2: Cochrane Risk of Bias 2 (RoB 2) assessment for SPID24 and SPID48 outcomes among included randomized controlled trials. Green indicates low risk of bias, yellow indicates some concerns, and red indicates high risk of bias.

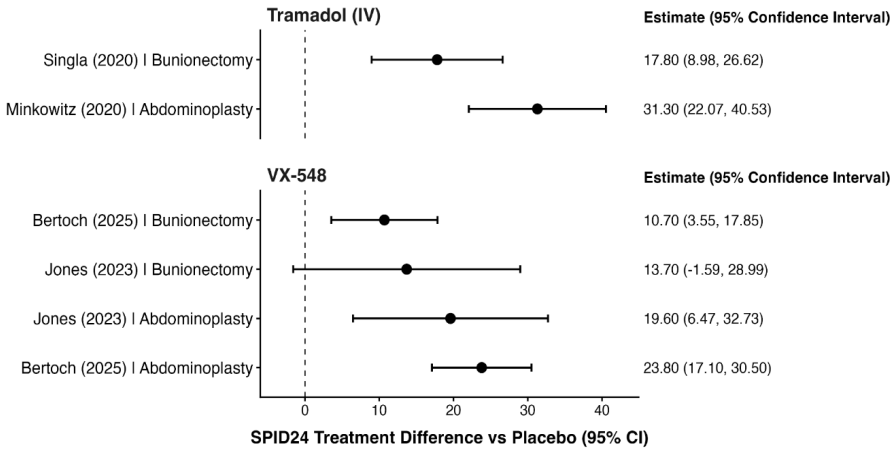

Figure 3: Forest plot showing SPID24 placebo-adjusted treatment differences for intravenous tramadol and VX-548 studies.

Table 2: Coefficient estimates from the random-effects meta-regression evaluating the association of treatment and surgery type with SPID24. Intravenous tramadol following abdominoplasty served as the reference category.

Term	Estimate (95% CI)	P-value
Average SPID24 for Tramadol in Abdominoplasty	30.66 (25.82, 35.50)	0.0003 ***
Average indirect effect of using VX-548 instead of Tramadol adjusted for surgery type	-7.46 (-12.52, -2.40)	0.0184 *
Average change in SPID24 from Abdominoplasty to Bunionectomy adjusted for treatment type	-12.28 (-17.01, -7.54)	0.0037 **

anchored to a common control. Statistical significance was then determined based on a 0.05 type I error rate.

Intravenous tramadol following abdominoplasty served as the reference group, with an estimated mean SPID24 of 30.66 (95% CI, 25.82–35.50; p = 0.0003). Compared with intravenous tramadol, suzetrigine was associated with a 7.46-point lower SPID24 after adjustment for surgery type (β = −7.46, 95% CI −12.52 to −2.40; p = 0.0184). Surgery type also significantly influenced analgesic response, with bunionectomy demonstrating a 12.28-point lower SPID24 than abdominoplasty after adjustment for treatment (β = −12.28, 95% CI −17.01 to −7.54; p = 0.0037). Residual heterogeneity was not statistically significant (QE = 0.49, df = 3; p = 0.92), and the residual I^2 was 0%. However, the small number of studies limits the power to detect residual heterogeneity. The omnibus test of moderators was statistically significant (F[2,3] = 42.87; p = 0.0062), suggesting that treatment and surgery types were associated with differences in SPID24. This finding should be interpreted cautiously as only six studies were included in the analysis.

SPID48 Analysis

A random-effects meta-regression was performed to examine the influence of treatment and surgery type on SPID48 (Figure 4, Table 3). Using tramadol following abdominoplasty as the reference group, the estimated mean SPID48 was 52.07 (95% CI, 30.32 to 73.82; p = 0.0047). After adjusting for surgery type, the indirect estimate for suzetrigine was associated with a 2.49-point lower SPID48 than tramadol; however, this difference was not statistically significant (β = −2.49, 95% CI, −24.83 to 19.84; p = 0.75).

