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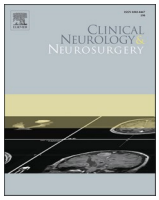

Review article

Serotonin norepinephrine reuptake inhibitors in managing neuropathic pain following spinal and non-spinal surgery: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: While serotonin norepinephrine reuptake inhibitors (SNRIs) offer promise in managing Post-surgical neuropathic pain (PSNP), uncertainties remain. This study aims to evaluate the effectiveness and adverse events of SNRIs in managing PSNP.

Methods: Systematic searches of PubMed, Embase, and Cochrane databases up to January 1st 2023 identified randomized controlled trials (RCTs) comparing SNRIs to placebo for PSNP. The primary outcome measures were pain at rest and adverse events post-surgery. Subgroup analyses were conducted based on surgical type and specific SNRIs.

Results: A total of 19 RCTs, encompassing 1440 participants (719 in the SNRI group vs 721 in the placebo group), met the inclusion criteria and were included. The pooled results demonstrated that pain scores were significantly lower in patients treated with SNRIs at 2 hours (MD:-0.26; 95%CI: −0.47 to −0.04; p=0.02), 6 hours (MD:-0.68; 95%CI: −1.01 to −0.34; p<0.0001), 24 hours (MD:-0.54; 95%CI: −0.99 to −0.09; p=0.02), and 48 hours (MD:-0.66; 95%CI: −1.23 to −0.10; p=0.02) post-surgery. In terms of adverse events, dizziness (OR:2.53; 95%CI: 1.34–4.78; p=0.004) and dry mouth (OR:2.21; 95%CI: 1.25–3.92; p=0.007) were significantly higher in the SNRIs group. Subgroup analysis showed that SNRI was found to significantly lower the 24-hour pain score after spinal surgery (MD:-0.45; 95%CI: −0.84 to −0.05; p=0.03). Duloxetine (MD:-0.63; 95%CI: −1.15 to −0.11; p=0.02) had a significant effect in lowering the 24-hour pain score at rest compared to placebo, whereas venlafaxine did not.

Conclusions: SNRIs yielded considerable pain score reductions across multiple post-surgical intervals, although accompanied by an increased incidence of dizziness and dry mouth.

1. Introduction

The etiology of neuropathic pain is multi-factorial, encompassing various pathological states and conditions. Commonly observed causes of neuropathic pain include metabolic disorders, such as peripheral diabetic neuropathy (PDN), viral neuropathies such as post-herpetic neuralgia, central nervous system autoimmune disorders such as multiple sclerosis, chemotherapy-induced peripheral neuropathies, and neural damage resulting from traumatic events [1]. Importantly, post-operative procedures can also result in neural damage, leading to the manifestation of neuropathic pain. Post-Surgical Neuropathic Pain (PSNP) refers to a complex type of chronic pain that develops following

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surgery. It is caused by injury to the peripheral or central nervous system, leading to the formation of pathological neural changes [2]. The surgically-induced alterations in the nervous system often result in a persistent and abnormal pain perception in response to stimuli, long after the initial surgical wound has undergone proper healing. This pain can persist for a prolonged duration, ranging from a minimum of two months to one year post-operatively [3]. It is a prevalent and pressing clinical issue, with reports indicating that a substantial proportion of individuals, ranging from 10% to 50%, may experience persistent pain following routine surgical procedures [4]. Studies have documented incidences rates of post-operative neuropathic pain that vary widely across different surgical procedures. For instance, amputation of a limb has been associated with incidences rates ranging from 50% to 85%, mastectomy from 11% to 57%, cardiac surgery from 30% to 55%, thoracotomy from 5% to 65%, and hernia repair from 5% to 63% [5]. PSNP is characterized by symptoms such as burning, tingling, shooting, and electric-shock-like pain. The pain is often accompanied by sensory alterations, such as heightened sensitivity to touch and decreased ability to tolerate cold and heat [6,7]. Despite being associated with elevated morbidity and extended hospital stays, PSNP presents as a challenging task with no established consensus on the optimal treatment approach [8].

Despite the fact that acute postoperative pain management has typically relied on pharmacologic treatments, including the use of opioids, there is growing interest in reducing or eliminating opioid use and utilizing multimodal analgesic regimens instead. Multimodal pharmacological analgesia offers a potential solution to the management of pain, as it decreases the doses of individual components, reduces side effects, and targets multiple pain components simultaneously [9]. This approach involves combining two or more agents with complementary mechanisms of action in an effort to decrease overall opioid consumption while still achieving adequate pain relief [10]. Advances in multimodal analgesia and a better understanding of the acute pain response following surgery hold the potential to effectively manage acute postoperative pain and potentially minimize the possibility of its transformation into a chronic condition [11]. Despite recent evidences indicating the efficacy of antidepressants in the management of neuropathic pain, not all antidepressant medications exhibit comparable effectiveness [12,13]. As a result, the utilization of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs) for the treatment of neuropathic pain has gained momentum due to the perception that these medications are better tolerated compared to traditional Tricyclic Antidepressants (TCA) [14]. The mechanism of action of SNRIs including bicifadine, duloxetine, tramadol, and venlafaxine is characterized by a more balanced inhibition of the reuptake of both serotonin and noradrenaline. This leads to increased levels of noradrenaline, which can interact with both postsynaptic alpha- and beta-adrenergic receptors as well as presynaptic alpha-2 receptors [15]. These presynaptic receptors play a crucial role in the modulation of antinociception within the central nervous system [16,17]. Despite the well-established local anesthetic-like effect of tricyclic antidepressants as potent voltage-gated sodium channel blockers, the clinical significance of this effect in SNRIs remains indeterminate at the present [14,18].

Despite the widespread use of SNRIs for managing this condition, the efficacy of these medications in comparison to placebo remains uncertain. This necessitates a comprehensive meta-analysis of the existing evidence to evaluate the impact of SNRIs in managing post-surgical neuropathic pain in adults. We hypothesize that SNRIs could effectively manage PSNP. Such an analysis will provide valuable insights into the clinical significance of these drugs in this specific patient population and contribute to the development of evidence-based guidelines for the management of post-surgical neuropathic pain.

2. Methods

2.1. Study design and inclusion criteria

In accordance with the PRISMA guidelines, this meta-analysis was conducted using strict methodology. The study protocol was registered and approved in the PROSPERO database (ID: CRD42023398538) prior to the initiation of the systematic search. The inclusion criteria for this meta-analysis consisted of randomized controlled trials up to January 1st 2024 examining the efficacy of SNRIs versus placebo in adults diagnosed with post-surgical neuropathic pain. The following criteria were employed: the studies had to clearly state the use of SNRIs as the intervention, direct comparisons of outcomes between SNRIs and placebo were required, participants are those that have undergone an open surgery, and the studies had to randomly allocate participants equally (1:1). Exclusion criteria included studies that did not follow up for at least 2 hours, studies conducted on pediatric population, participants post-chemotherapy, participants with mental or psychiatric conditions, and studies that did not specify the type of SNRIs used. Observational studies, case-control studies, case reports, pre-prints, congress abstracts, and review articles were excluded from the analysis. Ethical approval for patient enrollment at all participating sites was obtained from the relevant institutional review boards. The literature search was conducted by three authors, while data extraction and bias assessment were performed by another three authors, working collaboratively in each step to mitigate bias. Any discrepancies in study eligibility were resolved through consensus after review by one additional author. The primary outcomes of the study were the pain scores at rest, which were assessed at various intervals post-surgery (specifically at 2, 4, 6, 12, 24, and 48 hours). These measurements served as crucial indicators to evaluate the efficacy of SNRIs in pain reduction following surgery. Additionally, secondary outcomes included monitoring the incidence of adverse events such as vomiting, itching, drowsiness, dizziness, headaches, nausea, sedation, and dry mouth. These secondary measures were instrumental in assessing the safety profile of SNRIs administration post-surgery.