Residual heterogeneity was not statistically significant (QE = 2.26, df = 3; p = 0.52), with a residual I^2 of 0%. However, given the small number of included studies, these estimates have limited power to detect between-study heterogeneity and should not be interpreted as evidence of homogeneity. The omnibus test of moderators was also not statistically significant (F[2,3] = 5.11; p = 0.11), indicating insufficient evidence that treatment and surgery type jointly explain variability in SPID48. Although the estimated residual I^2 was 0%, the confidence intervals of the two tramadol studies showed minimal overlap, suggesting potential between-study variability. The limited number of studies may also have reduced the precision and statistical power of the indirect comparison, supporting the need for direct comparative studies.

Adverse Event Analysis

Per-trial adverse event counts, safety-population denominators, and adverse event ascertainment windows are provided in Supplementary Table S1. Zero cells occurred in one trial (Jones 2023, bunionectomy; constipation and vomiting, 0/60 in the suzetrigine arm), and the continuity correction described in Section 2.5 was applied to that trial.

The treatment effects were estimated by modeling the log odds ratio of each adverse event relative to a common placebo comparator across the clinical trials

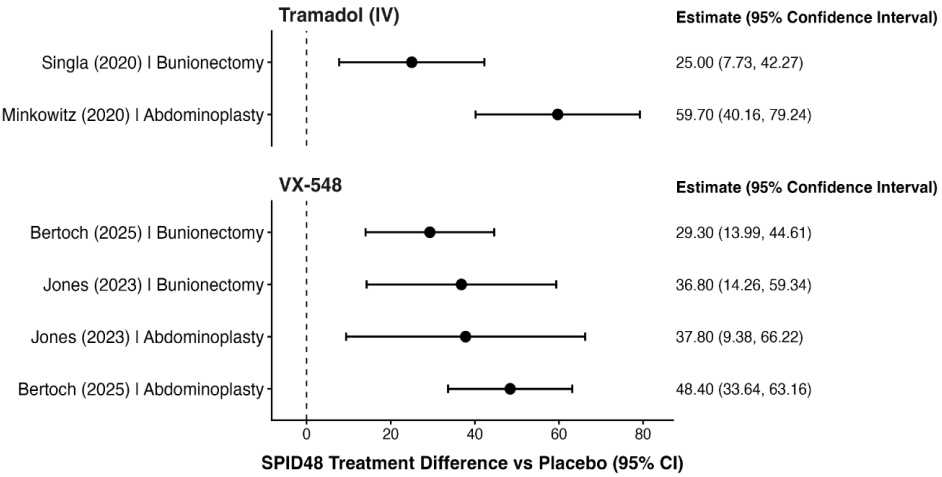

Figure 4: Forest plot showing SPID48 placebo-adjusted treatment differences for intravenous tramadol and VX-548 studies.

Table 3: Coefficient estimates from the random-effects meta-regression evaluating the association of treatment and surgery type with SPID48. Intravenous tramadol following abdominoplasty served as the reference category.

Term	Estimate (95% CI)	P-value
Average SPID48 for Tramadol in Abdominoplasty	52.07 (30.32, 73.82)	0.0047 **
Average indirect effect of using VX-548 instead of Tramadol adjusted for surgery type	-2.49 (-24.83, 19.84)	0.75
Average change in SPID48 from Abdominoplasty to Bunionectomy adjusted for treatment type	-21.11 (-42.18, -0.05)	0.0497*

Table 4: Descriptive Pooled Rates of treatment-emergent adverse events (TEAEs) for intravenous Tramadol and VX-548 across the included studies. Event rates were calculated by summing the number of patients experiencing each adverse event and dividing by the total number of participants receiving that treatment. Safety population denominators were based on treatment received and differed from the randomized population reported in Table 1. In the Bertoch et al. (2025) abdominoplasty trial, one participant randomized to placebo received suzetrigine and was therefore included in the suzetrigine population.[9] In the Singla et al. (2020) bunionectomy trial one participant assigned to tramadol 25 mg received tramadol 50 mg and was included in the 50 mg safety population.[13] In the Minkowitz et al. abdominoplasty trial, one participant randomized to placebo received tramadol 50 mg and was therefore included in the tramadol safety population.[12] Per-trial counts, safety-population denominators, and adverse event ascertainment windows are provided in Supplementary Table S1.

Outcome	Treatment	Active Risk	Control Risk
Nausea	Tramadol (IV)	144/282 (51.1%)	61/271 (22.5%)
	VX-548	139/1010 (13.8%)	112/574 (19.5%)
Constipation	Tramadol (IV)	15/282 (5.3%)	6/271 (2.2%)
	VX-548	69/1010 (6.8%)	38/574 (6.6%)
Headache	Tramadol (IV)	34/282 (12.1%)	33/271 (12.2%)
	VX-548	56/1010 (5.5%)	43/574 (7.5%)
Vomiting	Tramadol (IV)	83/282 (29.4%)	14/271 (5.2%)
	VX-548	19/1010 (1.9%)	15/574 (2.6%)

using a restricted maximum likelihood (REML) approach and Hartung-Knapp-adjusted confidence intervals. The statistical approach was consistent with the SPID24 and SPID48 analyses, with the log odds ratio for each adverse event serving as the modeled outcome. Because no head-to-head trials were available, the coefficients represent indirect treatment effects under the assumption of transitivity rather than a direct comparison. Negative coefficients represent lower odds of adverse events with suzetrigine relative to tramadol. Suzetrigine was associated with significantly lower odds of nausea (β = −1.874, 95% CI −2.518 to −1.230; p = 0.003) and vomiting (β = −2.333, 95% CI −3.596 to −1.070; p = 0.010), whereas no significant differences were observed for constipation (β = −0.977, 95% CI −2.142 to 0.189; p = 0.076) or headache (β = −0.071, 95% CI −1.095 to 0.953; p = 0.839). However, these findings should be interpreted cautiously in the context of the placebo event rates reported in Table 4. Differences in baseline risk or other effect modifiers across trials could threaten the transitivity assumption underlying the indirect comparison. Placebo event rates were relatively similar between the suzetrigine and tramadol studies for nausea (19.5% vs 22.5%) but differed more substantially for the other adverse events. This variability further supports the need for direct comparative trials. Residual I^2 was estimated to be 0% for each adverse-event model;

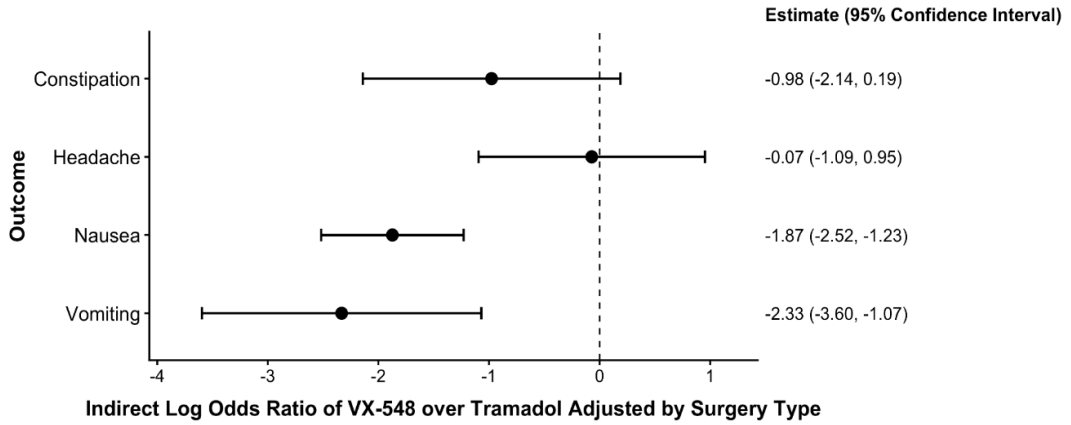

Figure 5: Forest plot showing adverse event treatment differences for intravenous tramadol and VX-548 studies as an adjusted logistic regression model.

Table 5: Coefficient estimates from the random-effects meta-regression evaluating the association of treatment with each adverse event, with surgery type included as a fixed-effect moderator. Intravenous tramadol served as the reference treatment.