2.2. Literature search and selection

A comprehensive and systematic literature search was performed utilizing the PubMed, Embase, and Cochrane databases without any restrictions on language. In cases where the literature is written in a foreign language, a translating software was utilized to translate the text, which was subsequently reviewed and confirmed by a native speaker of the language. The search strategy incorporated the use of Medical Subject Headings (MeSH) terms and free-text keywords relevant to the topic of interest, including ((((((((((Post-Surgical Neuropathic Pain) OR (Post Surgical Neuropathic Pain)) OR (Neuropathic Pain)) OR (Post Surgery Neuropathic Pain)) OR (Post-Surgery Neuropathic Pain)) OR (After Surgery Pain)) OR (Neuropathic Pain)) OR (Post-Surgical Pain)) OR (Post Surgical Pain) AND ((((((((((Serotonin Norepinephrine Reuptake Inhibitors) OR (SNRI)) OR (SNRIs)) OR (Serotonin and norepinephrine reuptake inhibitors)) OR (Serotonin-norepinephrine reuptake inhibitors)) OR (Bicifadine)) OR (Duloxetine)) OR (Venlafaxine)) OR (Tramadol) AND (Placebo).

2.3. Data extraction

A systematic extraction of the demographic, baseline clinical, and outcome data of the included studies was performed. The extracted information comprised details such as the number of trial centers and participants, location, age, gender, dosage, administration method, time of administration, post-operative analgesia, and duration of surgery. The results of the study were based on important indicators such as pain scores at rest taken at multiple time points after surgery (2, 4, 6, 12, 24, and 48 hours). These measures were used to assess the efficacy of SNRIs

in reducing pain. In addition, other indicators, such as the incidence of adverse events like vomiting, itching, drowsiness, dizziness, headaches, nausea, sedation, and dry mouth, were also used to evaluate the safety of SNRIs after surgery. The study performed two separate subgroup analyses, one based on the specific type of surgery (post-spinal, post-gynecological, and post-knee), and another based on the specific type of SNRIs utilized (either duloxetine or venlafaxine).

2.4. Quality assessment of included studies

Cochrane Collaboration's tool for Risk of Bias Assessment [19] was used for risk evaluation. This tool encompasses seven components, which were applied to examine the sources of potential bias in each study, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The tool evaluates the risk of bias within the trials, taking into consideration aspects such as randomization procedures, allocation concealment, and blinding of participants, among others. The risk of bias assessment ensured a comprehensive and rigorous evaluation of the quality of evidence in the included studies.

2.5. Data synthesis and analysis

In order to synthesize and analyze the data from the included studies, a comprehensive statistical approach was adopted. For binary outcomes, such as vomiting, itching, drowsiness, dizziness, headaches, nausea,

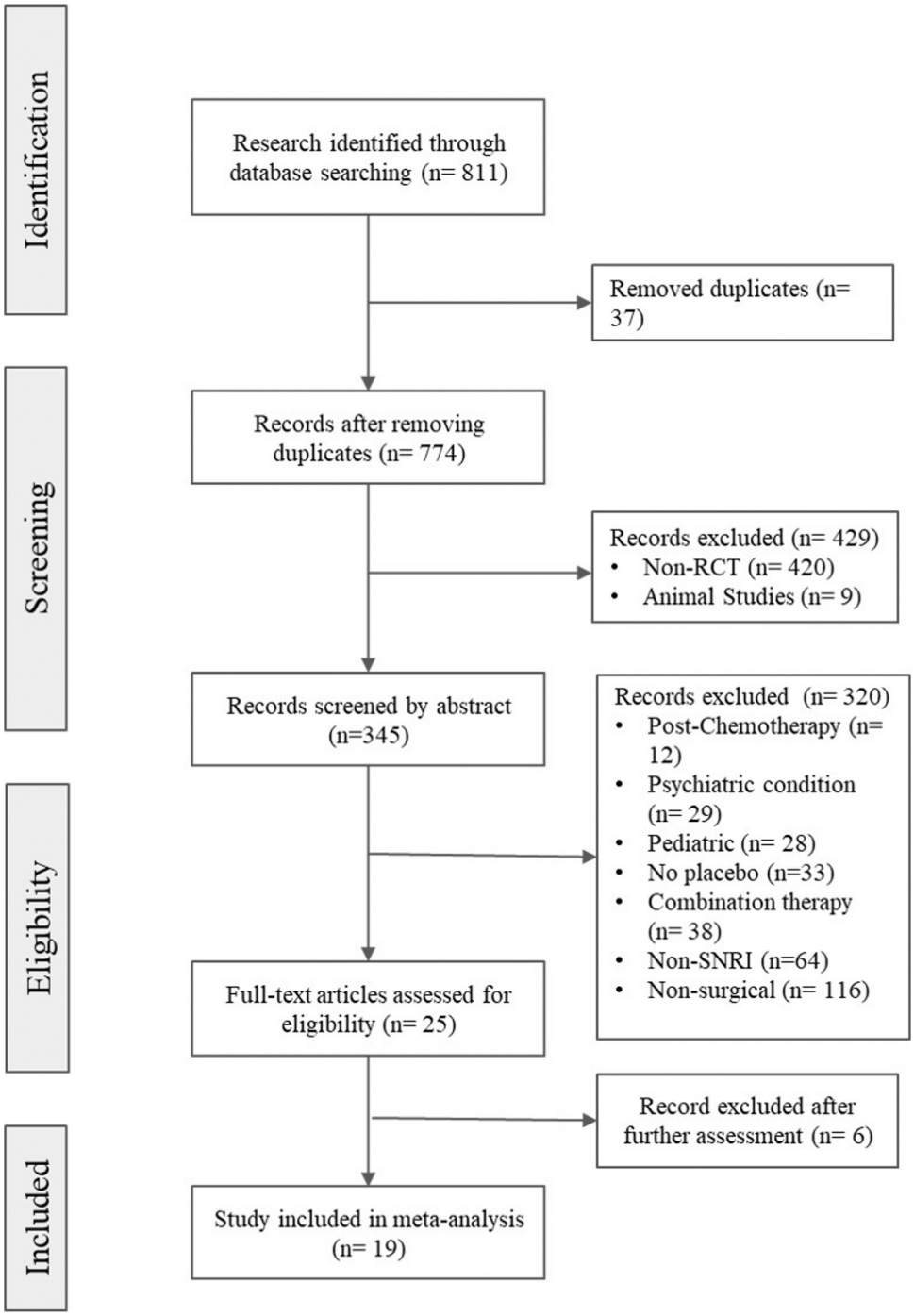

Fig. 1. PRISMA flowchart diagram.

sedation, and dry mouth, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. These ORs were combined using a random-effects model, specifically the DerSimonian and Laird model, with the estimate of heterogeneity determined through the Mantel-Haenszel method. For continuous outcomes, such as duration of longest pain scores at rest taken at multiple time points after surgery (2, 4, 6, 12, 24, and 48 hours), the summary statistic utilized was the standardized mean difference (SMD) with 95% CIs. The trial-specific data for these continuous outcomes was pooled using the inverse variance random-effects method and the weighted mean difference (MD) and 95% CIs were calculated. Forest plots were generated to graphically represent the mean and standard deviation results. The heterogeneity between studies was analyzed using the I2 statistic, and the fixed-effects model was employed if the I^2 value was less than 50%, otherwise, the random-effects model was used. All statistical analyses were carried out using Review Manager software version 5.4.1 [20], and a significance level of $p < 0.05$ was established.

2.6. Standard protocol approvals, registrations, and patient consents

Ethical approval was not required because of the nature of the study (no humans or animals).

2.7. Data Availability

Data generated in this study can be made available by reasonable request to the authors.