Outcome	Estimate (95% CI)	P-value	Test for Residual Heterogeneity (df=3, *p* value)	Omnibus Test of Moderators (*p* value)
Nausea	-1.874 (-2.518, -1.230)	0.003	QE = 1.903 (0.593)	F[2,3] = 44.041 (0.006)
Constipation	-0.977 (-2.142, 0.189)	0.076	QE = 1.352 (0.717)	F[2,3] = 3.572 (0.161)
Headache	-0.071 (-1.095, 0.953)	0.839	QE = 2.526 (0.471)	F[2,3] = 3.529 (0.163)
Vomiting	-2.333 (-3.596, -1.070)	0.010	QE = 2.000 (0.572)	F[2,3] = 18.813 (0.020)

however, given the small number of studies these estimates had limited power to detect between-study heterogeneity. The residual heterogeneity and results of the omnibus test of moderators are given in Table 5.

GRADE Assessment

The certainty of evidence was rated very low for SPID24 and SPID48, primarily because of serious indirectness and imprecision. Certainty was low for nausea and vomiting, and very low for constipation, with downgrading primarily due to indirectness resulting from the lack of head-to-head comparisons between oral suzetrigine and intravenous tramadol. Certainty for headache was rated very low because of serious indirectness and imprecision (Figure 6).

Discussion

This systematic review and meta-analysis evaluated the efficacy and adverse event profiles of suzetrigine and tramadol in the treatment of postoperative pain following bunionectomy and abdominoplasty. Across the six studies examined, both drugs showed improvement in postoperative pain compared with placebo after both procedures, according to SPID24 and SPID48 findings (Figures 3 and 4). The adverse event profiles differed between the treatments, with statistically significant differences identified for nausea and vomiting, but not constipation or headache (Table 5). Because these findings were derived from placebo-controlled trials without direct head-to-head comparisons, the observed differences should be interpreted as indirect treatment estimates rather than definitive evidence that one drug has a comparative advantage over the other. Overall, these findings suggest that tramadol may provide greater early analgesic relief, whereas suzetrigine was associated with lower odds of nausea and vomiting in the indirect analysis.

A larger SPID value indicates greater cumulative pain relief over the specified evaluation period. VX-548 was associated with a 7.46-point smaller placebo-adjusted SPID24 effect than tramadol (β = −7.46; 95% CI, −12.52 to −2.40; p = 0.0184), suggesting greater cumulative analgesic efficacy with tramadol during the first 24 hours in this indirect meta-regression (Table 2). Although this finding should be interpreted cautiously because it was derived from an indirect comparison, the statistically significant difference suggests a potential early difference in analgesic efficacy between the two treatments. This early difference could potentially reflect their distinct pharmacologic mechanisms and onset-of-action profiles, with tramadol exerting centrally mediated analgesic effects through μ-opioid receptor agonism and inhibition of norepinephrine and serotonin reuptake, whereas suzetrigine selectively inhibits peripheral NaV1.8 sodium channels in nociceptive pathways[5,7]. However, the present indirect analysis cannot determine whether these mechanistic differences account for the observed SPID24 finding.

By 48 hours, VX-548 was associated with a 2.49-point lower SPID48 than tramadol; however, this difference was

Author(s): Benjamin Klayman, Preet Patel, Raiya Patel, Sahil Patel, Maria Pino, Stephanie Lopez
Question: Oral Suzetrigine compared to Intravenous Tramadol for Acute postoperative pain in adults undergoing bunionectomy or abdominoplasty
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral Suzetrigine	Intravenous Tramadol	Relative (95% CI)	Absolute (95% CI)		
SPID24 (24-hour Sum of Pain Intensity Difference) (follow-up: 24 hours; assessed with: Numeric Pain Rating Scale (NPRS))												
6	randomised trials	serious[a,b]	not serious	serious[c]	serious[d]	none	1.009	280	-	MD 7.46 points lower (12.52 lower to 2.4 lower)	Very low[a,b,c,d]	CRITICAL
SPID48 (48-hour Sum of Pain Intensity Difference) (follow-up: 48 hours; assessed with: Numeric Pain Rating Scale (NPRS))												
6	randomised trials	serious[a,b]	not serious	serious[c]	serious[e]	none	1.009	280	-	MD 2.49 points lower (24.83 lower to 19.84 higher)	Very low[a,b,c,e]	CRITICAL
Nausea (assessed with: Occurrence of nausea)												
6	randomised trials	serious[a,b]	not serious	serious[f]	not serious	none	139/1010 (13.8%)	144/282 (51.1%)	OR 0.15 (0.08 to 0.29)	373 fewer per 1,000 (from 433 fewer to 277 fewer)	Low[a,b,f]	CRITICAL
Constipation (assessed with: Occurrence of constipation)												
6	randomised trials	serious[a,b]	not serious	serious[g]	serious[h]	none	69/1010 (6.8%)	15/282 (5.3%)	OR 0.38 (0.12 to 1.21)	32 fewer per 1,000 (from 46 fewer to 10 more)	Very low[a,b,g,h]	CRITICAL
Headache (assessed with: Occurrence of headache)												
6	randomised trials	serious[a,b]	not serious	serious[i]	serious[h]	none	56/1010 (5.5%)	34/282 (12.1%)	OR 0.93 (0.33 to 2.59)	7 fewer per 1,000 (from 77 fewer to 141 more)	Very low[a,b,h,i]	CRITICAL
Vomiting (assessed with: Occurrence of vomiting)												
6	randomised trials	serious[a,b]	not serious	serious[j]	not serious	none	19/1010 (1.9%)	83/282 (29.4%)	OR 0.10 (0.03 to 0.34)	255 fewer per 1,000 (from 283 fewer to 169 fewer)	Low[a,b,j]	CRITICAL

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

a. Risk of bias was downgraded one level because all six included trials were judged to have "some concerns" overall according to the RoB 2 assessment. Although no trials were judged to have a high overall risk of bias, the presence of methodological concerns across the evidence base warranted downgrading the certainty of evidence for risk of bias.
b. Risk-of-bias assessments were based on the Cochrane Risk of Bias 2 (RoB 2) tool and were applied to both the SPID24/SPID48 and adverse-event outcomes.
c. The comparison is indirect because no head-to-head trials directly compared oral suzetrigine with intravenous tramadol.
d. Although the 95% confidence interval excludes the null effect, it ranges from a 2.40-point to a 12.52-point reduction in SPID24, leaving uncertainty about the magnitude and clinical importance of the benefit. This uncertainty was considered sufficient to downgrade the certainty of the evidence for imprecision.
e. The 95% CI is wide and crosses the line of no effect, ranging from a potentially meaningful benefit to a potentially meaningful harm.
f. No head-to-head trials directly compared oral suzetrigine with intravenous tramadol; therefore, the treatment effect was estimated through an indirect comparison using placebo as the common comparator.
g. The comparison is indirect because suzetrigine and intravenous tramadol were evaluated in separate trials rather than directly compared in the same study population. Differences in study populations and surgical procedures may limit the applicability of the indirect comparison.
h. The confidence interval around the estimated treatment effect is wide and crosses the line of no effect, indicating substantial uncertainty about the magnitude and direction of the treatment effect.
i. The comparison is indirect because suzetrigine and intravenous tramadol were not directly compared in the same randomized trials; the estimates were derived from separate placebo-controlled studies.
j. No head-to-head trials directly compared oral suzetrigine with intravenous tramadol. The comparison was indirect through a common placebo comparator, and differences in route of administration may affect adverse-event rates and threaten the transitivity assumption.

Figure 6: GRADE Certainty of Evidence Assessment for Oral Suzetrigine Compared with Intravenous Tramadol.

not statistically significant (β = −2.49; 95% CI, −24.83 to 19.84; p = 0.75) (Table 3). Additionally, the wide confidence interval and limited number of included studies, particularly the two tramadol studies, indicate substantial uncertainty in the estimated treatment difference and may have limited the ability to detect a true difference at 48 hours. The SPID48 findings should be considered inconclusive rather than evidence of comparable or equivalent analgesic efficacy. Therefore, the available evidence supports a potential difference in early analgesic response but does not establish whether this difference persists over the first 48 hours.