3. Results

3.1. Study selection

The initial systematic literature search yielded into 811 articles which met the inclusion criteria, 37 among which were duplicates as shown in Fig. 1. The studies were excluded because the studies are non-RCT. The subsequent papers were then excluded based on the title and abstract due to the following reasons: post-chemotherapy (n = 12), psychiatric condition (n = 29), pediatric population (n = 28), missing placebo group (n = 43), combination therapy (n = 38), non-SNRI (n = 64), and incomplete non-surgical (n = 148). The remaining 25 papers underwent full-text screening and 6 studies [21–26] were discarded after further assessment due to unavailable full-text article and incomplete provision of data. Ultimately, 19 studies qualified and were included in the meta-analysis [27–45].

3.2. Characteristics of included studies and participants

The 19 randomized controlled trials (RCTs) in this meta-analysis were conducted in between 1997 and 2022. The studies were conducted in various countries, including Brazil, Egypt, Germany, India, Portugal, Singapore, South Korea, Thailand, Turkey, and the United States of America. All of the articles were published in English except for one article which was published in Thai or Siamese.

Oral duloxetine was examined in 15 studies, with 12 studies employing a dosage of 60 mg and 3 studies utilizing 30 mg. Oral venlafaxine was assessed in 2 studies, with one study administering a dosage of 37 mg and another using 75 mg. Intravenous tramadol was investigated in 2 studies, with one study employing a dosage of 20 mg and another utilizing 1.50 mg/kg. All of the studies conducted offered post-operative analgesia and all except for 5 studies, provided the patients with antiemetic drugs. Across the studies, the patients underwent surgery either with regional or general anesthesia. The types of surgeries performed include gynecological surgeries (n = 7), spinal surgeries (n = 5), knee surgeries (n = 4), obstetric surgery (n = 1), abdominal surgery (n = 1), tonsillectomy (n = 1), hemorrhoidectomy (n = 1), and hip surgery (n = 1). Due to gynecological surgery, the studies only involved female patients. The dosage ranges from 20 to 75 mg, most dosages given are either 30 or 60 mg. The administration schedule and methods also vary, most studies administer an hour or two after surgery and then 24 or 48 hours after. The details of the dosing regimen of the trials are further elaborated in Table 1. The participants are patients whom underwent surgery and have consented to the trial. The mean age of the participants ranges between 26.50 and 69.10 years old. As with the body mass index (BMI) score, the score varied between 22.40 and 32.42 in most of the studies, with the exception of two studies where the BMI could not be determined due to insufficient data.

Table 2 presents the patient characteristics for each randomized controlled trial. The study included a total of 1440 patients (719 vs 721), with a mean age of 48.27 years (48.67 vs 47.86). Among all participants, 76.12% were females (76.13% vs 76.10%), with an average BMI of 27.14 (27.24 vs 27.04). The two groups comprised an equal number of participants, with a ratio of 1:1. Furthermore, the two groups had similar mean age, sex ratio, and mean BMI, making them comparable for the purpose of comparison.

3.3. Quality assessment of the included studies

The quality of methodology was appraised using the risk of bias evaluation tool recommended by Cochrane as shown in Fig. 2. The assessment revealed that most studies showed a low risk of bias in the majority of domains. Out of the 19 studies, eight were found to have a high risk of bias due to various reasons [27,29,30,34,35,44,45]. One study did not disclose the method of allocation concealment, while another study was not double-blinded [30,35]. Furthermore, four studies excluded several patients from both the SNRI and placebo groups during follow-up without any intention-to-treat analysis, while some studies mentioned that patients were lost during follow-up without utilizing an intention-to-treat analysis [27,35,44,45]. Additionally, four studies reported more outcomes in their articles than in the published protocols [27,29,34,36]. In terms of the presented data, 3 out of 19 studies did not provide data for 24-hour pain score at rest post-surgery [29,34,41]. However, 4 out of 19 studies did not present any data regarding adverse events [28,33,35,36]. Furthermore, among the studies that employed tramadol, one study did not present pain scores at any hours post-surgery [34].

3.4. Pain and adverse events in SNRIs group vs placebo group

Table 3 presents the summary of this study. The mean pain scores for pain at rest at 2 hours, 6 hours, 24 hours, and 48 hours following surgical interventions were significantly lower in the SNRIs group compared to the placebo group. Regarding adverse events, dizziness and dry mouth were the only side effects found to be significantly higher in the SNRIs group. Subgroup analysis revealed that only the 24-hour pain at rest following spinal surgery had significantly lower score than that of the placebo group. Among the various types of SNRIs drugs used, only duloxetine was found to significantly reduce pain scores at the 24-hour post-surgical mark.

Fig. 3 shows the effects of SNRIs on pain at rest at different points in time. Non-significant effects of SNRIs on pain at rest was found at 4 hours (MD: −0.26; 95% CI: −1.39–0.36; p=0.25) and 12 hours (MD: −0.95; 95% CI: −2.12–0.23; p=0.11) post-surgery. Pain scores were significantly lower in patients treated with SNRIs at 2 hours (MD: −0.26; 95% CI: −0.47 to −0.04; p=0.02), 6 hours (MD: −0.68; 95% CI: −1.01 to −0.34; p<0.0001), 24 hours (MD: −0.54; 95% CI: −0.99 to −0.09; p=0.02), and 48 hours (MD: −0.66; 95% CI: −1.23 to −0.10; p=0.02) post-surgery compared to placebo. Ultimately, the pain score at rest following surgical intervention were significantly lower in the SNRIs group compared to the placebo group (MD: −0.57; 95% CI:-0.80 to −0.33; p<0.00001).

Fig. 4 shows the effects of SNRIs on adverse events post-surgery. Neither vomiting (OR: 0.80; 95% CI: 0.56–1.18; p=0.28), pruritus

Table 1
Characteristics of selected studies.

Study, year	Country	SNRI	Surgery	Surgery time (mins)	Postoperative analgesia	Dose	Administration time
Altiparmak, 2018 [27]	Turkey	D	LDH	90.00 ± 9.00	Pct 1000 mg IV, Dic 75 mg IM	60 mg oral	1 h pre and 24 h post-surgery
Attia, 2017 [38]	Egypt	D	LDH	113.20 ± 13.70	Pct 1000 mg IV, Mop 2 mg IV	60 mg oral	1 h pre and 24 h post-surgery
Bedin, 2017 [39]	Brazil	D	LSF	161.00 ± 55.00	Ktc 0.4 mg/kg IV, Fen IV	60 mg oral	1 h pre and 24 h post-surgery
Castro-alvez, 2016 [40]	Portugal	D	AH	110.00	Ktn 100 mg IV, Mop 2 mg IV	60 mg oral	1 h pre and 24 h post-surgery
El-Behairy, 2019 [42]	Egypt	D	HS	132.07 ± 13.70	Mop 2 mg IV	30 mg oral	12 h for 3d, 2 h pre and 12 h post-surgery
Gerber, 2022 [43]	Brazil	D	H	40.00	Ktn 100 mg IV, Dip 2 g IV	60 mg oral	2 h pre and 24 h post-surgery
Govil, 2020 [44]	India	D	LCS	113.40 ± 19.80	Pct 325 mg, Mop 0.05 mg/kg IV	30 mg oral	2d pre, surgery day, and 2 days post-surgery
Ho, 2010 [45]	Singapore	D	KR	78.00 ± 21.00	Pct 1000 mg IV, Mop IV	60 mg oral	2 h pre and 24 h post-surgery
Kassim, 2018 [29]	Egypt	D	LH	62.20 ± 8.80	Pethidine 0.5 mg/kg IV	60 mg oral	2 h pre-surgery
Koh, 2019 [30]	S. Korea	D	KA	-	Cxb 200 mg, Pgb 150 mg, Fen IV	30 mg oral	1d pre and 6w post-surgery
Mantay, 2016 [31]	Thailand	D	M	80.00	Pct 325 mg, Mop IV	60 mg oral	1d pre and 7d post-surgery
Nasr, 2014 [32]	Egypt	D	M	71.40 ± 3.60	Pct 1000 mg IV, Mop 2 mg IV	60 mg oral	2d pre and 2w post-surgery
Takmaz, 2019 [35]	Turkey	D	LH	120.00	Pct 1000 mg IV, Mop 1 mg IV	60 mg oral	2 h pre and 24 h post-surgery
YaDeau, 2016 [36]	USA	D	KA	-	Dex 4 mg IV, Ktc 30 mg IV, Mop 1 mg IV	60 mg oral	30 m pre and 2w post-surgery
YaDeau, 2022 [37]	USA	D	KA	-	Pct 1000 mg IV & p.o., Ktc 15 mg IV, Mlx 15 mg, Oxy 5–10 mg p.o.	60 mg oral	1d pre and 14d post-surgery
Amr, 2010 [28]	Egypt	V	M	73.00 ± 22.00	Mop 20–50 mcg/kg IV, Pct 500 mg or Cod 30 mg p.o.	37.5 mg oral	1d pre and 10d post-surgery
Reuben, 2004 [33]	USA	V	M	105.00 ± 12.00	Mop, Pct 325 mg p.o. or Oxy 5 mg p.o.	75 mg oral	1d pre and 2w post-surgery
Stamer, 1997 [34]	Germany	T	LH	147.70 ± 52.90	-	20 mg IV	Post-surgery for 2d
Demiraran, 2013 [41]	Turkey	T	CS	-	Dic 75 mg IV p.r.n.	1.5 mg/kg IV	At end of surgery