The adverse event profiles were characterized by comparisons of treatment effects relative to placebo. Specific events - including nausea, constipation, headache, and vomiting - were evaluated across the included studies (Table 4). The indirect meta-regression analysis found no statistically significant differences between VX-548 and tramadol for constipation and headache. However, tramadol was associated with significantly higher odds of nausea and vomiting compared with suzetrigine (Figure 5, Table 5). Interestingly, the descriptive pooled rates of both nausea and vomiting were lower in the suzetrigine groups than in the corresponding pooled placebo groups. This unexpected pattern should not be interpreted as evidence that suzetrigine reduces the risk of nausea or vomiting, as these descriptive rates were aggregated across separate trials and may have been influenced by between-study differences in patient characteristics, rescue analgesics, surgical procedures, and other confounding variables. These findings should be interpreted cautiously, as tramadol was administered intravenously whereas suzetrigine was administered orally. Therefore, the observed differences in nausea and vomiting cannot be attributed solely to differences in pharmacologic mechanism or drug-specific tolerability, as route of administration may have independently influenced adverse event rates. Intravenous administration is particularly associated with emetogenic effects, which may have confounded the adverse event profiles compared to oral administration[5]. This difference in route of administration represents a potential threat to the transitivity assumption underlying our indirect comparison, because route may function as an effect-modifying factor across studies. Consequently, although suzetrigine was associated with lower odds of nausea and vomiting in this analysis, future head-to-head trials using comparable routes of administration are necessary to determine whether this difference reflects a true drug-specific tolerability advantage.

With the ongoing opioid epidemic remaining a major public health challenge in the United States, the need for safer alternatives remains critical for reducing unnecessary perioperative opioid exposure. Opioid use remains common following abdominoplasties, with

91% of patients receiving an opioid prescription, and bunionectomies, with 90% of patients consuming opioids postoperatively[25,26]. Suzetrigine expands the availability of non-opioid treatment options and represents a clinically relevant comparator to established analgesics such as tramadol. Although the present findings do not establish equivalent analgesic efficacy or directly demonstrate an opioid-sparing effect, suzetrigine's non-opioid mechanism and demonstrated analgesic efficacy versus placebo support the hypothesis that it may have a role in future opioid-sparing or multimodal pain management strategies. This hypothesis should be evaluated in sufficiently powered head-to-head trials comparing suzetrigine with opioid-based analgesic regimens and directly assessing postoperative opioid consumption.

Clinical Integration

Suzetrigine represents a novel approach to postoperative pain control through selective inhibition of NaV1.8 without directly activating μ-opioid receptors. This distinct mechanism differentiates it from conventional opioid analgesics and provides a rationale for investigating its potential role in multimodal pain management strategies. Preclinical studies have demonstrated additive inhibition of NaV1.8-mediated currents when suzetrigine is combined with local anesthetics such as bupivacaine or ropivacaine, without evidence of antagonistic interactions[27]. However, these findings are based on preclinical models and should not be interpreted as evidence of clinical benefit from combining suzetrigine with local anesthetics. Clinical studies are needed to determine the efficacy and safety of incorporating suzetrigine into multimodal analgesic regimens.