Abbreviations: AH = Abdominal hysterectomy, Cod = Codein, CS = Caesarean section, Cxb = Celecoxib, D = Duloxetine, Dex = Dexamethasone, Dic = Diclofenac, Dip = Dipyrone, Fen = Fentanyl, H = Haemorrhoidectomy, HS = Hip surgery, IM = Intramuscular, IV = Intravenous, KA = Knee arthroplasty, Ktc = Ketoralac, Ktn = Ketoprofen, KR = Knee replacement, LDH = Lumbar disk herniation, LCS = Lumbar canal stenosis, LH = Laparoscopic hysterectomy, M = Mastectomy, Mlx = Meloxicam, Mop = Morphinen, Oxy = Oxycodone, p.o. = Per oral, p.r.n. = Pro re nata, Pct = Paracetamol, Pgb = Pregabalin, SD = Standard deviation, T = Tramadol, V = Venlafaxine

Table 2
Characteristics of patients.

Study, year	Patients (n)		Age (mean ± SD)		Female (%)		BMI (mean ± SD)		ASA I (n)		ASA II (n)		ASA IIII (n)	
	S	P	S	P	S	P	S	P	S	P	S	P	S	P
Altiparmak, 2018	31	33	53.00 ± 11.00	54.00 ± 11.00	-	-	28.00 ± 3.00	28.00 ± 3.00	13	10	18	23	-	-
Attia, 2017	30	30	48.36 ± 9.80	54.00 ± 11.00	40.00%	50.00%	29.46	28.97	17	18	9	7	4	5
Bedin, 2017	28	29	48.00 ± 12.00	46.50 ± 8.74	53.57%	55.17%	29.00 ± 5.00	27.00 ± 5.00	12	6	16	21	-	-
Castro-alvez, 2016	31	32	42.40 ± 5.80	48.00 ± 14.00	100.00%	100.00%	26.70 ± 3.60	27.90 ± 3.80	24	23	7	9	-	-
El-Behairy, 2019	30	30	45.70 ± 8.00	42.10 ± 4.60	46.67%	43.33%	22.20 ± 1.90	22.50 ± 2.10	-	-	-	-	-	-
Gerber, 2022	25	27	46.08 ± 11.07	43.00 ± 8.50	44.00%	44.44%	27.53 ± 4.77	28.16 ± 5.26	11	7	14	20	-	-
Govil, 2020	46	46	41.40 ± 14.60	50.41 ± 8.56	50.00%	52.17%	25.90 ± 2.30	26.60 ± 2.20	20	18	20	28	-	-
Ho, 2010	23	24	65.20	43.00 ± 15.10	69.57%	70.83%	28.85	27.49	1	2	18	19	4	3
Kassim, 2018	25	25	30.10 ± 1.90	30.80 ± 2.20	100.00%	100.00%	24.90	25.36	24	-	1	-	-	-
Koh, 2019	40	40	69.10 ± 5.80	68.60 ± 9.50	87.50%	85.00%	25.50 ± 2.30	26.40 ± 7.50	12	24	27	1	1	-
Mantay, 2016	25	25	56.00 ± 12.64	55.60 ± 8.31	100.00%	100.00%	25.58 ± 5.65	25.08 ± 4.57	8	9	16	31	1	0
Nasr, 2014	24	23	42.50 ± 6.00	41.70 ± 5.00	100.00%	100.00%	-	-	17	-	7	-	18	-
Takmaz, 2019	40	37	45.00	43.00	100.00%	100.00%	24.90	22.40	19	18	21	5	-	-
YaDeau, 2016	53	53	67.00	63.00	52.83%	49.06%	-	-	-	-	20	-	17	-
YaDeau, 2022	80	80	63.00 ± 11.00	64.00 ± 7.00	50.00%	43.75%	31.00 ± 8.00	30.00 ± 7.00	1	-	64	-	15	-
Amr, 2010	50	50	45.00 ± 6.00	44.00 ± 8.00	100.00%	100.00%	32.42	32.04	-	2	-	68	-	9
Reuben, 2004	48	47	46.00 ± 8.00	45.00 ± 7.00	100.00%	100.00%	26.81	26.40	-	-	-	-	-	-
Stamer, 1997	60	60	44.40 ± 12.40	44.90 ± 11.20	-	-	24.42	24.70	-	-	-	-	-	-
Demiraran, 2013	30	30	26.50 ± 4.40	27.80 ± 5.20	100.00%	100.00%	29.98	30.71	-	-	-	-	-	-
Total/Mean	719	721	48.67	47.86	76.13%	76.10%	27.24	27.04	179	137	258	232	60	17

Abbreviations: S = SNRI, P = Placebo

(OR: 1.21; 95% CI: 0.61–2.40; p=0.59), somnolence (OR: 0.93; 95% CI: 0.43–2.04; p=0.86), headache (OR: 1.67; 95% CI: 0.85–3.26; p=0.13), nausea (OR: 0.86; 95% CI: 0.63–1.18; p=0.36), nor sedation (OR: 2.02; 95% CI: 0.95–4.29; p=0.07) were significantly different between the SNRIs group compared to the placebo group post-surgery. Nevertheless, the occurrences of dizziness (OR: 2.53; 95% CI: 1.34–4.78; p=0.004) and dry mouth (OR: 2.21; 95% CI: 1.25–3.92; p=0.007) were significantly higher in the SNRIs group compared to the placebo group. The total effects of adverse events were not statistically different between the two groups (OR: 1.17; 95% CI: 0.98–1.39; p=0.09).

A subgroup analysis of 24-hour pain at rest score was conducted based on the type of surgical intervention (Fig. 5). SNRIs was found to significantly lower the 24-hour pain score after spinal surgery (MD: −0.45; 95% CI: −0.84 to −0.05; p=0.03) but not after gynecological surgery (MD: −0.50; 95% CI: −1.20–0.21; p=0.17) or knee surgery (MD: 0.06; 95% CI: −0.39–0.50; p=0.80) compared to placebo.