Limitations

There are several limitations to consider when interpreting the findings of this analysis. Only six studies were included, comprising two tramadol and four suzetrigine trials, and no head-to-head comparisons between the two treatments were available. Therefore, this indirect comparison relies on the transitivity assumption that the included studies were sufficiently comparable with respect to factors that may influence treatment effects. Only one tramadol trial was available within each surgical model, making the indirect treatment estimate particularly sensitive to the results of either tramadol study. The tramadol trials were conducted earlier than the suzetrigine trials, creating the possibility that changes in perioperative analgesic techniques, rescue medication protocols, or standards of care over time may have influenced the observed treatment effects, indicating a potential violation of the transitivity assumption (Table 1). Additionally, differences in dosing regimens and routes of administration—intravenous tramadol versus oral suzetrigine—may have influenced treatment effects and adverse event rates, particularly nausea and vomiting, further limiting the validity of the indirect comparison. Adverse event ascertainment windows also differed between trials: adverse events in the two tramadol trials were collected through 24 hours after the start of the last dose, whereas the four suzetrigine trials included a safety follow-up through 14 ± 2 days after the last dose (Supplementary Table S1), which may limit the comparability of adverse event rates. Given these limitations, the relative efficacy and safety of the two treatments cannot be definitively established from the available evidence. The small number of included studies also precluded a meaningful assessment of publication bias using methods such as funnel plot inspection or Egger's test. Restriction to English-language studies may have introduced a language bias. Finally, these findings are limited to bunionectomy and abdominoplasty and may not be generalizable to other procedures or postoperative conditions.

Conclusion

Overall, this systematic review suggests that suzetrigine may provide effective postoperative analgesia, although the indirect comparison favored intravenous tramadol at 24 hours. No statistically significant difference in SPID48 was observed; however, the wide confidence interval (β = −2.49; 95% CI, −24.83 to 19.84) indicates substantial uncertainty around the estimated treatment difference, and the absence of statistical significance should not be interpreted as evidence of comparable or equivalent analgesic efficacy. Suzetrigine was associated with lower odds of nausea and vomiting compared with intravenous tramadol; however, differences in route of administration and the absence of direct head-to-head comparisons limit conclusions regarding relative efficacy and tolerability. Future direct comparative trials using comparable dosing regimens and routes of administration are needed to better establish the relative efficacy and safety of suzetrigine and tramadol. Further research should also evaluate suzetrigine within multimodal analgesic strategies and identify surgical populations that may derive the greatest benefit.

List of Abbreviations

AE: Adverse event

CI: Confidence interval

df: Degrees of freedom

FDA: Food and Drug Administration

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

IV: Intravenous

MD: Mean difference

NaV1.8: Voltage-gated sodium channel 1.8

NPRS: Numeric Pain Rating Scale

NR: Not reported

NSAIDs: Nonsteroidal anti-inflammatory drugs

OR: Odds ratio

OSF: Open Science Framework

PO: By mouth (per os)

PRN: As needed (pro re nata)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

q4h: Every 4 hours

q6h: Every 6 hours

q12h: Every 12 hours

REML: Restricted maximum likelihood

RoB 2: Cochrane Risk of Bias tool, version 2

SD: Standard deviation

SE: Standard error

SPID24: Sum of Pain Intensity Differences over 24 hours

SPID48: Sum of Pain Intensity Differences over 48 hours

TEAEs: Treatment-emergent adverse events

VX-548: Suzetrigine

Conflict of Interest

The authors declare no conflict of interest.

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Ethics Statement

Ethical approval and informed consent were not required because this systematic review and meta-analysis used only previously published aggregate data and did not involve the collection of new data from human participants.

Author's Contributions

Preet Patel and Benjamin Klayman initiated the idea to study suzetrigine vs tramadol for this meta-analysis. Both authors participated in pharmacology discussions on this topic, were core in selecting and reviewing the literature, and the writing and editing of the manuscript. They share first authorship. Raiya Patel participated in all the meetings, the selection and discussion of the literature, while also writing, organizing, and editing this manuscript. Sahil Patel assisted with the statistical analysis. He was core in the synthesis of the tables and figures (Fig 3, 4 and data tables), while also contributing to the edits. Stephanie Lopez, the medical librarian, registered the protocol, compiled the articles for extraction, and helped synthesize the statistical methodology and PRISMA diagram. Maria A. Pino was the principal investigator. As a pharmacologist, she supported the idea of reviewing suzetrigine, led the discussions, guided the review process, while also commenting on the writing of this manuscript.

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Supplementary Material: Search Strategies

The search strategies for each database are shown in this document. The databases were searched until **April 6, 2026**.