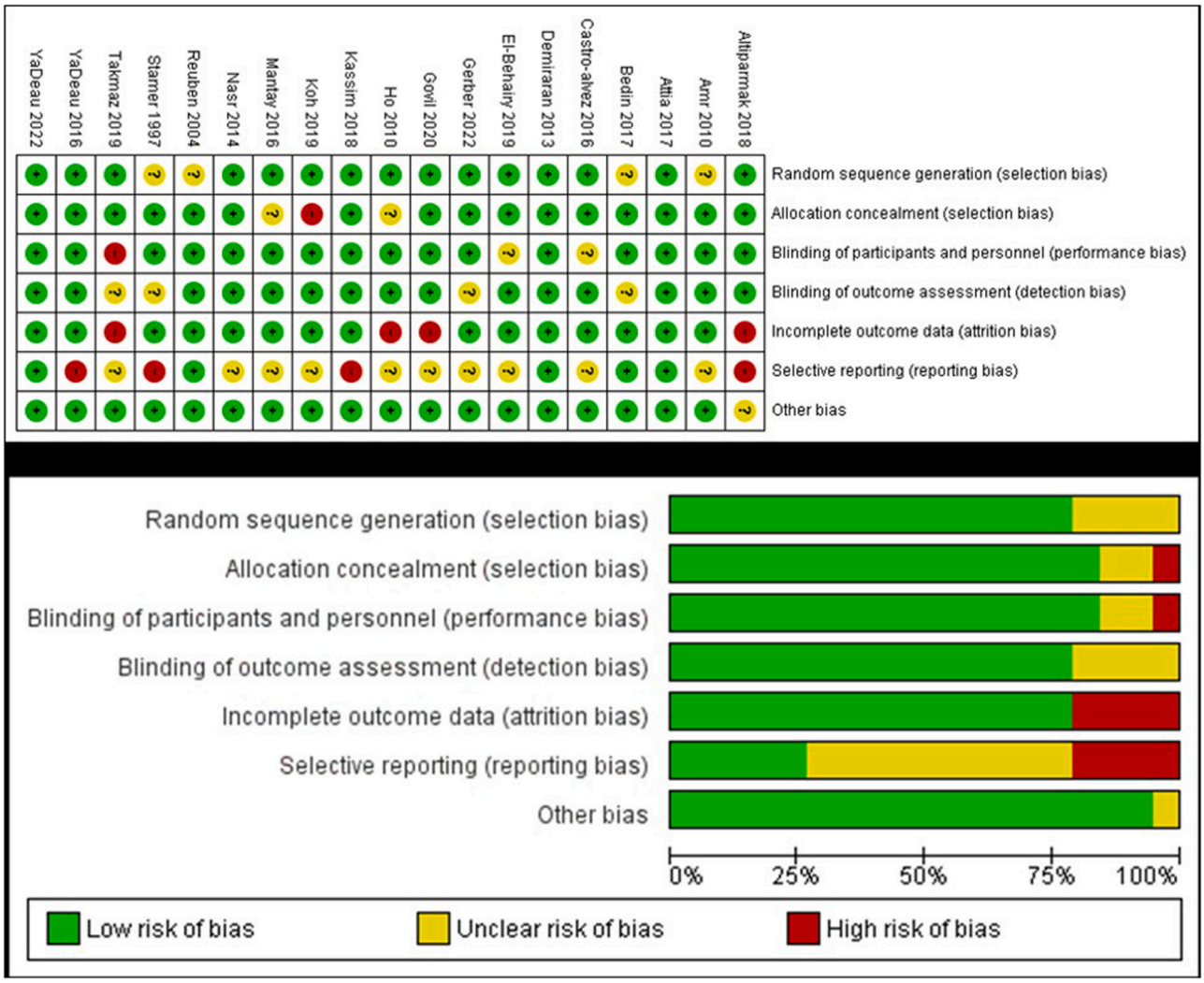

Fig. 2. Risk of bias summary and graph.

A subgroup analysis was performed to compare the 24-hour pain score at rest to placebo based on the specific type of SNRIs (Fig. 6). The results indicated that duloxetine (MD: −0.63; 95% CI: −1.15 to −0.11; p=0.02) had a significant effect in lowering the 24-hour pain score at rest compared to placebo, whereas venlafaxine (MD: 0.02; 95% CI: −0.57–0.61; p=0.95) did not exhibit any significant effect. However, it was not possible to conduct a subgroup analysis on tramadol due to the limited availability of data on the 24-hour pain score at rest.

4. Discussions

The findings of this study revealed significant outcomes in the pain at rest scores observed at 2 hours, 6 hours, 24 hours, and 48 hours in the SNRIs group following surgical interventions. Moreover, adverse events, specifically dizziness and dry mouth, were reported. Notably, a noteworthy reduction in the 24-hour pain score at rest was observed following spinal surgery, as well as a significant decrease in the 24-hour pain at rest score in patients who received duloxetine. To the best of our knowledge, this is the first meta-analysis that includes a broader range of SNRIs, not limited to duloxetine alone. Furthermore, no other meta-analysis has previously addressed and stratified the efficacy of SNRIs based on the type of surgery and the specific type of SNRIs. In concordance with another study reviewing the same comparison, our meta-analysis found that SNRIs exhibited significantly lower mean pain scores for pain at rest in the 24 and 48 hours following surgical interventions compared to placebo [46]. However, their study primarily focused on duloxetine, with only one study involving venlafaxine. Additionally, their examination of adverse events only encompassed dizziness, headache, and sleep disturbance. Wang et al. conducted a similar comparison with comparable results in terms of pain relief [47]. While their study encompassed both SNRIs and SSRIs, they placed more emphasis on the relationship with opioid consumption. The adverse events included in their analysis were also limited to nausea, dizziness, drowsiness, headache, and pruritus.

These two post-operative periods are often referred to as the acute postoperative phase, characterized by the highest level of post-operative pain [48]. Both of them represent the maximum peak intensity of pain, and SNRIs exert its highest effect in modulating pain pathways in the central nervous system, attenuating pain signal transmission, and increasing serotonin and norepinephrine neurotransmitters [49]. Pain during both postoperative time points could lead to central nervous system hyperexcitability and the amplification of pain signals. This is commonly referred to as central sensitization, which can be maximally counteracted by the administration of SNRIs [50]. Various cellular and molecular changes occur in the nervous system. A study also suggested that postoperative edema, reaching its peak at 24 and 48 hours after the surgery, could exacerbate pain and enhance the effectiveness of SNRI's action. This pain sensation is influenced by various factors, such as surgical trauma, tissue damage, inflammation, nerve irritation, swelling, and nerve sensitization [51]. The comparability of SNRIs' efficacy at 2

Table 3
Forest plots summary.

Parameters	Number of studies	Odds Ratio / Mean Difference [95% CI]	*p*
Pain at rest			
Pain at Rest at 2 h	7	MD −0.26 [-0.47, −0.04]	0.02*
Pain at Rest at 4 h	2	MD −0.51 [-1.39, 0.36]	0.25
Pain at Rest at 6 h	5	MD −0.68 [-1.01, −0.34]	<0.0001*
Pain at Rest at 12 h	4	MD −0.95 [-2.12, 0.23]	0.11
Pain at Rest at 24 h	16	MD −0.54 [-0.99, −0.09]	0.02*
Pain at Rest at 48 h	13	MD −0.66 [-1.23, −0.10]	0.02*
Total		**MD −0.57 [-0.80, −0.33]**	**<0.00001***
Adverse events			
Vomiting	13	OR 0.81[0.56, 1.18]	0.28
Pruritus	8	OR 1.21 [0.61, 2.40]	0.59
Somnolence	5	OR 0.93 [0.43, 2.04]	0.86
Dizziness	9	OR 2.53 [1.34, 4.78]	0.004*
Headache	8	OR 1.67 [0.85, 3.26]	0.13
Nausea	14	OR 0.86 [0.63, 1.18]	0.36
Sedation	3	OR 2.02 [0.95, 4.29]	0.07
Dry Mouth	4	OR 2.21 [1.25, 3.92]	0.007*
Total		**OR 1.17 [0.98, 1.39]**	**0.09**
24 h pain at rest based on type of surgery			
Post-Spinal Surgery	4	MD −0.45 [-0.84, −0.05]	0.03*
Post-Gynecological Surgery	6	MD −0.50 [-1.20, 0.21]	0.17
Post-Knee Surgery	4	MD 0.06 [-0.39, 0.50]	0.80
24 h pain at rest based on type of SNRIs			
Duloxetine	14	MD −0.63 [-1.15, −0.11]	0.02*
Venlafaxine	2	MD 0.02 [-0.57, 0.61]	0.95

and 6 hours postoperative with other studies is constrained by the limitations of the available meta-analyses, which primarily center on elucidating the cumulative effects of SNRIs during certain postoperative hours.

Consistent with other studies concerning the same comparison, our meta-analysis showed that spinal surgery has a significant reduction in the 24-hour pain score when treated with SNRIs [52,53]. It was due to the procedure of spinal surgery that involves direct manipulation to the spinal cord, nerve roots, and surrounding spinal tissues [52]. It resulted in higher pain scores, making it more susceptible to a greater reduction when norepinephrine reuptake was inhibited through SNRIs administration[52].

A study also suggested that pain signal processing pathways in the central nervous system involved in patients with spinal surgery were more responsive to norepinephrine modulation as a result of SNRI [54]. Spinal surgery is also classified as a complex procedure, leading to significant inflammation and intense pain. SNRIs, with its anti-inflammatory effects, play a crucial role in reducing this pain. This shows that the complexity of spinal surgery has a greater SNRIs effect on lower the 24-hour pain score than knee surgery [55]. Studies reviewing the effect of SNRIs on gynecological surgery are limited, it necessitates the need for more comprehensive and in-depth investigations to elucidate the potential benefits and risks associated with SNRIs utilization in managing postoperative pain and improving patient outcomes after various gynecological procedures.

Our meta-analysis aligns with the other studies in the same comparison, confirming that duloxetine demonstrated a notable impact on reducing the 24-hour pain score at rest [56,57]. Duloxetine was able to alleviate patients' pain by enhancing their mood and quality of life, such as by managing anxiety and depression [56,58]. It works by regulating the neurotransmission of inhibitory pain signals through descending pathways within the central nervous system [59]. Duloxetine also blocks the transmission of nociceptive signals throughout the vertebral canal. This leads to a reduction in the propagation of pain signals originating from peripheral receptors [59]. In another meta-analysis focusing on chronic musculoskeletal pain, duloxetine also exhibited the ability to delay the progression of knee osteoarthritis and fibromyalgia and improve patients' bodily functions, leading to an enhancement in various aspects of patients' life quality[56].

Another study, focusing on spinal cord injury and major depressive disorder, similarly supports our meta-analysis in showing the less beneficial effect of venlafaxine [60]. It shows that venlafaxine effectively reduced pain severity and specific interference related to nociceptive pain only, but it did not have a significant effect on neuropathic pain in individuals with spinal injuries [61]. It occurs because venlafaxine primarily works only by inhibiting the reuptake of serotonin and norepinephrine within the central nervous system, thus reducing the transmission of pain signals in cases of nociceptive pain. However, in the context of spinal neuropathic pain, there is damage to sensory nerve pathways and abnormal neurotransmitter release, rendering the mechanism of action of venlafaxine less effective [33,60].

In accordance with other meta-analyses in the same comparison, our meta-analysis found that dizziness and dry mouth were the two significant adverse events in the SNRIs group compared with the placebo group [46,62]. It has been proven that dizziness was the most relevant adverse event during treatment and is still taken into account in individual instances currently [46]. The brain's ability to balance serotonin and norepinephrine could be impacted by SNRIs, which result in dysregulation of neurotransmitter activity that could make a person feel lightheaded. Research discovered that SNRIs might boost the availability of serotonin and norepinephrine by reducing their absorption in the brain, which impacts dopamine activities and was able to increase vertigo [63].

Another meta-analysis concentrating on the treatment of depressive disorders with second-generation antidepressants revealed that SNRIs were linked with a significantly higher risk of dry mouth than in placebos [62]. It occurs as the result of SNRIs' anticholinergic characteristics, which allow them to suppress acetylcholine's effects. Blocking the activity of acetylcholine, a neurotransmitter involved in the stimulation of saliva production, can also result in dry mouth [64]. In line with other meta-analyses looking into the same comparison, our meta-analysis found that the remaining adverse events—vomiting, pruritus/itching, somnolence, headache, nausea, and sedation/drowsiness—were not statistically different between the SNRIs and placebo group [46]. It may be difficult to compare across groups because there may be frequent side effects of numerous drugs, low in both groups, and variable in terms of their severity and duration from person to person [65].

Vomiting was one of the adverse events that occurs less frequently with SNRIs than with placebos. This occurs as a result of SNRI's antiemetic action, which might lessen the likelihood of vomiting. Antiemetics are drugs that either prevent or treat nausea and vomiting. They work by preventing certain neurotransmitters from reaching the brain [66]. Pruritus/itching occurred more in SNRIs than in placebos. It occurred as a result of SNRIs' capacity to influence brain neurotransmitter levels, such as serotonin and norepinephrine, which could also have an impact on the skin and induce itching [67]. Placebos had a slightly higher chance of causing somnolence than SNRIs. It could arise as a result of the research population perhaps having an impact on the occurrence of somnolence. For instance, the incidence of somnolence in the placebo group would rise if it included individuals with a greater prevalence of sleep problems or other diseases that might make a person feel sleepy [68].

Compared to placebos, headache occurred more in SNRIs group. The levels of neurotransmitters in the brain are impacted by SNRIs, which could disrupt blood flow and pressure and result in headaches. Vasoconstriction or dilatation may also be brought on by certain SNRIs, which can potentially lead to headaches [69]. Similar to when vomiting occurred, more cases of nausea occurred in placebo group than in SNRIs group. Research stated that the underlying ailment being treated may have some correlation to nausea. In clinical studies for major depressive