PubMed
("suzetrigine" [Supplementary Concept] OR "Tramadol"[Mesh] OR tramadol[tw] OR suzetrigine[tw] OR vx-548[tw] OR journavx[tw]) AND ("Bunion/surgery"[Mesh] OR "Abdominoplasty"[Mesh] OR bunion*[tiab] OR abdom*[tiab] OR feet[tw] OR foot[tw] OR pannicu* OR osteotom*) 183

Ovid MEDLINE(R) and Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

1	suzetrigine.nm,mp.	146
2	tramadol.nm,mp.	8133
3	(vx-548 or journavx).mp.	55
4	Tramadol/	4086
5	1 or 2 or 3 or 4	8287
6	exp Bunion/su	108
7	exp Abdominoplasty/	1303
8	(bunion* or abdom* or feet or foot or pannicu* or osteotom*).kw,ti,ab.	684985
9	6 or 7 or 8	685094
10	5 and 9	182

Scopus via Elsevier
TITLE-ABS-KEY(tramadol OR suzetrigine OR vx-548 OR journavx) AND (bunionectomy OR bunion* OR abdom* OR feet OR foot OR pannicu* OR osteotom*) **result count not retrieved**

Cochrane Central Register of Controlled Trials via EBSCO
((MH Tramadol) OR tramadol OR suzetrigine OR vx-548 OR journavx) AND ((MH Bunion/surgery) OR (MH Abdominoplasty) OR (TI bunion* OR AB bunion*) OR (TI abdom* OR AB abdom*) OR feet OR foot OR pannicu* OR osteotom*) **not retrieved**

ClinicalTrials.gov
COVERAGE[Contains](Suzetrigine OR VX-548 OR JOURNAVX OR Tramadol) AND COVERAGE[Contains](bunionectomy OR abdominoplasty) 6

medRxiv
Does not allow for advanced searching as the other database so concluded it was best to search by drug.
suzetrigine or vx-548 or journavx or tramadol 8

Supplementary Table S1: Per-trial adverse event counts, safety-population denominators, and adverse event ascertainment windows for the six included trials.

Trial	Safety N (active/ placebo)	Nausea, n/N	Constipation, n/N	Headache, n/N	Vomiting, n/N	AE Ascertainment
Singla 2020, bunionectomy	140/135	45/140 vs 11/135	8/140 vs 3/135	8/140 vs 13/135	28/140 vs 5/135	During/after treatment through 24h after start of last dose
Bertoch 2025, bunionectomy	426/216	35/426 vs 23/216	15/426 vs 9/216	21/426 vs 20/216	7/426 vs 6/216	TEAEs from first dose through safety follow up, 14 ± 2d after last dose
Jones 2023, bunionectomy	60/59	5/60 vs 5/59	0/60 vs 1/59	5/60 vs 7/59	0/60 vs 1/59	AE collection through safety follow-up 14 ± 2d after last dose
Minkowitz 2020, abdominoplasty	142/135	99/142 vs 50/135	7/142 vs 3/135	26/142 vs 20/135	55/142 vs 9/135	During/after treatment through 24h after start of last dose
Bertoch 2025, abdominoplasty	448/222	85/448 vs 56/222	47/448 vs 24/222	19/448 vs 11/222	10/448 vs 3/222	TEAEs from first dose through safety follow up, 14 ± 2d after last dose
Jones 2023, abdominoplasty	76/77	14/76 vs 28/77	7/76 vs 4/77	11/76 vs 5/77	2/76 vs 5/77	AE collection through safety follow-up 14 ± 2d after last dose

Values are n/N for the active arm versus the placebo arm. Safety N is the safety population, defined by treatment received, and may differ from the randomized populations in Table 1. Active arms were intravenous tramadol 50 mg (Singla 2020; Minkowitz 2020) or oral suzetrigine, 100 mg loading dose followed by 50 mg every 12 hours (Bertoch 2025; Jones 2023). Counts shown are raw counts; a 0.5 continuity correction was applied in the meta-regression to the zero cells in Jones 2023 (bunionectomy; constipation and vomiting, suzetrigine arm). AE, adverse event; TEAEs, treatment-emergent adverse events.