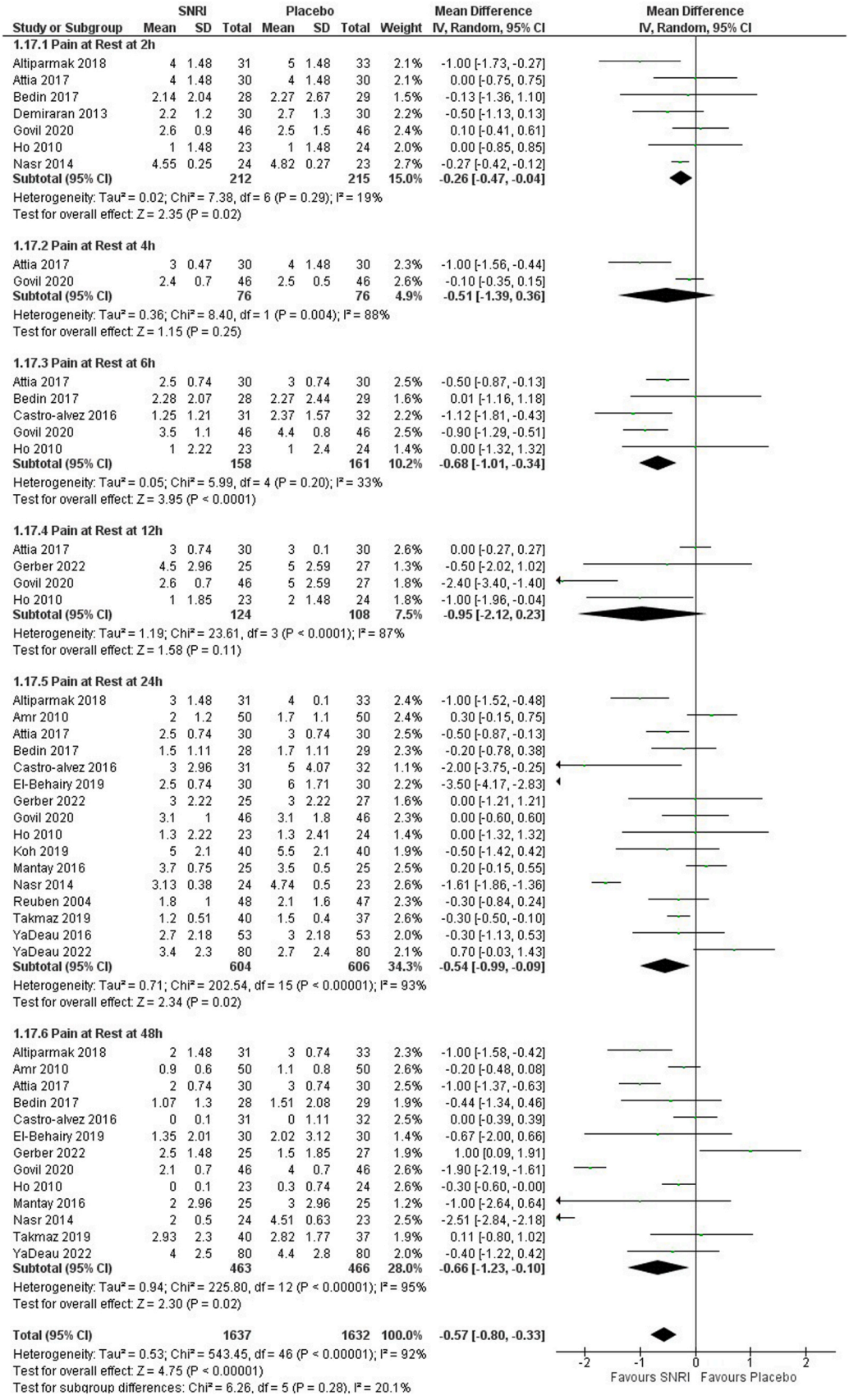

Fig. 3. Effects of SNRIs on pain at rest at 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, and 48 hours post-surgery compared to placebo.

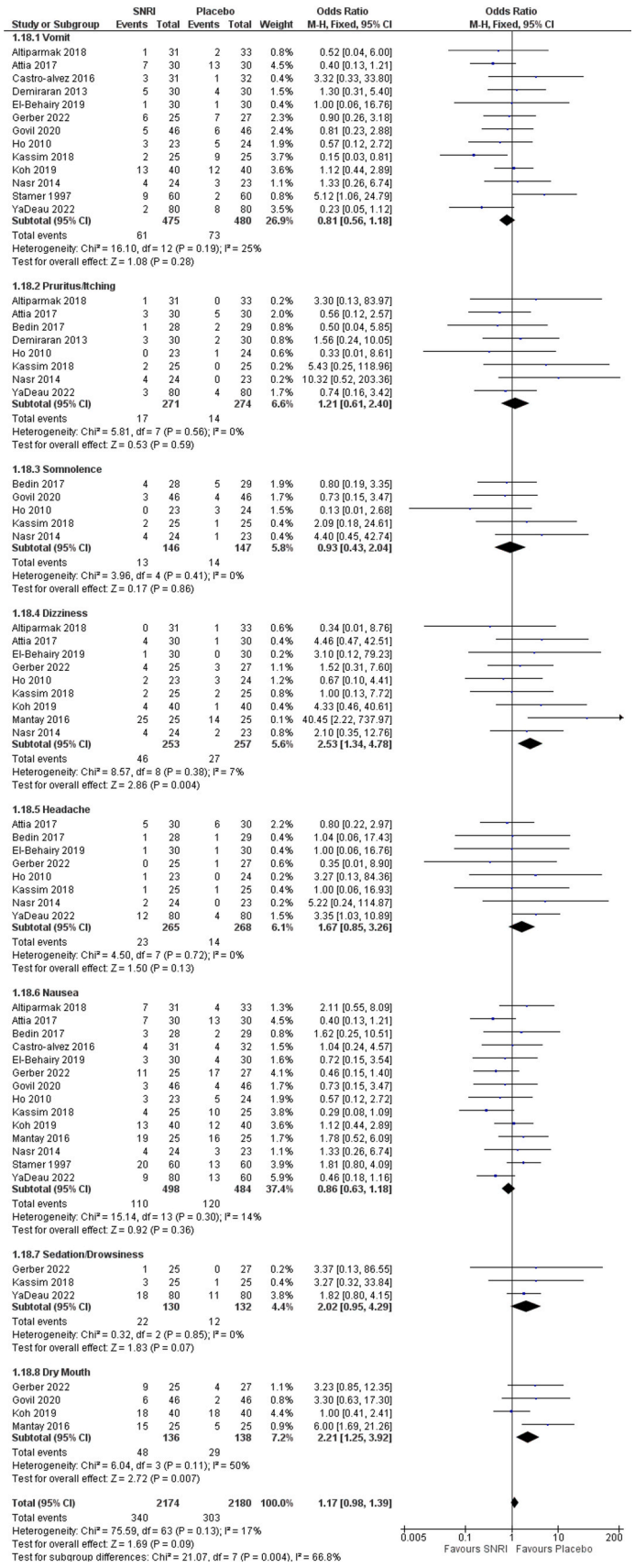

Fig. 4. Effects of SNRIs on adverse events post-surgery compared to placebo.

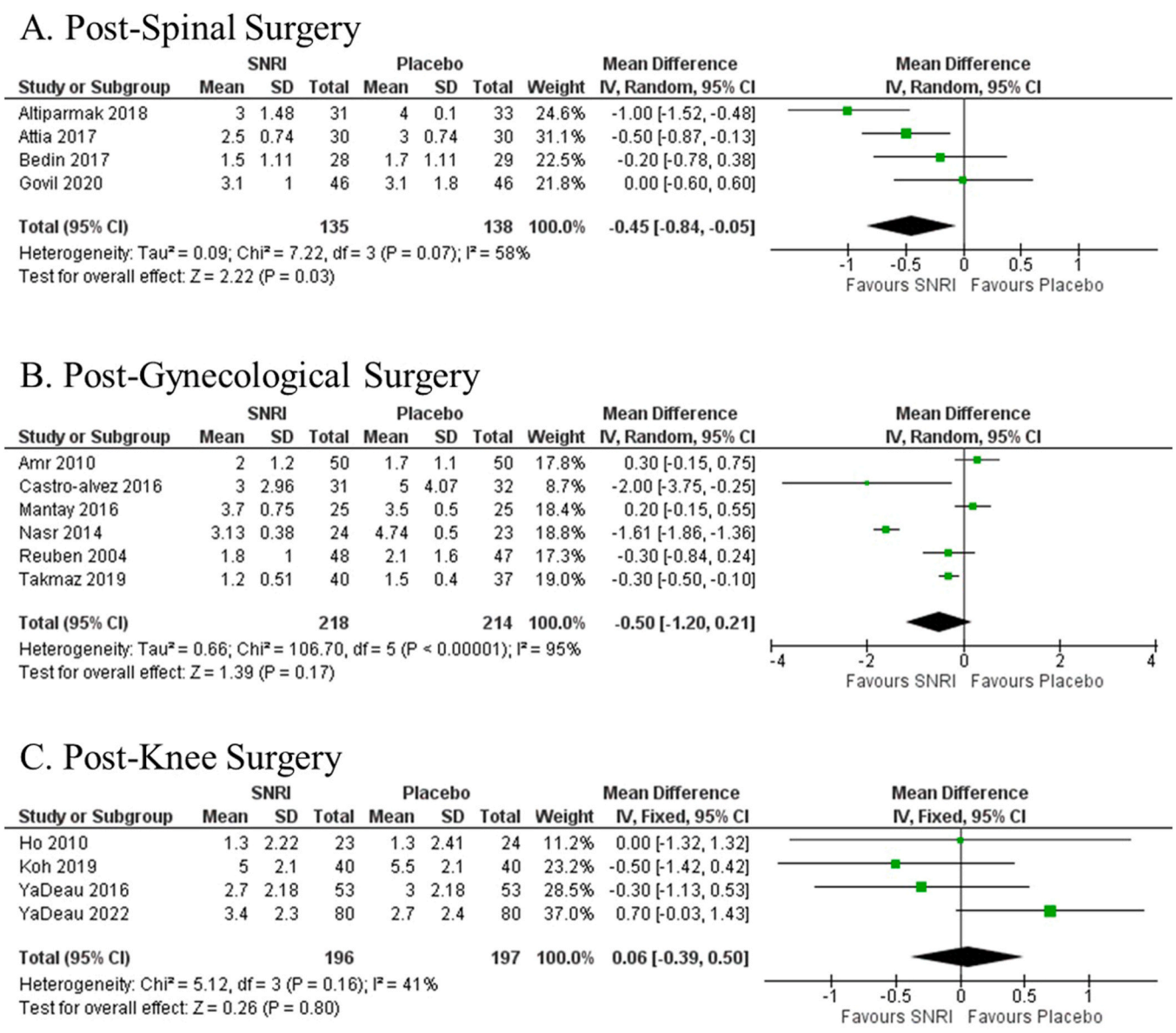

Fig. 5. Effects of SNRIs on 24-hour pain at rest based on type of post-surgery compared to placebo. (A) Post-spinal surgery, (B) Post-gynecological surgery, and (C) Post-knee surgery.

disorder, for instance, individuals could feel nauseous due to their depressive symptoms rather than the medicine being studied. As a result, the placebos group could experience more nausea than the SNRIs group did. Another explanation is that those who received the placebos were more likely to worry or feel anxious about the experiment and their health, which manifested physically as symptoms like nausea [66]. More sedation incidents occurred with SNRIs than with placebos. It resulted from their mechanism of action. SNRIs increase the levels of serotonin and norepinephrine in the brain, which, especially at higher dosages, can result in sleepiness and exhaustion. SNRIs can also impact dopamine, as one of the neurotransmitters involved in controlling alertness and wakefulness. Dopamine levels that are reduced by SNRIs may increase drowsiness and weariness [70].

The study is not without limitations. The study utilized a comprehensive search approach, including a cited reference search, but potential research eluded our investigation. Unpublished papers supporting our data were unavailable, and obtaining certain studies was challenging due to limited access and author contact difficulties. Furthermore, the research focused solely on pain at rest, limiting insights into pain during movement, which can introduce confounding elements. Nonetheless, studying pain at rest facilitated a controlled experimental environment, aiding in the identification of factors influencing pain perception. A significant limitation is our inability to guarantee that postoperative adverse events solely resulted from the tested treatment. Underlying medical conditions may contribute to adverse outcomes, potentially affecting group comparisons. The reliability of adverse event results was also impacted by patients taking other substances before the study, leading to potential inaccuracies. Researchers should be mindful of these limitations when interpreting the findings and consider future investigations to address these challenges effectively.

5. Conclusions

In conclusion, this systematic review and meta-analysis demonstrate a significant reduction in mean pain scores in the SNRIs group compared to the placebo group at various postoperative time points (2 hours, 6 hours, 24 hours, and 48 hours). However, it is noteworthy that

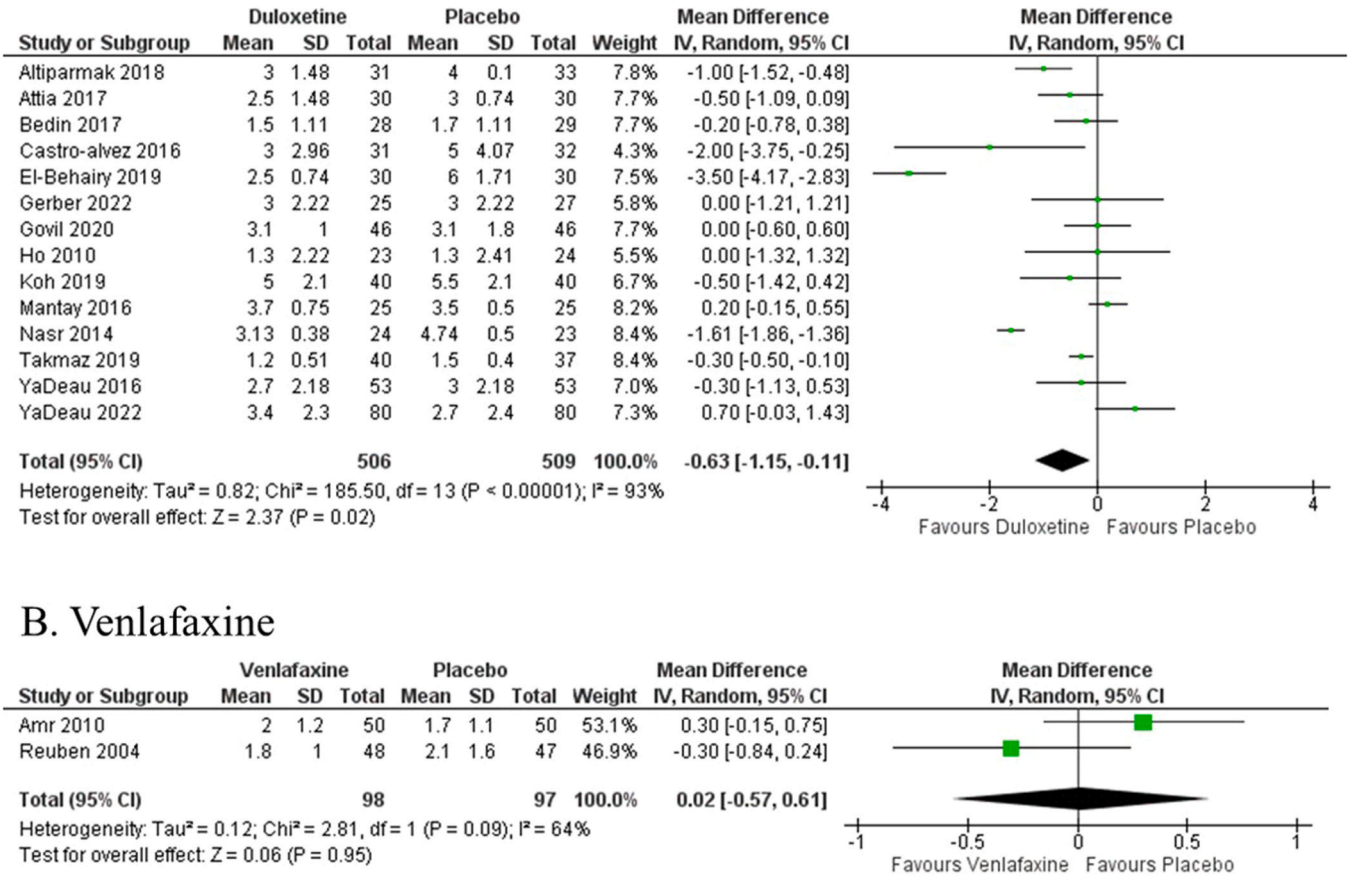

Fig. 6. Effects of SNRIs on 24-hour pain at rest based on type of SNRI compared to placebo. (A) Duloxetine and (B) Venlafaxine.

adverse effects such as dizziness and dry mouth were observed with higher frequency in the SNRIs group compared to the placebo group. Nevertheless, SNRIs administration shows substantial benefits for post-spinal surgery patients. The specific SNRIs, duloxetine, has proven to be highly effective in significantly reducing pain scores. Furthermore, the included studies exhibit a moderate to high level of evidence quality, making them reliable and robust in supporting the use of SNRIs for managing postoperative neuropathic pain.

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CRediT authorship contribution statement

Ni Luh Putu Saswatasya Widha Putri: Writing – original draft. **Made Favian Budi Gunawan:** Writing – original draft. **Jane Carissa Sutedja:** Writing – original draft, Investigation, Formal analysis, Data curation. **David Christopher Tjandra:** Writing – original draft, Resources. **Bryan Gervais de Liyis:** Writing – review & editing, Writing – original draft, Software, Methodology, Conceptualization. **Rizaldi Taslim Pinzon:** Validation, Supervision. **I Putu Eka Widyadharma:** Validation, Supervision, Project administration. **Chrysanta Paramitha Karuniamaya:** Writing – original draft. **Jimmy Fransisco Abadinta Barus:** Validation, Supervision.

Declaration of Competing Interest

The authors declared that there is no competing interest.

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